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### ***Impact of cancer metabolism on therapy resistance - Clinical implications***

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## **Abstract**

Despite an increasing arsenal of anticancer therapies, many patients continue to have poor outcomes due to the therapeutic failures and long-term tumor relapses. Indeed, the clinical efficacy of anticancer therapies is markedly limited by intrinsic and/or acquired resistance mechanisms that can occur in any tumor type and with any treatment. There is thus an urgent clinical need to implement fundamental changes in the tumor treatment paradigm by the development of new experimental strategies that can help to predict the occurrence of clinical drug resistance and to identify alternative therapeutic options. Apart from mutation-driven resistance mechanisms, tumor microenvironment (TME) conditions generate an intratumoral phenotypic heterogeneity that supports disease progression and dismal treatment outcomes. Tumor cell metabolism is a prototypical example of dynamic, heterogeneous, and adaptive phenotypic trait, resulting from the combination of intrinsic [(epi)genetic changes, tissue of origin and differentiation dependency] and extrinsic (oxygen and nutrient availability, metabolic interactions within the TME) factors, enabling cancer cells to survive, metastasize and develop resistance to anticancer therapies. In this review, we summarize the current knowledge about metabolism-based mechanisms conferring adaptive resistance to chemo-radio and immunotherapies as well as targeted therapies. More precisely, we report the role of TME-mediated intratumoral metabolic heterogeneity in therapy resistance and how adaptations in amino acid, glucose, and lipid metabolism support the growth of therapy-resistant cancers and/or cellular subpopulations. We also report the intricate interplay between tumor signaling and metabolic pathways in cancer cells and discuss how manipulating key metabolic enzymes and/or providing dietary changes may help to eradicate relapse-sustaining cancer cells. Finally, in the current era of personalized medicine, we describe the strategies that may be applied to implement metabolic profiling for tumor imaging, biomarker identification, selection of tailored treatments and monitoring therapy response during the clinical management of cancer patients.

## **Keywords:**

Cancer metabolism, therapy resistance, tumor microenvironment, intratumor heterogeneity, metabolic plasticity, glycolysis, oxidative phosphorylation

**Abbreviation:** <sup>18</sup>F-DOPA, <sup>18</sup>F-3,4-dihydroxyphenylalanine; <sup>18</sup>F-FDG, 2-deoxy-2-[fluorine-18] fluoro-D-glucose; 2-DG, 2-deoxy-D-glucose; 2HG, 2-hydroxyglutarate; 5-FU, 5-fluorouracil; AAD, antiangiogenic drugs; ABC, ATP-binding cassette transporter; ADT, androgen deprivation therapy; AI, artificial intelligence; ARE, antioxidant response elements; ASC, adipose-derived mesenchymal stem cell; Asn, asparagine; ASNS, asparagine synthetase, ASS1, argininosuccinate synthase 1; BCAT1, branched-chain amino acid transaminase 1; BDNF, brain-derived neurotrophic factor; BPTES, bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl)ethyl sulfide; BSO, buthionine sulfoximine; BTKi, Bruton's tyrosine kinase inhibitor; C1P, Cer-1-phosphate; CAA, cancer-associated adipocytes; CAF, cancer-associated fibroblasts; CAXII, carbonic anhydrase XII; Cer, ceramide; CEBP-β, CAAT enhancer binding protein-β; CLCF1, cardiotrophin-like cytokine factor 1; cPLA2, cytosolic phospholipase A2; CSC, cancer stem cells; CSK, C-terminal SRC kinase; DON, 6-diazo-5-oxo-L-norleucine; DRM, detergent-resistant membrane; ECM, extracellular matrix; EGF, epidermal growth factor; EMA, European Medicines Agency; EMT, epithelial-to-mesenchymal transition; ENO, enolase; ER, estrogen receptor; ET, endocrine therapy; EVs, extracellular vesicles; FA, fatty acid; FAO, Fatty acid oxidation; FASN, fatty acid synthase; FDA, Food and Drug Administration; FGF, fibroblast growth factor; FPP, farnesyl pyrophosphate; G6PD, glucose-6-phosphate dehydrogenase; GCLC, glutamate-cysteine ligase catalytic subunit; GCN2, general control non-depressible 2; GGPP, geranylgeranyl pyrophosphate; GLS, glutaminase; GLUTs, glucose transporters GPAT1, glycerol 3-phosphate acyltransferase; GPER, G-protein-coupled estrogen receptor; GSH, reduced glutathione; GSSG, oxidized glutathione; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide; HIF-1α, hypoxia-inducible factor 1α; HIF, hypoxia-inducible factor; HKII, hexokinase II; HMGCR, 3-β-hydroxy-3-β-methyl glutaryl coenzyme A reductase; HMGCS1, 3-β-hydroxy-3-β-methylglutaryl coenzyme A synthase 1; ICIs, immune checkpoint inhibitors; IDH, isocitrate dehydrogenase; IDO1, indoleamine 2,3-dioxygenase; IFN-γ, interferon gamma; LD, lipid droplets; LDH, lactate dehydrogenase; LDL, low density lipoprotein; LKB1, liver kinase B1; LPA, lysophosphatidate; LPAR, LPA receptor; LPCAT2, lysoPC acyltransferase 2; LXR, liver X receptor; LysoPL, lysophospholipids; MCT, monocarboxylate transporter; MDR, multidrug resistance; ME, malic enzyme; MPC, mitochondrial pyruvate carrier; MSI, mass spectrometry imaging; mtDNA, mitochondrial DNA; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NHE, Na<sup>+</sup>/H<sup>+</sup> exchanger; NMR, nuclear Magnetic Resonance; NQO1, NAD(P)H quinone oxidoreductase; O<sub>2</sub><sup>•-</sup>, superoxide anion; <sup>•</sup>OH, hydroxyl radical; OXPHOS, oxidative phosphorylation; P-gp, P-glycoprotein; PAG1, phosphoprotein associated with glycosphingolipid-enriched microdomains; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PET-CT, positron emission tomography coupled to computed tomography; PFK, phosphofructokinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PGD, phosphogluconate dehydrogenase; pHe, extracellular pH; PHGDH, phosphoglycerate dehydrogenase; PKM2, pyruvate kinase M2; PL, phospholipid; PLIN4, perilipin 4; PPAR, peroxisome proliferator activated receptor; PPI, proton pump inhibitors; PPP, pentose phosphate pathway; PTMA, prothymosin α; ROS, reactive oxygen species; RTK, tyrosine kinase receptors; S1P, Sph-1-phosphate; SAT1, spermidine/spermine N1-acetyltransferase; SCD-1, stearoyl-coenzyme A desaturase-1; SLC, solute carrier transporters; SMS, sphingomyelins; SOD, superoxide dismutase; Sph, sphingosine; SREBP1, sterol

regulatory element-binding protein 1; STAT3, signal transducer and activator of transcription 3; TCA, tricarboxylic acid; TDO, tryptophan 2,3-dioxygenase; TG, triglyceride; TIF, tumor interstitial fluid; TKI, tyrosine kinase inhibitors; TME, tumor microenvironment; TPP<sup>+</sup>, phenol triphenyl alkyl phosphonium; TSG, tumor suppressor gene; V-H<sup>+</sup>-ATPase, vacuolar H<sup>+</sup>-ATPase; VEGF, vascular endothelial growth factor; YAP, yes-associated protein;  $\alpha$ -KG,  $\alpha$ -ketoglutarate.

## 1. Introduction

Despite significant improvements in tumor prevention, diagnosis, and treatment, the prognosis for cancer patients remains frequently dismal due to drug resistance and consequent tumor relapse. Therapeutic failures in clinics can affect all types of tumors, hematological and solid tumors, and may even occur virtually with all anticancer treatments, including conventional chemo/radiotherapy to targeted therapy or immunotherapy. Indeed, the clinical efficacy of anticancer therapies is strongly limited by drug resistance mechanisms that may exist at diagnosis or develop throughout treatment referred to as intrinsic and acquired drug resistance, respectively (Gonen and Assaraf, 2012; Li et al., 2016; Wang et al., 2019b; Wijdeven et al., 2016). The current clinical protocols, primarily based on the application of a maximum-tolerated dose, aim to kill the largest proportion of cancer cells in a short time but, at the same time, may select for resistant tumor cell phenotypes (Enriquez-Navas et al., 2015; Gillies et al., 2012). Apart from genetic alterations, intratumor phenotypic heterogeneity has been widely recognized to support resistance to anticancer treatments in various cancer types (Marine et al., 2020). Therapy resistance is indeed often associated with the existence of specific tumor microenvironment (TME) conditions (the so-called niches) that can shape adaptive stem-like tumor cell phenotypes more prone to contribute to minimal residual disease and long-term clinical relapse (Boumahdi and de Sauvage, 2020). Acquired resistance may arise from a Darwinian selection of rare pre-existing resistant clones within the heterogeneous tumor cell population (Assaraf et al., 2019; De Angelis ML, 2018). Although therapy-resistant or drug-tolerant state may be found in any tumor cell, it is notoriously found in stem-like tumor cells that may be present within any type of malignancy (Balça-Silva et al., 2017; Freitas et al., 2014; Li et al., 2021).

However, the mechanisms mediating drug resistance are multifactorial, often interconnected, and typically involved in tumor progression. Most of them have been recognized as either associated with cancer hallmarks or with interactions between the TME and tumor cells (Assaraf et al., 2019). These mechanisms include, among others, enhanced escape from cell death (Lima et al., 2004) tumor intracellular genetic instability and tumor dynamics due to mutations (Dagogo-Jack and Shaw, 2018), along with epigenetic alterations (Garnier-Suillerot et al., 2001; Ozyerli-Goknar and Bagci-Onder, 2021) or alterations in microRNAs (miRs) expression (Hugo et al., 2013; Lima et al., 2011; Alves et al. 2019). Furthermore, intercellular communication with stromal and immune cells from TME (Bu et al., 2020; Kadel et al., 2019; Xavier et al., 2021), escape from immune surveillance (Sharma et al., 2017; Vasan et al., 2019), induction of (partial) epithelial-to-mesenchymal transition (EMT) (Faheem et al., 2020; Zheng

et al., 2015), alterations in intracellular drug concentration mediated by several mechanisms (Alves et al., 2015; Joyce et al., 2015; Law et al., 2021; Namee and O'Driscoll, 2018; Sousa et al., 2015) and metabolic alterations (Boedtkjer and Pedersen, 2020; Wang et al., 2021) are other mechanisms involved in cancer drug resistance (**Figure 1**). Tumor metabolism perfectly illustrates how TME peculiarities strongly influence tumor cell phenotypes and hence treatment outcomes in patients (Faubert et al., 2020; McCann and Kerr, 2021). In this review, we summarize the current knowledge about metabolism-based mechanisms of adaptive resistance to anticancer therapies. More precisely, we report on the role of TME-mediated intratumor metabolic heterogeneity in drug resistance and the reliance of many therapy-resistant cancer types and/or subpopulations on amino acid (AA), glucose, and lipid metabolism. We also discuss the therapeutic avenues of interference with tumor metabolism that may achieve the eradication of relapse-sustaining cancer cells. This review finally explores the strategies that may be applied to implement metabolic profiling of tumors for rational clinical decision-making in cancer patients.

## **2. Metabolic reprogramming in cancer and therapy resistance**

Metabolic needs and preferences evolve along disease progression to facilitate cancer cell survival, proliferation, metastasis, and the development of resistance to anticancer therapies. Compelling evidence has shown that tumor cells display high metabolic flexibility, i.e., the capacity to utilize different nutrients as well as plasticity reflected in their capacity to metabolize the same nutrient differently. Additionally, tumor cells can either cooperate (i.e., metabolic symbiosis) or compete with non-cancerous cell populations. These scenarios are not mutually exclusive and participate in the intratumoral metabolic heterogeneity, thereby equipping cancer cells with multiple adaptations and escape options when facing stressful and hostile conditions, including therapy-induced stress (**Figure 2**).

### **2.1. Pyruvate as a central metabolic gatekeeper in therapy-resistant cancer cells**

Cancer cells displaying therapy resistance have been reported to be either Warburg-like or oxidative phosphorylation (OXPHOS)-addicted. Pyruvate appears as a critical metabolite since it is at the crossroads of cytoplasmic glycolysis and mitochondrial oxidative metabolism, and it has been widely described to support both stem-like cell phenotype and drug resistance (Corbet, 2017). A study has reported that the mitochondrial pyruvate carrier (MPC) is transcriptionally regulated by the androgen receptor and its function (i.e., mitochondrial

pyruvate import) is indispensable to support tumor growth in *in vitro* and *in vivo* models of hormone-responsive and castration-resistant prostate adenocarcinoma (Bader et al., 2019). Conversely, decreased MPC expression and activity have been correlated with increased stem-like features and poor survival in several cancer types, including lung, colon, clear cell renal, prostate, and esophagus squamous cell carcinomas (Schell et al., 2014; Wang et al., 2016a; Zhong et al., 2015). Recent studies have also documented that low expression of *BRP44L*, the MPC1-encoding gene, is associated with poor prognosis and resistance to temozolomide in glioblastoma (GB) and radioresistance in pancreatic cancer (PaC) cells (Chai et al., 2019; Takaoka et al., 2019). Besides the capacity to take up pyruvate into mitochondria *via* MPC activity, key rate-limiting steps that determine the metabolic fate between glycolysis *versus* mitochondrial OXPHOS are the conversion of phosphoenolpyruvate into pyruvate and the metabolism of the latter to acetyl CoA by pyruvate kinase M2 (PKM2) and pyruvate dehydrogenase (PDH), respectively. Several studies have provided new insights into the molecular mechanisms that couple glycolysis to drug resistance in cancer cells. Shanmugasundaram and co-authors have reported that NADPH oxidase isoform NOX4, preferentially localized to the inner mitochondrial membrane, induces production of reactive oxygen species (ROS) that in turn inhibit p300/CBP-associated factor-dependent acetylation and lysosomal degradation of PKM2 and support etoposide resistance in renal cell carcinoma (RCC) models *in vitro* and *in vivo* (Shanmugasundaram et al., 2017). In ovarian cancer (OC) cells, PDH activity is regulated by the mitochondrial calcium uptake 1 protein (MICU1/CBARA1). This protein promotes PDH dephosphorylation and subsequent activation, leading to increased glycolysis and lactate production, which are associated with cisplatin resistance and poor prognosis in OCs (Chakraborty et al., 2017).

Over the last years, there has been growing evidence that glycolysis can support resistance to anticancer therapies in several tumor types [reviewed by (Marcucci and Rumio, 2021)]. Glycolysis-induced drug resistance is associated with the induction of several molecular mechanisms, including inhibition of apoptosis, EMT activation, enhanced autophagy, and drug influx/efflux regulation. Importantly, it occurs in response to various internal and/or external cues such as oncogenic signaling or hypoxia. For instance, in estrogen receptor (ER)-positive breast cancer (BC) cells, tamoxifen resistance has been associated with enhanced glycolytic pathway upon activation of EGFR signaling (He et al., 2019). Tamoxifen-resistant BC cells exhibit a downregulation of miR-186-3p that results in the increased expression of EREG, an agonist of EGFR, and subsequent upregulation of glycolysis-related genes, thereby positioning the miR-186-3p/EREG axis and enhanced aerobic glycolysis as potential targets to overcome

endocrine resistance in breast tumors. Several studies have also reported a role for glycolytic pathway stimulation in the resistance to lapatinib (Tykerb), a small-molecule EGFR/HER2 tyrosine kinase inhibitor (TKI), in HER2-overexpressing BCs. Overexpression of LDHA increased expression of the glucose deprivation response network (Komurov et al., 2012; Zhao et al., 2011), and phosphorylation changes in glycolysis-mediating enzymes [e.g., LDHA, enolase 1 (ENO1), phosphoglycerate mutase] (Ruprecht et al., 2017) have been indeed described to support lapatinib resistance in BC cells. Aberrant expression of hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ) is well known to trigger an increased glycolytic metabolism and contributes to drug resistance in cancer cells. A recent study has shown that HIF1 $\alpha$ -mediated hexokinase II (HKII) overexpression in hepatocellular carcinoma (HCC) cells leads to increased glycolytic metabolism and resistance to sorafenib, a multi-kinase inhibitor (Gao et al., 2021). Furthermore, increased expression of glycolytic enzymes has been found in melanoma and lung cancer patient samples poorly infiltrated by T cells (Cascone et al., 2018). Importantly, in this study, the authors show that enhanced glycolytic activity in tumor cells is associated with a lower response to adoptive T cell therapy. This is actually reminiscent of the observation of a metabolic competition for glucose between tumor cells and T cells that metabolically restrict the latter and therefore limit the development of an effective antitumor immune response (Chang et al., 2015; Ho et al., 2015).

Beyond the “Warburg effect” dogma, compelling experimental evidence has reported a detailed contribution of oxidative mitochondrial metabolism to anticancer drug resistance. First, low mitochondrial DNA (mtDNA) content has been correlated with a better outcome in BC patients treated with anthracycline-based chemotherapy (Weerts et al., 2017). Moreover, mtDNA mutations have been reported to alter the response to therapy in several tumor types (Hertweck and Dasgupta, 2017; Ju et al., 2014; Stewart et al., 2015). For instance, a somatic mutation in the gene encoding for the ND4 subunit of the electron transport chain (ETC) complex I has been associated with chemoresistance in serous OCs (Guerra et al., 2012), while several mutations in non-coding mtDNA regions correlate with chemoresistance in colorectal cancer (CRC) patients (Lièvre et al., 2005). Increased reliance on mitochondrial energy metabolism, in particular OXPHOS, has been reported as a distinctive hallmark of therapy-resistant cancer cells in a variety of tumor types, including OC (Gentric et al., 2019; Matassa et al., 2016), PaC (Viale et al., 2014), colon (Vellinga et al., 2015), prostate (PC) (Ippolito et al., 2016), melanoma (Vashisht Gopal et al., 2019; Vazquez et al., 2013), BC (Echeverria et al., 2019; Lee et al., 2017; Wang et al., 2018b), GB (Hoang-Minh et al., 2018), as well as large B cell lymphoma (Caro et al., 2012), acute myeloid leukemia (AML) (Farge et al., 2017; Lagadinou et

al., 2013; Ye et al., 2016), and chronic myeloid leukemia (Kuntz et al., 2017) (**Table 1**). In addition, therapy-resistant oncogene-addicted cancers, such as *EGFR*-mutant non-small cell lung cancer (NSCLC) and *BRAF*-mutant melanoma, have been found to undergo metabolic reprogramming towards an OXPHOS-driven metabolism (Hirpara et al., 2019). Notably, a recent study has observed that resistance to two anthracyclines, doxorubicin and epirubicin, is associated with distinct primary metabolic vulnerabilities in human BC cells (McGuirk et al., 2021). Indeed, while doxorubicin-resistant BC cells mostly rely on glutamine metabolism and *de novo* glutathione biosynthesis, epirubicin-resistant cell counterparts exhibit increased OXPHOS-mediated ATP production. These specific therapy-induced metabolic adaptations have been correlated with a distinct sensitivity towards buthionine sulfoximine (BSO), an inhibitor of glutathione biosynthesis, and phenformin, an OXPHOS inhibitor in doxorubicin- and epirubicin-resistant BC cells, respectively. These observations reveal that for the same tumor cell type, metabolic vulnerabilities can vary with the therapeutic agent. It is still unclear whether drug-mediated stress induces *de novo* metabolic reprogramming by oxidative metabolism and/or selects the pre-existing cancer cells with high OXPHOS status. The shift towards OXPHOS may confer to cancer cells some metabolic/growth advantages that allow them to become resistant to therapy (Bosc et al., 2017). Notably, a recent study has revealed important new insights by showing that mitochondrial oxidative metabolism can provide ATP as an energy source necessary to support drug efflux through ATP binding cassette (ABC) transporter activity (Giddings et al., 2021), pinpointing the crucial role of mitochondrial energy metabolism in supporting drug resistance. However, in most of the studies described above, the nature of the substrates (*i.e.*, glucose, lactate, glutamine, and/or fatty acids) fueling the mitochondrial metabolism in OXPHOS-addicted therapy-resistant cancer cells has not been clearly identified and requires further investigation.

## **2.2. Lipid metabolism in cancer cells and drug resistance**

Lipid metabolism can contribute to tumor progression by supporting cell proliferation, invasion, and resistance to stress cues in cancer cells (Corbet and Feron, 2017a). Both intrinsic tumor and TME-associated lipids can sustain the therapy-resistant cancer cell phenotype. Moreover, despite the diversity in tumor types and anticancer therapies, virtually all lipid classes have been associated with the onset of resistance and maintenance.

In most tumors, the sterol regulatory element-binding protein 1 (SREBP1) is increased, promoting fatty acid (FA) and triglyceride (TG) synthesis, leading to the accumulation of lipid

droplets (LD) within the cell. Inhibiting SREBP1 and reducing lipogenic pathways chemosensitize colon cancer cells to gemcitabine (Shen et al., 2019), suggesting that LD play a role in chemoresistance. Indeed, LD can sequester lipophilic drugs, such as docetaxel, as documented in BC (Schlaepfer et al., 2012), and LD-related proteins have an active role in inducing chemoresistance. For instance, the LD-associated enzyme lysoPC acyltransferase 2 (LPCAT2) mediates resistance to oxaliplatin and 5-fluorouracil (5-FU) in CRC because it alters the phospholipid (PLs) composition of endoplasmic reticulum, mediating resistance to endoplasmic reticulum-stress dependent apoptosis and immunogenic cell death elicited by chemotherapy (Cotte et al., 2018). Similarly, the LD-associated stearoyl-coenzyme A desaturase-1 (SCD-1) mediates the resistance to cytoskeleton-targeting drugs as docetaxel (Schlaepfer et al., 2012), likely because it alters the composition and fluidity of membranes and the junctions between membrane and cytoskeleton. Prothymosin  $\alpha$  (PTMA) is a SREBP1-activating protein and an inducer of LD in colon cancer cells. The higher the expression of PTMA and the amount of LD are, the higher is the resistance to gemcitabine, caused by the PTMA/LD-mediated activation of the pro-survival factor signal transducer and activator of transcription 3 (STAT3) (Jin et al., 2021a). The LD-associated cytosolic phospholipase A2 (cPLA2) is another interesting target to chemosensitize OC to carboplatin and paclitaxel. cPLA2 is phosphorylated and activated by PFKFB3, a serine/threonine kinase and a glycolysis regulator, and in this form, it prevents lipophagy from LD by interacting with the pro-autophagic protein P62. This phenotype is associated with chemoresistance. In contrast, the PFKFB3 inhibitor, PFK158, deactivates cPLA2 and lipophagy, restoring apoptosis in response to chemotherapeutic drugs (Mondal et al., 2019). This work opens a new avenue of reversing chemoresistance by disrupting the metabolic crosstalk between glucose and lipid metabolism.

Lipogenesis has a role not only in the maintenance but also in the acquisition of drug resistance. In an elegant model of acute exposure to doxorubicin, the surviving clones of triple-negative breast cancer (TNBC) cells showing resistance to the drug had an increase in mitochondria and LD, coupled to a shift from glycolysis- to OXPHOS-dependent metabolism. These changes are supported by the increase in peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ) and  $\gamma$  (PPAR $\gamma$ ), two proteins involved in mitobiogenesis and lipid oxidation (Sirois et al., 2019). If TG stored in LD may provide FA that undergo fatty acid oxidation (FAO), supporting the OXPHOS metabolism, this process is antagonized by the simultaneous increase in perilipin 4 (PLIN4), a natural antagonist of hormone-sensitive lipase. If, on the one hand, the PPAR $\alpha$ /PPAR $\gamma$ /PLIN4<sup>high</sup> signature identified a subset of patients refractory to neoadjuvant

chemotherapy, it also unveiled a metabolic vulnerability, as demonstrated by the reversion of doxorubicin resistance by FAO or PPAR $\gamma$  inhibitors (Sirois et al., 2019).

Chemoresistant tumor cells often have a simultaneous activation of FAO and FA synthesis, controlled by HIF-1 $\alpha$  (Belisario et al., 2020b). This interplay between FAO and FAS also finely tunes the balance between energy and building blocks supply, making cells less dependent on glucose and glutamine, more resilient to energy-depleted TME and chemotherapy (DeBerardinis and Thompson, 2012).

Tissue Cancer Genome Atlas (Kuzu et al., 2016), Gene Ontology (Greife et al., 2015), and Ingenuity Pathway (Hossian et al., 2021) analyses highlighted that patients with poor response to chemotherapy have an increased endogenous biosynthesis of cholesterol. The rate-limiting enzyme 3- $\beta$ -hydroxy-3- $\beta$ -methyl glutaryl coenzyme A reductase (HMGCR) is more active in drug-resistant cells because of its reduced ubiquitination by the TRC8 E3 ubiquitin ligase, which has a lower activity in these cells (Gelsomino et al., 2013). The increased cholesterol results in more rigid detergent-resistant membrane (DRM) domains, where the drug efflux ABC transporters ABCB1 (P-glycoprotein, P-gp), ABCC1 (MRP1), and ABCG2 (BCRP) proteins are abundant. The increased rigidity maintains the ABC transporters within the DRM domain, where they actively efflux multiple chemotherapeutic drugs (Gelsomino et al., 2013). High activity of HMGCR has been reported in cancer-stem-like cells (CSCs) of prostate origin, making them particularly resistant to docetaxel. The deregulated HMGCR activity, due to the removal of enzyme inhibition by AMPK, maintains high levels of the transcription factor yes-associated protein (YAP) that contributes to the stemness maintenance and the expansion of chemoresistant CSCs (Iannelli et al., 2020). Therefore, targeting HMGCR activity with statins could be an attractive option to eradicate chemorefractory tumor cells, more prone to support long-term clinical relapse. Recently, the enzyme upstream of HMGCR, 3- $\beta$ -hydroxy-3- $\beta$ -methylglutaryl coenzyme A synthase 1 (HMGS1), has been indicated as a mediator of resistance to doxorubicin and cytarabine because it increases the resistance to endoplasmic reticulum- and mitochondria-stress mediated cell death (Zhou et al., 2021). Although the mechanism has not been investigated, it is likely that HMGS1 increases the amount of cholesterol within these organelles and makes them less susceptible to cytotoxic damage. Intriguingly, both endogenous and exogenous cholesterols are delivered by low-density lipoproteins (LDL), which are taken up avidly by drug-resistant cancer cells (Kopecka et al., 2011), and transcriptionally up-regulate ABCB1, ABCC1 (Celestino et al., 2015), and ABCG2 (Wu et al., 2015). Indeed, the cholesterol-derivative oxysterols can activate the transcription factor SREBP1, which cooperates with HIF-1 $\alpha$  in inducing ABCB1 transcription (Furuta et al., 2008),

and the liver X receptor $\beta$  (LXR $\beta$ ), which activates ABCB1 and ABCG2. This coordinated program resulted in the protection of ovarian cells from the pro-apoptotic activity of cisplatin (Kim et al., 2018). More recently, LXR $\alpha$  too has been highly correlated with the expression of ABCB1 and chemoresistance in TNBC cells and ER-negative BC patients (Hutchinson et al., 2021). The increased endogenous synthesis of cholesterol is also associated with an increased accumulation of upstream metabolites, such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) that activate convergent pathways such as RAS/ERK1/2 and RhoA/RhoB kinase that stabilize HIF-1 $\alpha$ , thereby up-regulating ABCB1 (Belisario et al., 2020a). Collectively, the observations linking chemoresistance, cholesterol metabolism, cholesterol-activated transcription factors, or upstream pathways have a significant translational interest because all of these pathways are druggable by cholesterol-lowering agents such as statins, aminobisphosphonates, LXR antagonists, and some kinase inhibitors, successfully employed at the preclinical level (Hutchinson et al., 2021; Iannelli et al., 2020; Kopecka et al., 2016).

Apart from neutral lipids, PLs or their precursors, the lysophospholipids (lysoPL), have been recently re-considered as mediators of chemoresistance (Kopecka et al., 2020b). The FA composition of PLs depends on acyltransferase enzymes that – under this perspective – appear attractive druggable targets to enhance chemosensitivity. For instance, lysophosphatidate-1 (LPA-1), a precursor shared by most PLs, activates the NRF2 transcription factor that in turn up-regulates several antioxidant enzymes and several transporters involved in chemoresistance, namely ABCC1, ABCC2, ABCC3, and ABCG2 (Venkatraman et al., 2015). In melanoma cells, the mechanisms, underlying resistance that is induced by LPA, are mediated by the signaling pathways that are dependent on the LPA receptor (LPAR) 5 (Minami et al., 2019) and 2 (Minami et al., 2020); although this mechanism must be elucidated, it is independent of ABC transporters overexpression. Furthermore, lysophosphatidylcholine and lysophosphatidylethanolamine have been associated with resistance to the five common cytotoxic drugs used in PaC treatment – gemcitabine, oxaliplatin, 5-FU, SN-38, and docetaxel – in patient-derived tumor xenografts (PDX), highlighting a new metabolic signature predictive of resistance, but also a new therapeutic approach. Indeed, FSG67, an inhibitor of glycerol 3-phosphate acyltransferase (GPAT1), impairs the first step of the *de novo* biosynthesis of PLs and sensitizes patient-derived cells to the chemotherapeutic drugs in use (Kaoutari et al., 2021).

Among sphingolipids as sphingomyelins (SMs), chemosensitivity or resistance depends on the ratio between ceramide (Cer), the precursor of SM, and sphingosine (Sph), the precursor of

Cer, as well as by the levels of their phosphorylated forms, Cer-1-phosphate (C1P) and Sph-1-phosphate (S1P). C24:0- and C24:1-Cer are inducers of chemoresistance by increasing the antiapoptotic protein BCL2L13 (Jensen et al., 2014) and the acidification of lysosomes through the up-regulation of the vacuolar H<sup>+</sup>-ATPase (V-H<sup>+</sup>-ATPase) (Wang et al., 2017). This process favors the sequestration of hydrophobic weak base drugs, followed by the exocytosis of the sequestered drugs (Cui et al., 2018; Stark et al., 2020; Zhitomirsky and Assaraf, 2014; Zhitomirsky and Assaraf 2016; Zhitomirsky et al., 2018). Both C1P and S1P transcriptionally up-regulate ABCB1, ABCC1, and ABCG2 by activating the autocrine production and signaling of prostaglandin E2 (Brachtendorf et al., 2018) or HIF-1 $\alpha$  and HIF-2 transcription factors (Gstalter et al., 2016). Finally, glucosylceramide is also known to mediate chemoresistance: first, it is preferentially incorporated into DRM domains (Wegner et al., 2018), where – together with cholesterol – they contribute to increased membrane rigidity, supporting the activity of the ABC efflux transporters which are integral plasma membrane transporters (Gelsomino et al., 2013). Second, GC activates specific tyrosine kinase receptors (RTKs) abundant in DRM domains, triggering AKT- and ERK1/2-dependent signaling that increases cell survival (Wegner et al., 2018) and transcriptionally induces *ABCB1* (Kopecka et al., 2016).

Several tumors of distinct cancer lineages with a high-mesenchymal cell state have been associated with resistance to multiple treatments. This cell state promotes the biosynthesis of polyunsaturated lipids that creates a lipid metabolism dependency on pathways converging on the GPX4 that prevents the induction of ferroptosis (Viswanathan et al., 2017). In BC cells, tamoxifen resistance can be acquired via inhibition of lysosomal membrane permeabilization. This fact is supported by the increase in neutral lipids into lipid droplets and the accumulation of free cholesterol in the lysosomes (Hultsch et al., 2018). Poor response to gemcitabine and survival in PaC patients as well as disease progression in a spontaneous PaC mouse model were associated with increased fatty acid synthase (*FASN*) expression (Tadros et al., 2017). These authors analyzed, using *in vitro* and *in vivo* models (PaC cells in culture and orthotopic implantation models, respectively), a combination treatment of orlistat with gemcitabine, and observed a synergistic effect in part due to induction of endoplasmic reticulum stress that resulted in apoptosis (Tadros et al., 2017). Similarly, *FASN* inhibition, in castration-resistant prostate cancer, antagonized tumor cell growth, affecting the synthesis and oxidation of FAs and the metabolism of TGs and PLs. These changes in the lipid homeostasis decreased the protein expression of the androgen receptor, as well as the emerging resistance mechanism to the second-generation nonsteroidal anti-androgen drug, enzalutamide, and the androgen synthesis inhibitor, abiraterone (Zadra et al., 2019).

### 2.3. Amino acid metabolism in cancer cells and therapy resistance

Tumor cells undergo profound changes in AA metabolism to meet their increased demand for the cellular macromolecule building blocks (proteins, nucleic acids, and lipids) to obtain energy and reducing agents for biosynthetic pathways. Indeed, besides the utilization of glucose and lipids, tumor cells often depend on AA uptake and/or synthesis to sustain disease progression. Surprisingly, some studies have reported that several nonessential AA limit tumor growth *in vivo* (Loayza-Puch et al., 2016; Sullivan et al., 2018). Targeting AA metabolism has thus emerged as an attractive therapeutic strategy to thwart tumor evolution and enhance response to anticancer treatments in therapy-refractory tumors. Several approaches have been proposed to deregulate AA homeostasis in cancer cells, with either the inhibition of enzymes and transporters regulating the uptake, utilization, or synthesis of AA or the depletion of exogenous pools of AA in order to overcome acquired resistance to conventional anticancer therapies (**Table 2**) (Butler et al., 2021). Recent studies have documented changes in the expression of AA transporters in cancer cells, thereby altering AA homeostasis and supporting resistance to anticancer treatments. Indeed, hypoxia has been shown to trigger upregulation of SNAT2/SLC38A2, an AA transporter, thereby causing endocrine therapy (ET) resistance in ER-positive BC (Morotti et al., 2019). A new variant for the glutamine transporter SLC1A5/ASCT2 has been recently identified to be induced by hypoxia in a HIF2 $\alpha$ -dependent manner (Yoo et al., 2020). Such variant has an N-terminal targeting signal for mitochondrial localization and can support glutamine-induced ATP production and glutathione synthesis to confer resistance to gemcitabine in PaC cells. Another study has reported that ET resistance in BC is associated with a downregulation of the neutral and basic AA transporter SLC6A14, while import of acidic AA (aspartate and glutamate) is enhanced through the SLC1A2 transporter (Bacci et al., 2019). Notably, the authors report that increased aspartate and glutamate levels in PDX correlate with ET resistance and, impairing their transport reduces the metastatic potential of resistant BC cells *in vivo*. Another AA transporter, namely xCT carrier, which transports cystine into the cell while exporting glutamate, has been shown to play a role in therapy resistance in a variety of cancer types, including PaC (Lo et al., 2008), TNBC (Timmerman et al., 2013), head and neck squamous cell carcinoma (Yoshikawa et al., 2013), and GB (Long et al., 2020). Treatment with sulfasalazine, an inhibitor of xCT-dependent cystine transport, actually decreased tumor growth *in vivo*, sensitized TNBC cells to carboplatin (Timmerman et al., 2013), and depleted CD44v-expressing undifferentiated head and neck

squamous cell carcinoma cells improving anti-EGFR therapy response in the remaining differentiating cells (Yoshikawa et al., 2013).

Glutamine is a prototypical AA for which metabolism-interfering therapeutic strategies have been investigated to treat cancer. Allosteric inhibitors of glutaminase (GLS) and glutamine analogues, *e.g.*, bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl)ethyl sulfide (BPTES) and 6-diazo-5-oxo-L-norleucine (DON), respectively, have shown promising (pre)clinical results in a variety of therapy-refractory tumor models. GLS inhibition has been indeed reported to overcome resistance to BRAF inhibitors in melanoma (Baenke et al., 2016; Hernandez-Davies et al., 2015), gemcitabine in *KRAS*-mutant PaC (Mukhopadhyay et al., 2020), and anti-NOTCH1 therapies in T cell acute lymphoblastic leukemia (ALL) (Herranz et al., 2015). More recently, treatment with CB-839 (Telaglenastat), an orally bioavailable GLS1 inhibitor, has been shown to resensitize human esophageal squamous cell carcinoma to anti-CDK4/6 treatment (palbociclib) *in vitro* and in xenograft tumor models (Qie et al., 2019). Combined treatment with CB-839 and everolimus, an mTOR inhibitor, also interrupted the growth of endocrine-resistant BC (Demas DM, 2019). An intimate relationship between glutamine metabolism and mTOR activation has been observed in various tumor types, with a compensatory upregulation of glutamine utilization in GB and lung squamous cell carcinoma resistant to mTOR inhibitors (Momcilovic et al., 2018; Tanaka et al., 2015). Glutamine-dependent metabolic alterations and PPAR $\delta$ -mediated reductive glutamine carboxylation and lipid biosynthesis have also been identified as potential therapeutic targets to overcome sorafenib resistance in HCC (Kim et al., 2017).

A recent study has also reported that mantle cell lymphoma cells, resistant to the Bruton's tyrosine kinase inhibitor (BTKi) ibrutinib, mainly rely on glutamine-fueled OXPHOS that can be therapeutically targeted with IACS-010759, an ETC complex I inhibitor, to overcome the BTKi resistance (Zhang et al., 2019). Besides blockade of glutamine catabolism, genetic abrogation of glutamine synthetase, an enzyme converting glutamate and ammonia into glutamine, has been shown to overcome radiation resistance in nasopharyngeal carcinoma and glioma cell lines via delayed DNA repair, impaired nucleotide metabolism and enhanced radiosensitivity, both *in vitro* and *in vivo* (Fu et al., 2019). Finally, cisplatin-resistant lung cancer and OC cells have been found to rely on glutamine metabolism; glutamine starvation leads to the impairment of nucleotide biosynthesis, which can re-sensitize these cells to cisplatin-induced cell death (Obrist et al., 2018).

Asparagine (Asn) is undoubtedly one of the most successful and documented targets for applying AA depletion therapy in cancer treatment. The Asn-depleting enzyme asparaginase

has become a critical component of the treatment regimen for pediatric ALL. Although under clinical investigation in some solid tumors, albeit its therapeutic efficacy is still very limited. Recent studies have shown upregulation of asparagine synthetase (ASNS) (Williams et al., 2020) or aspartate/glutamate transporter SLC1A3 (Sun et al., 2019b) as resistance mechanisms to asparaginase in several solid tumor types. Another study has reported that Asn metabolism mediates resistance to OXPPOS inhibitors in PaC (Halbrook et al., 2020) and identifies Asn-depleting modalities (genetic silencing of ASNS and depletion of exogenous Asn upon asparaginase treatment) as potential therapeutic strategies to re-sensitize pancreatic tumor cells to phenformin treatment. In addition, it has been shown that Phenformin is a genuine tumor disruptor not only by producing hypoglycemia due to caloric restriction via energy-sensing AMP-activated protein kinase, but also as a blocker of the mTOR regulatory complex (Rubiño et al., 2019).

Arginine metabolism has also been described to contribute to therapy resistance in some tumor types. More specifically, argininosuccinate synthase 1 (ASS1) and spermidine/spermine N<sup>1</sup>-acetyltransferase (SAT1), two central enzymes for arginine metabolism, are downregulated in cisplatin-resistant bladder cancer (BIC) cells, thereby sensitizing them to arginine deprivation upon treatment with PEGylated arginine deiminase (Yeon et al., 2018). Branched-chain AA metabolic reprogramming, in particular the upregulation of branched-chain amino acid transaminase 1 (BCAT1), has also been reported to support resistance to anti-EGFR inhibition in lung cancer (Wang et al., 2019c) as well as to ET in BC (Thewes et al., 2017). Evidence of serine metabolism in therapy resistance has also been documented in several cancer types (Montrose et al., 2021; Ross et al., 2017), with phosphoglycerate dehydrogenase (PHGDH) being a critical driver for resistance to erlotinib in EGFR mutation-positive lung adenocarcinomas (Dong et al., 2018) and sorafenib in HCC (Wei et al., 2019). Histidine catabolism has also been reported to increase the sensitivity of cancer cells to the antifolate methotrexate (Kanarek et al., 2018). Mechanistically, histidine catabolism drains the intracellular pool of tetrahydrofolate, which is particularly harmful to cells treated with methotrexate, suggesting that the effectiveness of methotrexate could be increased through simple dietary intervention (Kanarek et al., 2018).

the histidine degradation pathway markedly influences the sensitivity of cancer cells to methotrexate and may be exploited to improve methotrexate efficacy through a simple dietary intervention.

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In the last years, compelling evidence revealed that tryptophan is a potential modulator of the response to immune checkpoint blockade in cancer patients. Blockade of the immunosuppressive tryptophan catabolism mediated by indoleamine 2,3-dioxygenase (IDO1) and tryptophan 2,3-dioxygenase (TDO) has been shown to reduce the production of the immunosuppressive metabolite kynurenine, to overcome the immunosurveillance escape, and to improve the response to immunotherapy (Bader et al., 2020; Lemos et al., 2019). Finally, although the metabolism of other AA, such as aspartate (Birsoy et al., 2015; Garcia-Bermudez et al., 2018; Sullivan et al., 2018), alanine (Sousa et al., 2016), and methionine (Wang et al., 2019d) has been shown to play pleiotropic roles in tumor cells to support disease progression, the straightforward contribution to therapy resistance is still largely unknown and needs further investigation.

### **3. Microenvironment-mediated intratumoral metabolic heterogeneity and therapy resistance**

Cancer is now undoubtedly viewed as a dynamic ecosystem in which subclonal cancer cell populations behave cooperatively with non-cancer stromal cells to support disease progression (Tabassum and Polyak, 2015). Cancer cells can metabolically cooperate or compete with other cell types, such as cancer-associated fibroblasts (CAFs), cancer-associated adipocytes (CAA), and immune cells to support tumor progression and therapy resistance. Metabolic reprogramming has also been reported to be indispensable for cancer cells to adapt highly selective TME barriers, including hypoxia, acidosis, and oxidative stress, along with tumor progression.

#### **3.1. Tumor metabolic symbiosis and therapy resistance**

Microenvironment-driven metabolic heterogeneity within the tumor bulk is well exemplified by the occurrence of a lactate shuttle between hypoxic (lactate-generating) and oxidative (lactate-consuming) cancer cells in various cancer types (Doherty and Cleveland, 2013; Sonveaux et al., 2008). Such lactate-based metabolic symbiosis has been described to support adaptive resistance to antiangiogenic therapies in pancreatic neuroendocrine tumors (Allen et al., 2016), murine BC models (Pisarsky et al., 2016), PDX models, and human clinical samples of RCC (Jiménez-Valerio et al., 2016). Indeed, upon treatment with antiangiogenic and an initial regression, murine and human tumors resume growth by exhibiting a compartmentalized expression of monocarboxylate transporters (MCT) 4 and MCT1 that support the export of

glycolysis-derived lactate from hypoxic cancer cells and its import (and subsequent metabolic utilization) in normoxic cancer cells, respectively. A similar metabolic symbiosis has been reported in TNBC, with lactate being used as a primary source of energy, in an MCT1-dependent manner, to allow cancer cells to survive under long-term glucose deprivation as well as to resist anti-PI3K/mTOR targeted therapies (Park et al., 2016). Inhibition of glycolysis upon 3-PO treatment or MCT4 genetic knockout (Pisarsky et al., 2016) or blockade of mTOR- and estrogen-related receptor alpha-associated signaling pathways (Allen et al., 2016; Jiménez-Valerio et al., 2016; Park et al., 2016) has been shown to prevent lactate-based metabolic symbiosis and to sensitize cancer cells to therapies both *in vitro* and *in vivo*. More recently, a study has also documented a role for lactate metabolism in the resistance to MET and EGFR TKI (JNJ-605; crizotinib and erlotinib, respectively) (Apicella et al., 2018). The authors have indeed shown that glycolytic metabolism is exacerbated, with enhanced lactate secretion, in patient-derived NSCLC and GC cells upon continuous treatment with anti-MET or-EGFR TKI. Released lactate exhibits paracrine effects by acting as a signaling molecule on CAFs to induce the subsequent overproduction of hepatocyte growth factor, which, in turn, activates MET in cancer cells, thereby overcoming TKI-induced growth inhibitory effects. Genetic or pharmacological interference with enzymes/transporters related to lactate metabolism (*e.g.*, MCT1, MCT4, LDHs) has been reported to overcome resistance. Another recent study has also reported that GC cells, exposed to the multi-target tyrosine kinase inhibitor anlotinib, release lactate that can then instruct CAFs to produce brain-derived neurotrophic factor (BDNF) in a NF- $\kappa$ B-dependent manner (Jin et al., 2021b). CAF-derived BDNF activates TrkB downstream signaling pathways in GC cells, thereby reducing the response to anlotinib. Similarly, CAF-derived lactate has been shown to fuel oxidative metabolism in both ER-positive and -negative BC cells, thereby conferring upon tumor cells a multidrug resistance (MDR) phenotype towards several conventional clinical treatments, including ET (tamoxifen), HER-2-targeted therapy (trastuzumab/Herceptin) and chemotherapy (epirubicin) (Yu et al., 2017). This metabolic interplay is intricately linked to a signaling crosstalk between the two cell types, with the tumor-activated PI3K/AKT signaling pathway that induces the cytoplasmic G-protein-coupled estrogen receptor (GPER) translocation and activation of PKA/CREB downstream signaling pathway in CAFs. Altogether, these studies pinpoint the contribution of such lactate-based metabolic symbiosis in therapy resistance and the potential clinical relevance to use symbiosis-interfering therapeutic avenues (Corbet et al., 2018; Martinez-Outschoorn et al., 2017).

A metabolic crosstalk between CAAs or adipose-derived mesenchymal stem cells (ASCs) and cancer cells has also been reported to alter the response to anticancer treatments. Over the

years, several epidemiological studies have indeed reported worse clinical outcomes in obese cancer patients compared with non-obese patients, although both received the same treatment regimen [see (Cao, 2019) for review]. A study has shown that implantation of CRC, HCC, or pancreatic ductal adenocarcinoma tumors in adipocyte-rich tissue results in intrinsic resistance to antiangiogenic drugs (AAD). In contrast, genetically identical tumors implanted in non-adipose tissue are sensitive to the same AAD treatment (Iwamoto et al., 2018). Another study has identified the gonadal adipose tissue as a niche for a subpopulation of leukemic stem cells to evade chemotherapy (Ye et al., 2016). Similarly, the co-culture of adipocytes with ALL cells has been shown to support chemotherapy resistance and treatment failure (Tucci et al., 2021). In all these studies, adipocytes have been shown to release free FAs (initially stored as TGs in LDs) that can be taken up and used by cancer cells to support metabolic demands and survival under drug-induced stress conditions. Finally, a lipid-based metabolic cooperation has also been observed between macrophages and prostate cancer cells to support therapy resistance (El-Kenawi et al., 2021). The authors have observed that macrophages can transfer cholesterol to tumor cells *in vitro*, supporting a persistent androgen receptor signaling despite androgen deprivation therapy (ADT). Macrophage depletion reduces androgen levels within prostate tumors and overcomes ADT resistance.

The presence of ASCs significantly up-regulates the expression of C-terminal SRC kinase (CSK)-binding protein (CBP)/phosphoprotein associated with glycosphingolipid-enriched microdomains (PAG1) complex, which favors tumor proliferation and resistance to doxorubicin, by activating a downstream cascade that increases the prosurvival AKT/mTOR axis (Lu et al., 2017). Since the ASC conditioned medium produces the same phenotype, it is likely that a secreted metabolite or cytokine/chemokine produces these effects, although a precise analysis of the secretome has not been performed yet. In BC, leptin and insulin-growth factor 1 secreted by adipocytes have been considered as the most likely candidates inducing resistance to anthracyclines because they activate antiapoptotic pathways in BC and alter the recruitment of immune cells within the TME (Mentoor et al., 2018), thus impairing the immunogenic cell death mediated by these chemotherapeutic agents. Similarly, the IL-6 abundantly produced by CAAs has been correlated with chemoresistance because it activates the CAAT Enhancer Binding Protein- $\beta$  (CEBP- $\beta$ ) (Mentoor et al., 2018), a transcription factor that induces *ABCB1* transcription (Riganti et al., 2015). Another interesting mechanism of chemoresistance is the up-regulation of cytosolic vesicles containing the major vault protein in cancer cells cultured with adipocytes: this phenotype increases the sequestration and the subsequent efflux of doxorubicin, paclitaxel, and 5-FU (Lehuédé et al., 2019), thus conferring a

MDR phenotype. Since major vault protein is particularly abundant in the invasion front of BC, in the proximity of breast adipose tissue (Lehuédé et al., 2019), this observation may indicate that in patients, the presence of abundant adipose tissue within the mammary glands can predict a poor response to chemotherapy. The same increased risk is observed in obese patients (Mentoor et al., 2018), indicating that not only paracrinely produced factors but also systemic factors released by adipose tissues may contribute to chemoresistance. Since mammary glands are physiologically rich in adipocytes, it is not surprising that most studies were focused on BC. However, the presence of chemoresistance driven by CAAs is not tissue-specific, as demonstrated by the observation that PaC cells cultured with a CAA-conditioned medium also displayed increased migration and resistance to 5-FU. In this case, the effect was due to the increased serum amyloid A1 protein expression within cancer cells, a well-known marker of clinical aggressiveness and poor outcome (Takehara et al., 2020). The panorama of the circuitries linking adipocytes and chemoresistance largely remains to be elucidated. It is likely that this open field will pave the way to the discovery of new druggable targets in the next future.

Mitochondrial transfer also illustrates how cancer cells and stromal cells can cooperate to support resistance to anticancer treatments. In the last decade, several studies have reported that the acquisition of mitochondria from neighboring stromal cells, via the formation of tunneling nanotubes, increases oxidative metabolism and enhances resistance to chemotherapy in a variety of cancer types, including BC (Pasquier et al., 2013), T-ALL (Burt et al., 2019; Wang et al., 2018a), AML (Marlein et al., 2017; Moschoi et al., 2016), multiple myeloma (MM) (Matula et al., 2021), GB (Salaud et al., 2020), and radioresistance in brain tumors (Osswald et al., 2015). Importantly, another study has shown that horizontal transfer of mtDNA via CAF-derived circulating extracellular vesicles (EVs) may promote ER-independent OXPHOS and an exit from dormancy of therapy-induced cancer stem-like cells, thereby leading to ET resistance in metastatic BC (Sansone et al., 2017). It is noteworthy that the levels of circulating cell-free mtDNA are decreased in the plasma of BC patients (vs. healthy control group) (Kohler et al., 2009). Further investigations are thus needed to understand better the functional role of mtDNA and its potential as a biomarker in the clinical management of (breast) tumor patients.

### **3.2. Hypoxia, acidosis, and oxidative stress: roles of TME selection barriers in therapy resistance**

TME is most often associated with therapy resistance through its physicochemical components. Hypoxia is well known to be associated with multiple pathways accounting for therapy resistance (*e.g.*, oxidative stress, apoptosis inhibition, genomic instability, and cell cycle arrest) (Wilson and Hay, 2011). Acidosis also contributes to therapy resistance by affecting the transport of charged compounds through the cell membrane (the so-called ion trapping phenomenon) (Corbet and Feron, 2017b; Kolosenko et al., 2017). Several studies have recently identified an interplay between TME peculiarities, associated metabolic phenotypes, and resistance to anticancer treatments.

Adaptation to a hypoxic environment is an important characteristic of a tumor. HIF-1 $\alpha$  is a key regulator of response to low oxygen, and when activated by hypoxic stimuli, it promotes tumor growth by inducing the expression of its downstream genes related to angiogenesis, metabolic reprogramming, and invasion (Shirai et al., 2021). This central transcription factor is responsible for the activation of the transcription of several glycolytic genes, including glucose transporter (*GLUT*)1 and *GLUT3*, *HK*, *PFKFB3*, and *PKM2*. The induction of these genes enhances glycolysis and pentose phosphate pathway (PPP) (Ghanbari Movahed et al., 2019). Pyruvate dehydrogenase kinase (PDK) is also transcriptionally activated by HIF-1 $\alpha$  and is responsible for the inhibition of PDH, disconnecting the tricarboxylic acid (TCA) cycle from glycolysis and leading to a decrease in ATP and citrate by the mitochondria (Kim et al., 2006; Lu et al., 2008). A recent study by Xu *et al.* showed a high PPP activity in imatinib-resistant gastrointestinal stromal tumors cell lines through a positive correlation between HIF-1 $\alpha$  and PPP enzyme phosphogluconate dehydrogenase (PGD) (Xu et al., 2020). In this respect, HIF-1 $\alpha$  has been studied in preclinical and clinical models as a therapeutic target in cancer resistance phenotypes once it might redirect aerobic glycolysis toward mitochondrial OXPHOS (Semenza, 2003; Shukla et al., 2017; Wei et al., 2020).

Acidic extracellular pH (pHe) has become an important hallmark of the TME in solid tumors, with mean pH values ranging from 6.2 to 6.8. It is now well accepted that it can act as a highly selective barrier for adaptive cancer cell phenotypes to sustain tumor progression (Corbet and Feron, 2017b; Gatenby and Gillies, 2008; Vander Linden and Corbet, 2019). Tumor acidosis results not only from the exacerbated glycolysis in tumor cells and the disorganized tumor vasculature but also from the mitochondrial respiration-derived CO<sub>2</sub> hydration. Acidic pHe induces pleiotropic effects on tumor cells, including increased migration/invasion capacities *in vitro* and metastatic potential *in vivo* (via the activation of a variety of proteinases and acquisition of an EMT-like phenotype), apoptosis evasion, low proliferation, and epigenetic reprogramming (Pillai et al., 2019). Additionally, tumor acidosis has been reported to induce a

stem-like phenotype in a variety of cancers, including malignant melanoma (Andreucci et al., 2020), glioma (Filatova et al., 2016; Hjelmeland et al., 2011), and BC (Pellegrini et al., 2016), suggesting that acidosis-exposed cancer cells may contribute to the occurrence of drug resistance and metastatic dissemination. Several studies have reported an association between extracellular acidity and increased chemoresistance in various types of tumors. For instance, the unfolded protein response pathway is activated in endothelial cells from oral squamous cell carcinoma in response to an acidic microenvironment, leading to sunitinib resistance (Visioli et al., 2014). A study using rat prostate cancer cells demonstrated that the drug efflux activity of the pump protein P-gp depends on the microenvironmental pH, which seems to be mediated by p38 activation. Thus, an extracellular acidosis in solid tumors might lead to a chemoresistance phenotype due to increased P-gp activity (Sauvant et al., 2008). Moreover, another study demonstrated that a short-term (24-48 hours) acidosis induced resistance to different chemotherapeutic drugs, such as doxorubicin, cisplatin, and methotrexate in osteosarcoma cells (Avnet et al., 2016).

The use of proton pump inhibitors (PPI) has been proposed to increase pH and enhance tumor chemosensitivity by repressing the transport of protons driven by ATP (Corbet and Feron, 2017b; Taylor et al., 2015). For example, LASS2 (a tumor metastasis suppressor gene that interacts with a subunit of V-H<sup>+</sup>-ATPase) enhanced the chemosensitivity of BC cells to doxorubicin by counteracting the acidic TME through inhibition of the V-ATPase proton pump activity (Fan et al., 2013). Similarly, TM9SF4, a V-ATPase-interacting protein, modulated tumor pH and its suppression decreased cytosolic pH, thus reducing the extracellular acidity, and consequently increasing sensitivity to 5-FU in colon cancer cells (Lozupone et al., 2015). Also, the exposure of osteosarcoma cells to low pH combined with omeprazole, a PPI targeting lysosomal acidity, enhanced doxorubicin cytotoxicity (Avnet et al., 2016).

Importantly, extracellular acidification increased the release of EVs by different types of malignant cells, which was associated with tumor malignancy (Logozzi et al., 2018). For instance, an enhancement in EVs secretion under acidic stress was associated with the elimination of toxic substances, which otherwise would accumulate in stressed cells (Bång-Rudenstam et al., 2019). Furthermore, some studies link the release of EVs to a reduction in the effectiveness of anticancer drugs. For example, an increase in the number of EVs released by human melanoma cells and low pH was associated with the reduced effectiveness of cisplatin (Federici et al., 2014). Moreover, microenvironment acidification obtained by lowering the pH in 2D cultures and 3D spheroids caused an increase in the production of EVs

by mammary carcinoma cells, leading to doxorubicin resistance (Ralph et al., 2020). Nevertheless, the exact mechanism linking low pH and EVs release is still under investigation.

Acidic pH conditions have also been linked to drug resistance and long-term clinical relapse via their effects on immune function. Acidosis has been reported to decrease T cell proliferation and produce several cytokines, including interleukin-2, interferon- $\gamma$ , granzyme B, and perforin (Fischer et al., 2007). Tumor acidosis also hampers immune response by reducing dendritic cell maturation (Gottfried et al., 2006; Trempolec et al., 2020), natural killer cell activity (Liao et al., 2007), and monocyte-derived tumor necrosis factor secretion (Dietl et al., 2010). When chronically established in the TME, acidosis has been found to induce profound metabolic reprogramming. Indeed, acidosis-exposed cancer cells shift their metabolic preferences from glucose utilization towards enhanced glutamine and FA metabolism (Corbet et al., 2014; Corbet et al., 2016; LaMonte et al., 2013). Acidosis also triggers changes in mitochondrial morphology to sustain efficient ATP production regardless of  $O_2$  levels (Khacho et al., 2014). It has been reported to induce a strong reliance on an OXPHOS-related metabolic phenotype that can support cancer cell aggressiveness (Corbet et al., 2020). Importantly, reliance on oxidative metabolism, particularly FA oxidation, in cancer cells exposed to acidic pH conditions offers new therapeutic opportunities. A study in melanoma has demonstrated that the acidic TME, besides promoting tumor progression and resistance to therapy, also renders cancer cells susceptible to mitochondrial inhibitors, such as oligomycin or phenformin (Noguchi et al., 2017). Similarly, prostate cancer cells are more prone to the effect of niclosamide, a mitochondrial inhibitor, in the presence of an acidic pH (Ippolito et al., 2016). A recent study has also shown that FA addiction in acidosis-exposed cancer cells can be therapeutically exploited by adding exogenous cytotoxic polyunsaturated FA that triggers ferroptosis cell death in these cells (Dierge et al., 2021). All these studies revealed that in addition to pH modulation to counteract drug resistance, it is also possible to directly target the associated (metabolic) phenotype to hamper tumor progression.

Redox homeostasis – a balance between cellular oxidants and antioxidants with reductive potential – is essential for the maintenance of normal physiological functions but also plays an important role in growth, survival, and therapy resistance of cancer cells (Chun et al., 2021). Oxidative stress, defined as an altered redox balance towards the oxidative reactions, implicates high levels of ROS brought about by an increase in ROS production or a decrease in antioxidant activities (Hayes et al., 2020). Tumor cells contain higher levels of ROS than normal cells, promoting cancer progression and development (Cui et al., 2018). On the other hand, when ROS concentrations become extremely high, they cause tumor cell death. A mild and

persistent oxidative stress induced by chemotherapy induces adaptive stress responses with consequently excessive accumulation/production of reductive molecules, which may stimulate survival, resistance to chemotherapy, and stemness of tumor cells (Chun et al., 2021). This fact suggests that tumors shift their TME to more reductive conditions by adapting to the ROS threshold in response to chemotherapy. For these reasons, various drugs with direct or indirect effects on ROS levels have been employed as cancer therapies (Cui et al., 2018).

Mitochondria are the primary producers of ROS and are the main site of metabolic reprogramming in response to oxidative stress (Faubert et al., 2020). As anticipated, several tumors rely on mitochondrial respiration rather than glycolysis (Olivier et al., 2021). During OXPHOS, oxygen molecules are partially reduced, leading to the formation of ROS, first with the formation of superoxide ( $O_2^{\cdot-}$ ), which can be then converted into other reactive species such as hydrogen peroxide ( $H_2O_2$ ), hydroxyl radical ( $\cdot OH$ ) (Kausar et al., 2018). The main mitochondria antioxidant systems include superoxide dismutase (SOD2), the thioredoxin system – thioredoxin 1 and 2, thioredoxin reductase-2, and peroxidase 3. The upregulation of the thioredoxin system is considered a negative prognostic factor in several types of cancers and is observed in drug-resistant tumors favoring cell proliferation, invasion, and migration and preventing apoptosis (Scalcon et al., 2018). As a result of accelerated metabolism, tumors produce more ROS and upregulate antioxidant pathways in response to OS. For example, oncogenic KRAS, BRAF, and MYC inhibit ROS generation by regulating the NRF2 transcription factor, which is considered one of the key actors of the cellular antioxidant response. Indeed, NRF2 controls the expression of several genes that contain antioxidant response elements (ARE) important to proliferation, apoptosis, angiogenesis, immunity and inflammation, genome instability, and metabolic reprogramming (Rojo de la Vega et al., 2018).

A soluble endogenous antioxidant metabolite present in all tissues is glutathione (GSH). In physiological conditions, the levels of the reduced form of GSH prevail over oxidized glutathione (GSSG), whereas, in the presence of a high level of  $H_2O_2$  and lipid peroxide, GSH is oxidized to GSSG by the GSH peroxidase. GSSG can be reduced back to GSH in the presence of NADPH, another important reductive molecule. The ratios between GSH/GSSG and NADPH/NADP<sup>+</sup> are important to determine the cellular redox state (Kennedy et al., 2020). PPP and glutamine metabolism are essential for the production of GSH and are controlled by NRF2 (Rojo de la Vega et al., 2018). In particular, the first reaction of the oxidative branch of PPP, catalyzed by the glucose-6-phosphate dehydrogenase (G6PD), produces NADPH molecules necessary for the regeneration of GSH (Kennedy et al., 2020). Tumors with high GSH levels display worse prognoses because GSH confers resistance to several drugs (Emmings et al.,

2019). In relapsed ALL patients, an increase of GSH was observed, contributing to drug resistance and therapeutic failure (Sarmiento-Ribeiro et al., 2012). On the contrary, GSH depletion increases the tumor sensitivity to chemotherapies (Emmings et al., 2019). Cisplatin, a compound commonly used in cancer treatment, causes DNA damage-induced cell apoptosis and increases ROS. Cisplatin-resistant ovarian cancer and lung cancer cells have a high ROS production and have an active glutathione GSH synthesis pathway to cope with cisplatin-induced oxidative stress (Cruz-Bermúdez et al., 2019). Other chemotherapeutic agents, as paclitaxel or doxorubicin, also induce changes in cellular GSH level (Barrera et al., 2021; Kim et al., 2019) or in PPP flux (Polimeni et al., 2011) as protective mechanisms.

Another frequent metabolic alteration relevant for antioxidant response in cancer is the high demand for glutamine that can be converted by glutaminase and further incorporated into glutathione by glutathione cysteine ligase (Shah and Chen, 2020). The upregulation of glutaminolysis also leads to an increase of GSH and NADPH, whereas inhibition of glutamine metabolism results in increased ROS. This provides the rationale for using glutaminase inhibitors as a potential anticancer agent (Matés et al., 2020). They could be proposed as indirect agents decreasing GSH in order to sensitize tumors to chemotherapy.

Beyond NRF2, the other players that increase the antioxidant potential in chemoresistant cancer cells are NF- $\kappa$ B, FOXO family, and AP-1 transcription factors, directly regulating the classic antioxidant genes *SOD1* or *SOD2* (Barrera et al., 2021). MYC also plays a role in inducing mitochondrial biogenesis and function, increasing OXPHOS. Genomic events occurring in tumors also affect the redox balance and chemoresistance. MYC, one of the oncogenes most frequently amplified or hyper-activated in cancer, stimulates peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 $\alpha$ ), which regulates mitochondrial biogenesis and activates antioxidant enzymes, sustaining a drug-resistant phenotype. Since MYC can cooperate with HIF-1 in increasing glycolysis under hypoxic conditions, this could be important for cell adaptation to different TMEs and different responses to chemotherapeutic agents (Kopecka et al., 2020a; Marengo et al., 2019). Mitochondrial chaperone tumor necrosis factor-associated protein 1 is another important player in the metabolic and oxidative reprogramming of cancer cells: indeed, it shifts the metabolism towards OXPHOS, promotes a stress-adaptive response in cancer cells, and triggers resistance to chemotherapeutic treatments (Avolio et al., 2020). Moreover, alterations in tumor-suppressor genes (TSG) contribute to resistance to oxidative stress and chemotherapy. Missense mutant TP53 interacts with NRF2 and controls specific transcriptional programs that promote pro-survival

toward oxidative stress (Cordani et al., 2020), activating a coordinated response that also mediates chemoresistance.

#### **4. Intricate interplay between tumor signaling and metabolic pathways in therapy resistance**

Cell signaling pathways are critical in metabolic regulation for the maintenance of homeostasis. The aberrant dysregulation of one or more signaling pathways is strongly associated with cancer progression and plays a crucial role in therapy resistance (**Figure 3**). One of the most commonly dysregulated pathways in human cancer is the PI3K/AKT/mTOR network, contributing to cancer cell growth and survival. The activation of the PI3K/AKT/mTOR pathway in cancer can occur through different processes, from mutations in TSG like *PTEN* to abnormal signaling of RTKs, leading to PI3K/AKT-mediated activation of mTOR (Zhang et al., 2017b). This axis is also a key regulator of aerobic glycolysis and glucose metabolism and is an important signaling network for MDR in multiple cancers. Its activation alone is not responsible for MDR; however, PI3K/AKT/mTOR provides an important link between different cellular processes, such as apoptosis, cell growth, and cellular metabolism, that are strongly associated with the MDR phenotype (Liu et al., 2020). AKT plays a key role in this pathway, regulating the transcription and translation of glycolytic effectors, such as GLUTs, HKs, and phosphofructokinase (PFKs), directly or through mTOR and its downstream transcription factors, including HIF and MYC (Lee et al., 2018). Activation of the AKT axis is sufficient to prompt the switch to aerobic glycolysis characteristic of cancer cells (Elstrom et al., 2004). Inhibiting this pathway alone or combined with chemotherapy enhances drug sensitivity, suggesting a correlation of chemoresistance with the aberrant activation of AKT in different cancer types (Gong et al., 2018; Gremke et al., 2020). Resistance to Sorafenib, a multi-kinase inhibitor, indicated for the treatment of HCC, RCC, and thyroid carcinoma, was associated with enhanced glycolysis in HCC cells by activation of PI3K/AKT pathway via the upregulation of cardiotrophin-like cytokine factor 1 (CLCF1) and activation of *GLUT3*, *HKII*, and *PDK1* genes (Zhang et al., 2020c). Another study conducted by Zhang *et al.* demonstrated an upregulation of the PI3K/AKT pathway in a doxorubicin-resistant leukemia cell line related to glucose metabolism reprogramming, favoring the adaptation of tumor cells to stressful conditions as chemotherapy (Zhang et al., 2017a). In this context, inhibiting aerobic glycolysis has been an effective therapeutic strategy for overcoming MDR in different cancer types (Cui et al., 2021; Zhang et al., 2018). Moreover, this inhibition seems more efficient when combining glycolysis inhibitors with PI3K/AKT axis inhibitors (Liu et al., 2016).

Another pathway is RAS/RAF/ERK/MEK signaling, which affects metabolism via MYC. This oncogene regulates glucose uptake, glycolysis, and the PPP and upregulates the expression of glutamine transporters and GLS, which converts glutamine into glutamate that can be metabolized in mitochondria. It also regulates the expression of nucleotide and AA biosynthesis enzymes and, in turn, an alternative splice form of PKM2 found in most cancer cells. Furthermore, the loss of the tumor suppressor liver kinase B1 (*LKB1*) can lead to metabolic alterations, inducing inactivation of AMPK, a cellular energy regulator, and activation of mTORC1, which promote protein synthesis and lipogenesis (Sever and Brugge, 2015).

AMPK is an evolutionarily conserved cellular energy and nutrient sensor that also controls cellular energy homeostasis. It is a negative regulator of aerobic glycolysis and cellular biosynthesis in tumor cells. Cells lacking the catalytic alpha subunit(s) of AMPK present a higher aerobic glycolysis rate through the increase in lactate production from glucose, and downregulation of AMPK activity is sufficient to induce the Warburg effect in cancer cells (Faubert et al., 2013). AMPK is activated in response to insufficient energy supply and acts by allocating nutrients towards the catabolic/energy-producing (generating ATP) or the anabolic/growth-promoting (consuming ATP) metabolic pathways (Carling, 2017; Hardie, 2011). Due to its role as a stress-responder, AMPK, a tumor suppressor gene, is a canonical downstream effector of *LKB1*, a previously known TSG. After tumor development, AMPK becomes a tumor promoter once it protects from several cellular stresses and is involved in drug resistance (Vara-Ciruelos et al., 2019). AMPK also regulates CSC self-renewal and induces autophagy, two important contributors to chemotherapy resistance (Tan et al., 2019; Wang et al., 2016b).

Besides the dysregulated signaling within cancer cells, cancer progression (at least in solid tumors) and drug resistance also depends on the TME (Roma-Rodrigues et al., 2019), which consists of extracellular matrix (ECM) and a variety of normal resident cells and recruited cells, as already mentioned. All these cells are involved in complex and dynamic interactions with cancer cells that alter cell signaling mechanisms, representing new targets for therapeutic strategies (**Figure 3**) (Lasfar et al., 2019) to circumvent drug resistance.

Components of the ECM as fibronectin, laminin, and collagen, serve as ligands that activate integrin signaling mediated by RAS/ERK/MEK and PI3K/AKT/mTOR pathways. ECM with a different composition has been associated with CAFs in advanced carcinomas, affecting cell signaling within the tumor (Liu et al., 2019). Further, endothelial cells are essential to form new blood vessels (angiogenesis) through several factors, such as vascular endothelial growth

factor (VEGF), platelet-derived growth factor, and angiopoietin, which also activates the PI3K-AKT pathway. In turn, this pathway activates HIF-1 $\alpha$ , stimulating cancer cells to synthesize and secrete VEGF, and plays an important role in angiogenesis (Sever and Brugge, 2015). Immune cells also produce VEGF and matrix metalloproteinases, which promote angiogenesis, ECM remodeling, and the release of other bioactive molecules (Sever and Brugge, 2015). In addition, inflammatory cells secrete other growth factors, including epidermal growth factor (EGF) and fibroblast growth factor (FGF), all important regulators of RAS/ERK and PI3K/AKT pathways, contributing to abnormal cell proliferation, cell death, metabolism, and migration. Another signaling pathway important in cancer and tumor-associated inflammatory cells is mediated by the transcription factor NF- $\kappa$ B, which is mutated in some lymphoid malignancies, promotes cell survival and proliferation, and stimulates cytokine production (Grondona et al., 2018; Sever and Brugge, 2015).

The complex interplay of cell signaling between cancer cells and TME and the fact that several components of RAS/ERK and AKT/PI3K pathways are commonly mutated or present abnormal expression in several cancers justified the development of targeted therapeutic approaches directed to these pathways. However, despite the inhibition of these pathways, the TME secretes factors that stimulate alternative pathways maintaining cell viability or can select cells containing drug-resistant variants of the targeted protein in other pathways (Sever and Brugge, 2015), contributing to drug resistance and clinical relapse. In a recent study, Zervantonakis and collaborators showed, by using a panel of HER2<sup>+</sup> BC cell lines co-cultured with diverse fibroblast populations, that these fibroblasts protect cancer cells from lapatinib cytotoxic effects. This reduction in drug sensitivity involves an increased expression of antiapoptotic proteins and activation of the PI3K/AKT/mTOR pathway. However, when they used a combined therapeutic regimen with mTOR inhibitors or the antiapoptotic proteins BCL-XL and MCL-1, the sensitivity to lapatinib was re-established. These results suggest that, besides the activation of the constitutive PI3K/AKT/mTOR pathway in tumor cells, factors secreted by fibroblasts may maintain this pathway in the context of HER2 inhibition, indicating the relevance of combined therapies to circumvent drug resistance and/or to restore drug sensitivity (Zervantonakis et al., 2020).

## **5. Enhancing cancer therapy by targeting cancer metabolism**

### **5.1. Tumor metabolism: more than a clinical illusion?**

Since the development and clinical introduction, more than 70 years ago, of the antimetabolite drugs to impair the activity of key enzymes in the nucleotide biosynthetic pathways (*e.g.*, dihydrofolate reductase and thymidylate synthase), tumor metabolism has become a significant source of inspiration to develop new anticancer drugs (Fendt et al., 2020; Luengo et al., 2017). The antimetabolites represent a relatively large group of anticancer agents that include folic acid antagonists (*e.g.*, methotrexate, pemetrexed, and pralatrexed), purine antimetabolites (*e.g.*, 6-mercaptopurine, fludarabine phosphate, pentostatin, and cladribine), and the pyrimidine antimetabolites (*e.g.*, 5-FU, cytarabine, and gemcitabine). These compounds disrupt nucleic acid biosynthesis, interfering with major nucleotide metabolites production or replacing the natural metabolite (Avendaño and Menéndez, 2008). 5-FU and methotrexate were the first chemotherapeutic drugs used to treat cancer, which remain the standard first-line treatment for several solid tumors and some solid and hematological pediatric cancers, respectively (Issaq and Heske, 2020; Ngoi et al., 2019; Rahman and Hasan, 2015). However, usual pharmacokinetics and pharmacodynamics issues and the toxicity to healthy cells/tissues limit the number of breakthrough discoveries of new metabolic drugs under clinical evaluation. Additionally, the development of drug resistance limits the therapeutic effectiveness of antimetabolites.

Several metabolic specificities or vulnerabilities were identified and allowed the development of drugs currently approved or enrolled in preclinical programs or clinical trials (**Table 3**). These drugs mainly target enzymes involved in the glucose uptake and glycolytic pathways, signaling pathways that modulate cancer metabolism, nucleotides, AA, and FAs biosynthesis pathways, and immunometabolism. Among the handful of metabolism-interfering drugs that have reached late clinical phases, two oral small-molecule inhibitors, ivosidenib (Tibsovo) and enasidenib (Idhifa), were approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to treat patients with relapsed/refractory AML with a mutation in isocitrate dehydrogenases 1 (*IDH1*) and 2 (*IDH2*) genes, respectively (DiNardo et al., 2018b). Although both of these IDH inhibitors induce an overall response rate of about 40% in relapsed or refractory AML (DiNardo et al., 2018b; Stein et al., 2017), some primary and acquired resistance to IDH inhibitors were already detected (Intlekofer et al., 2018; Sarmiento-Ribeiro et al., 2019). A recent analysis revealed that leukemia stemness is a major driver of intrinsic (primary) resistance to IDH inhibitors. In contrast, selection of mutations in *RUNX1/CEBPA* or *RAS-RTK* pathway genes is the main driver of acquired (secondary) resistance to IDH inhibitors, along with *BCOR*, homologous *IDH* gene, and *TET2* (Wang et al., 2021).

As emphasized above, metabolic plasticity and flexibility are thought to enable tumor cells to adapt TME modifications and evade therapy-induced stress (McGuirk et al., 2020). Targeting tumor metabolism, particularly inhibiting a single metabolic pathway, may be more complex than anticipated due to the fast selection of drug-resistant cancer subclones. After treatment, limiting the options for metabolic adaptations has been increasingly considered a modality to identify the most efficient metabolism-based anticancer modalities (Ngoi et al., 2019). Several treatment combinations targeting tumor metabolism such as the association of an LDH inhibitor with the IACS-010759, an inhibitor of the complex I of the mitochondrial ETC (Oshima et al., 2020), metformin with the MCT1 inhibitor AZD3965 (Beloueche-Babari et al., 2017) or, more recently, the glycolysis inhibitor 3-bromopyruvate with the anti-inflammatory drug diclofenac, repurposed as an MCT4 inhibitor (Vander Linden et al., 2021), has been reported as efficient therapeutic strategies to overcome metabolic plasticity and to enhance overall antitumor effects in *in vitro* and *in vivo* cancer models. Similarly, Méndez-Lucas *et al.* demonstrated that the synergistic inhibition of glutaminases and amidotransferases or glycolysis-related HKII significantly affected the growth of MYC-induced liver tumors *in vivo* (Méndez-Lucas et al., 2020).

The concept of metabolic synthetic lethality also illustrates how some mutations in oncogenes may reprogram tumor cell metabolism and therefore offer opportunities for developing selective therapies that would target cancer cells while sparing healthy tissues (Zecchini and Frezza, 2017). For instance, a recent study reported that IDH1-mutant glioma cells rely on NRF2-driven glutathione metabolism to survive under elevated ROS levels (Yu et al., 2020). Pharmacological inhibition of the transcriptional activity of NRF2 induced apoptosis in *IDH1*-mutated glioma cells through oxidative damage, establishing a synthetic lethality interaction with the neomorphic *IDH1* mutation.

Another therapeutic approach is applying evolutionary (Darwinian) principles to cancer therapy to overcome acquired resistance in cancer patients (Gatenby and Brown, 2020). The general aim of such strategies, called “double-bind” or “sucker’s gambit”, is to apply sequential treatments during which phenotypic adaptation of tumor cells to a first-line treatment renders them more vulnerable (than the initial population) to a second-line therapy (Antonia et al., 2006; Ramakrishnan et al., 2010). Interestingly, a similar approach has been recently applied to metabolism-targeting drugs, with the use of diclofenac and koningic acid to inhibit MCT and GAPDH activity, respectively (Ordway et al., 2021). In this study, the authors have shown that the application of both antimetabolic drugs can control the growth of BC cells *in vitro* and *in vivo* more efficiently than when applied in monotherapy. Several recent studies have also

identified metabolic bottlenecks upon drug-induced stress and have reported the successful use of metabolic inhibitors to target drug-tolerant cancer cells. For instance, Goldman *et al.* have shown that taxane-treated BC cells become resistant to doxorubicin and rely more on glucose metabolism (Goldman et al., 2019). They have further observed that co-administration of lonidamine, a glycolysis inhibitor, with doxorubicin is effective to target BC cells, pre-challenged with a taxane, and delay tumor growth in cultured cell lines and PDX models of BC. Similarly, Van Gastel *et al.* have shown that AML cells, persisting upon chemotherapy application, have a strong reliance on glutamine and pyrimidine biosynthesis pathways (van Gastel et al., 2020). Notably, sequential treatment, but not combinatorial treatment, with chemotherapy as a first-line treatment and inhibitors of glutamine metabolism or pyrimidine synthesis as second-line therapy, has been reported to reduce the number of residual leukemia-initiating cells and improve survival in leukemia mouse models and PDX. Consistently, Levin et al. recently showed that cytarabine resistance in AML cell lines and patient specimens could be overcome with a highly synergistic combination of hydroxyurea and azidothymidine (Pérez-Ruiz et al., 2020). Collectively, these studies have thus highlighted not only the potential of metabolism-interfering compounds in cancer therapy but also the importance of therapy dynamics/sequence in order to achieve successful clinical outcomes.

The notion of collateral vulnerability in the field of tumor metabolism has led to the identification of mutations in specific metabolic enzymes giving rise to druggable cancer cell vulnerabilities (Dey et al., 2017; Mavrakis et al., 2016; Muller et al., 2012). Indeed, this concept refers to the co-deletion of TSG with neighbor passenger genes playing diverse roles in cell homeostasis (Muller et al., 2015). ENO1/2 encoding for enolase 1 and 2 as well as malic enzyme (ME) 2/3 are examples of metabolic genes involved in collateral lethality in GB and PaC cells, respectively (Dey et al., 2017; Muller et al., 2012). The ENO1 gene is deleted in approximately 1-5% of GB patients (Muller, 2012). However, this deletion is compensated for by the expression of the ENO2 gene. Therefore, ENO2 inhibition selectively suppresses the growth, survival, and tumorigenic potential of ENO1-deleted GB cells but does not affect ENO1-expressing cells (Muller et al., 2012). The ablation of a redundant metabolic enzyme rendered cells dependent on the other metabolic enzyme that compensates for that pathway, creating a druggable therapeutic target.

Altogether, these studies highlight the complexity of targeting tumor metabolism and make it evident that metabolism-interfering drugs may have a very limited clinical applicability as monotherapy in cancer patients. However, many recent studies described above have provided a better understanding of how genetic background, microenvironmental cues, and

therapy-induced stress drive tumor cell metabolic phenotypes and thus enable novel strategies interfering with metabolic vulnerabilities to overcome therapy resistance in a variety of tumor types.

## **5.2. The crosstalk between metabolism and therapy resistance**

The advances in cancer treatment substantially improved the survival and quality of life of cancer patients. However, most patients relapse or are refractory to treatment due to primary, secondary, and adaptive resistance. Increasing evidence reveals that changes in metabolism modulate therapy response and contribute to resistance to most types of anticancer therapies (Zaal and Berkers, 2018). In general, anticancer drugs target uncontrolled proliferation of cancer cells, while the metabolic rewiring required to overcome anticancer drug effects is to restore growth and survival (Fendt et al., 2020). Additionally, tumor cells exhibit high heterogeneity and plasticity that render cells more prone to resist therapy or develop resistance, contributing to poorer clinical outcomes (Dagogo-Jack and Shaw, 2018; McGuirk et al., 2020).

Cisplatin is a chemotherapeutic drug that can alkylate purine bases and decrease GSH, causing DNA damage and inducing apoptosis in cancer cells (Dasari and Bernard Tchounwou, 2014). Ovarian and cervical cancer cells resistant to cisplatin show higher glycolysis rates and reduced mitochondrial activity than sensitive cells (Catanzaro et al., 2015; Rashmi et al., 2018). On the other hand, lung cancer resistant cells display lower glucose uptake, glycolysis rate, and lactate production accompanied by increased OXPHOS (Sullivan et al., 2014; Wangpaichitr et al., 2017). The metabolic modulation with a glutaminase inhibitor and a FASN sensitizes cisplatin-resistant OC cells to chemotherapy (Masamha and LaFontaine, 2018; Papaevangelou et al., 2018). Cisplatin-resistant cells highlight the heterogeneity of metabolic rewiring in therapy response and resistance and the importance of intrinsically resistant populations with distinctive metabolic and structural profiles, highlighting the relevance of combination therapies. On the other hand, tamoxifen-resistant MCF-7 cells have increased antioxidant defenses due to the upregulation of NAD(P)H quinone oxidoreductase (NQO1) and glutamate-cysteine ligase catalytic subunit (GCLC). The tamoxifen-resistant metabolic phenotype was characterized by increased mitochondrial biogenesis, increased ATP production, and reduced glutathione levels. The use of dicoumarol, a NQO1 inhibitor, restored tamoxifen sensitivity in resistant BC cells (Fiorillo et al., 2017). Furthermore, in ER-positive BC patients that received

endocrine therapy, the expression of the *NQO1* gene strongly predicts high-risk patient relapse (Fiorillo et al., 2017).

The resistance to targeted therapy is also mediated by metabolic reprogramming. For example, lung cancer cells resistant to erlotinib, an ERK inhibitor, depend on mitochondrial respiration for proliferation and survival (De Rosa et al., 2015). Multiple myeloma cell lines and patients resistant to bortezomib, a proteasome inhibitor, exhibit higher mitochondrial function, expression of mitochondrial genes, and OXPHOS activity, demonstrating that bortezomib-resistant cells are more dependent on OXPHOS (Song et al., 2013; Thompson et al., 2017). Other studies show that bortezomib resistance is associated with higher glucose uptake and glycolytic activity (Soriano et al., 2016; Zaal et al., 2017). However, the combination of targeted therapy with metabolic drugs can potentiate and overcome resistance to treatment. For example, the combination of lapatinib, an EGFR and HER2 tyrosine kinase inhibitor to treat HER2<sup>+</sup> BC patients, with phenformin, a mitochondrial complex I inhibitor that induces bioenergetic stress, elicits cell death through the modulation of AA metabolism in several cancer cell lines (Hulea et al., 2018). Furthermore, in MM cells and myeloma bearing mice, dichloroacetate, a PDK1 inhibitor, increases the sensitivity to bortezomib (Fujiwara et al., 2013; Sanchez et al., 2013).

Immune checkpoint inhibitors (ICIs) revolutionized cancer treatment in several tumors, including solid (cervical cancer, CRC, GC, liver cancer, and NSCLC) and hematological malignancies (diffuse large B cell lymphoma and Hodgkin's lymphoma) (Twomey and Zhang, 2021). However, patients who received ICIs treatment can develop primary, adaptive, and acquired resistance (Pérez-Ruiz et al., 2020), limiting the efficacy of these treatments (Chiappa et al., 2021; Dal Bo et al., 2020; Kon and Benhar, 2019; Leonetti et al., 2019; Pérez-Ruiz et al., 2020; Sarmiento-Ribeiro et al., 2019; Schoenfeld and Hellmann, 2020). Cancer cells have great biosynthetic demands depleting glucose, AA, and FAs from the TME and inducing immune cells to undergo metabolic reprogramming and affecting their fate and functions (Weng et al., 2021). Cancer cells with high aerobic glycolysis induce a hypoxic and acidic TME, inhibiting the normal metabolism of immune cells, which leads to inhibition of mTOR activity, intracellular interferon-gamma (IFN- $\gamma$ ) production, glycolytic capacity in T cells, and diminished T-cell function (Fumarola et al., 2018). However, the mitigation of TME hypoxia in combination with ICIs can improve the infiltration level of T cells and circumvent the therapy resistance of "cold tumors" (Jayaprakash et al., 2018). Amino acid depletion is also a mechanism of resistance to ICIs. Tryptophan is fundamental for T cell activation, and its depletion leads to intracellular accumulation of uncharged tryptophan transfer ribonucleic acid and activation of general

control non-depressible 2 (GCN2), which can inhibit T cells clonal proliferation and induce their apoptosis (Bai et al., 2020). *In vivo* experiments using indoximod, a tryptophan mimetic, reversed the tumor-associated immunosuppression by reducing the tumor-infiltrating myeloid-derived suppressor cells and regulatory T cells and eliminating the suppressive function of these cells (Fumarola et al., 2018; Holmgaard et al., 2015). Emerging evidence suggests that cancer metabolic rewiring and adaptability markedly impact resistance development to immunotherapy by altering the TME. Therefore, the study of therapeutic strategies using immunotherapy and metabolic targeted drugs is needed to promote successful and viable antitumor responses.

The pleiotropic effects of altered cellular cancer metabolism contribute to chemotherapy and TKI resistance and highlight the need to understand the complex metabolic phenotypes of therapy resistance. Understanding cancer metabolism can improve cancer therapy response, identify new and valuable prognostic biomarkers for therapy response, and provide insights into the molecular mechanisms of resistance. Several clinical trials are currently testing new therapeutic combination treatments with metabolic drugs to improve patient management.

### **5.3. Impact of the targeting of cancer metabolism on circumvention of therapy resistance**

Considering the peculiarities in the metabolism of chemoresistant tumors, targeting cancer metabolism is considered a powerful approach to chemosensitize refractory tumors. Several preclinical studies have demonstrated the utility of inhibiting glycolysis, for instance, by using 2-deoxy-D-glucose (2-DG), which blocks glycolytic flux and increases the efficacy of doxorubicin (Wang et al., 2015), 5-FU (Pepe et al., 2017) and etoposide (Hagenbuchner et al., 2013), simply causing a metabolic collapse in highly glycolytic tumors. Other metabolic inhibitors have a dual action that synergizes with chemotherapeutic agents: 3-bromopyruvate inhibits HKII, reducing the glucose-dependent ATP production, but it is also an alkylating agent of HKII and antioxidant enzymes. Based on this property, it synergized with DNA alkylating agents such as carmustine (Sun et al., 2020). In other cases, metabolic inhibitors target moonlight enzymes, thereby altering different metabolic or physiological functions. PFK158, an inhibitor of PFKFB3, reduces glycolytic flux by reducing PFK2 activity and, at the same time, induces lipophagy by reducing LD accumulation. The inhibition of PFKFB3 double-action results in the sensitization of OC cells to carboplatin and docetaxel (Mondal et al., 2019).

Overcoming intratumor acidosis could be useful to restore the efficacy of chemotherapeutic drugs that are weak bases, such as anthracyclines. In this perspective, the recent development

of MCT1 inhibitors such as  $\alpha$ -cyano-4-hydroxycinnamate, AR-C155858, and AZD3965 have raised interest (Marchiq and Pouysségur, 2016), although they suffered some limitations. First, both MCT1 and MCT4 are present, and the blockage of one isoform is often associated with the increase of the other one (Marchiq and Pouysségur, 2016), leading to the persistence of lactate and  $H^+$  within the TME. Second, MCT1 is also expressed on non-tumor cells, particularly on infiltrating  $CD8^+$ T-lymphocytes that decrease their metabolic efficacy and become anergic in the case of MCT1 blockade (Fischer et al., 2007). The use of  $Na^+/H^+$  exchanger (NHE) inhibitor ethyl-isopropyl amiloride (Miraglia et al., 2005) or synthetic carbonic inhibitors (Kopecka et al., 2015; Mujumdar et al., 2019; Salaroglio et al., 2018) and antibodies (von Neubeck et al., 2018) targeting carbonic anhydrase XII (CAXII), as acidosis correctors and chemosensitizer agents, have been more encouraging. Indeed, NHE1 and CAXII are specifically overexpressed in tumors, limiting the toxicity on healthy tissues or immune-infiltrating cells. CAXII inhibitors look particularly promising because they indirectly inhibit ABCB1 activity, altering the optimal pH at which the pump works. This inhibition results in increased accumulation of chemotherapeutic drugs within the tumor cells (Kopecka et al., 2015; Mujumdar et al., 2019; Salaroglio et al., 2018), coupled with their lower pH-dependent inactivation.

Lipogenesis is another pathway that offers a new possibility of chemosensitization. As previously demonstrated, the abundance of LD (Shen et al., 2019) and CAAs (Mentoor et al., 2018) is a cause of chemoresistance. The FA synthase inhibitor orlistat reduces lipid storage and chemosensitized T-cell lymphoma to cisplatin (Kant et al., 2014). The mechanism has not been reported in detail, but it is likely that the decrease in FAO triggers a mitochondrial derangement, reducing the ATP fueling of ABC transporters and increasing the mitochondrial ROS at dangerous levels. In this perspective, agents impairing the mitochondrial metabolism termed “mitocans” and inducing OXPHOS uncoupling are under intensive investigations in oncology research (Zielonka et al., 2017). Indeed, the decrease in ATP and the increase in ROS levels create the optimal condition to synergize with chemotherapeutic drugs that generate ROS as anthracyclines, platinum-derivatives, or gemcitabine (Sinha, 2020; Wang et al., 2019a; Yang et al., 2018; Zhang et al., 2020a). Examples of mitocans potentially useful to chemosensitize drug-resistant tumors are the phenol triphenyl alkyl phosphonium ( $TPP^+$ )-derivatives OXPHOS inhibitors (Gazzano et al., 2018), as dichloroacetate- $TPP^+$ , which inhibits the PDH step and the OXPHOS (Pathak et al., 2014), and the inhibitor of the mitochondrial respiratory chain complex IACS-010759. They are under evaluation in phase I trials to treat AML and GB (Molina et al., 2018).

Since metabolic pathways are strictly interconnected, the combination of two metabolic modifiers has been tested as a more potent chemosensitizer strategy. For instance, the concomitant use of MCT and OXPHOS inhibitors has shown a strong killing of the most hypoxic and chemoresistant cells (Marchiq and Pouyssegur, 2016). Similarly, the inhibition of glycolysis with 2-DG and FAO with etomoxir chemosensitized acute pro-myelocytic leukemia cells to arsenic trioxide, causing massive decrease in ATP production and downregulating pro-survival kinases, such as ERK1/2 and AKT (Estañ et al., 2014). The main limitation of these approaches is their high toxicity towards normal cells that rely on the same pathways to meet their bioenergetic demands.

In solid tumors, hypoxia remains an obstacle to effective radiation therapy, and the “metabolic radiosensitization” is a therapeutic concept that targets the metabolic demand for oxygen (Benej et al., 2018). Benej *et al.* demonstrated that papaverine, an ergot alkaloid, reduces tumor hypoxia transiently through the inhibition of mitochondrial ETC complex I, providing a clinically manageable therapeutic window to deliver more effective radiotherapy (Benej et al., 2018). Another study by Corbet *et al.* showed that 7ACC2, an inhibitor of mitochondrial pyruvate transport that blocks pyruvate import into mitochondria, sensitized BC xenografts to radiotherapy (Corbet et al., 2018). This compound blocks the TCA cycle and inhibits mitochondrial pyruvate transport, reducing the oxygen consumption rate and sensitizing tumors to radiotherapy. This fact indicates that inhibition of MPC profoundly alters OXPHOS and increases oxygen availability (Corbet et al., 2018). The tumor mitochondrial oxidative consumption also contributes to resistance to ICIs by blocking the PD-1 response. The deregulation of oxidative metabolism was associated with increased hypoxia in animal models of melanoma, and oxygen was shown to be a fundamental metabolite for the appropriate differentiation of tumor-infiltrating T cells after PD-1 blockade (Najjar et al., 2019). Similarly, in squamous cell carcinoma of the head and neck, hypoxia-induced immunosuppression also creates a barrier to immunotherapy response. Zandberg *et al.* showed that oxidative metabolism increased during the resistance to anti-PD-1 blockade with a subsequent increase in intratumoural hypoxia in the murine models of this tumor type (Zandberg et al., 2021). These facts suggest that targeting tumor oxidative metabolism may be a viable strategy to improve immunotherapeutic response.

The OXPHOS is also implicated as a resistance mechanism to venetoclax, a BCL-2 inhibitor. This drug was approved to treat chronic lymphocytic leukemia (Roberts et al., 2015) and AML (DiNardo et al., 2018a). Guièze and colleagues showed that resistance to venetoclax in lymphoid cells involved not only the reprogramming of the outer mitochondrial membrane

biology, changing the expression of BCL-2 family members, but also the increase in OXPHOS activity (Guièze et al., 2019). In AML, the clinical efficacy of venetoclax, as a single agent or in combination with hypomethylating agents, is impaired by intrinsic and acquired resistance (Sharon et al., 2019). Using tedizolid, an antibiotic targeting the 50S ribosome that inhibits mitochondrial protein synthesis, it was possible to overcome venetoclax resistance in AML effectively. The combination treatment of tedizolid with venetoclax suppressed mitochondrial respiration, mounting an integrated stress response, which suppresses glycolytic capacity and reduces leukemic burden in mice engrafted with venetoclax-resistant AML cells (Sharon et al., 2019). In this context, the introduction of metabolic modulators in the therapeutic schemes of venetoclax-resistant patients can be a strategy to circumvent the resistance to this BCL-2 inhibitor.

One possible solution to circumvent the toxicity of metabolic modifiers could be using clinically used drugs whose side-effects and pharmacokinetic/pharmacodynamics profiles are already known. In this perspective, one of the first drugs that have been re-purposed as an anticancer drug is metformin, an antidiabetic drug that inhibits complex I (Saraei P, 2019). By increasing mitochondrial ROS, it worked as a radio-sensitizer in PaC cells (Saraei P, 2019), and the same mechanism could be at the basis of a potential chemosensitization.  $\omega$ -3 FAs, used as dietary supplements in cardiovascular diseases, chemosensitize resistant colon cancer cells to doxorubicin and irinotecan because they reduce the endogenous synthesis of cholesterol and increase the fluidity of DRM-domains, thereby reducing the efflux activity of ABCB1, ABCC1, and ABCG2 (Gelsomino et al., 2013). Given their low intrinsic toxicity,  $\omega$ -3 FAs have been well-tolerated by patients and have been shown to increase the efficacy of anthracyclines in BC patients (Bougnoux et al., 2009), cisplatin and vinorelbine in NSCLC patients (Murphy et al., 2011). The molecular basis of these clinical effects likely relies on the inhibition of ABC transporters that efflux all the drugs mentioned above. Clearly, the most studied agents in the drug repurposing process have been statins and aminobisphosphonates, which inhibit HMGCR and FPP synthase steps in the cholesterol-synthetic pathway, respectively. By reducing cholesterol synthesis, statins increase DRMs fluidity (Kopecka et al., 2011), as  $\omega$ -3 FAs did. At the same time, by decreasing the production of isoprenoids downstream HMGCR, they reduce the activity of RAS/ERK1/2/HIF-1 $\alpha$  and RhoA/RhoA kinase/HIF-1 $\alpha$  axes, thereby decreasing the transcription of ABCB1. This effect was shared by aminobisphosphonates, anti-osteoporotic drugs already used to reduce bone metastasis, which lower the FPP production (Belisario et al., 2020a). In another case, the chemosensitizing effect of cholesterol-targeting drugs is an off-

target effect: for instance, simvastatin interferes with autophagic flux in GB, and this process has been linked to chemosensitization to temozolomide (Shojaei et al., 2020).

Despite the encouraging results in preclinical models, the clinical scenario using these drugs is quite variable and most trials using statins or aminobisphosphonates have shown disappointing results (Beckwitt et al., 2018). The unfavorable pharmacokinetic profile may explain the unsatisfactory results (*e.g.*, the first-passage effect that strongly reduces the half-life of specific statins, the fast uptake by bone tissue for aminobisphosphonates) by the lack of specificity for tumor tissues over liver or excretory organs and the concurrent administration of chemotherapeutic drugs, which may contribute to the faster metabolic inactivation of statins via cytochrome p450 system. Although targeting metabolism can offer a broad variety of targets to achieve a good chemosensitization, the translation of the results obtained in preclinical models is still at the beginning because of major limitations, including the tumor specificity, undesired side-effects, and drug-drug interactions that must be overcome.

Finally, dietary changes can influence the blood concentration of several metabolites impairing tumor growth (McGuirk et al., 2020; Vernieri et al., 2016). Diets restricting specific nutrients in combination with pharmacological treatments are emerging as anticancer strategies in clinical trials. Gao *et al.* demonstrated that methionine restriction combined with 5-FU in colorectal PDX models or radiation in an autochthonous model of soft-tissue sarcoma inhibited tumor growth and sensitized tumor cells to chemo- and radiotherapy (Gao et al., 2019). Diet modulation produces pleiotropic effects on different metabolic pathways, but some of these interventions, such as short-term fasting or ketogenic diets, have poor acceptability or are inapplicable to cachectic patients (Vernieri et al., 2016).

## **6. Implementing tumor metabolic profiling for clinical decision-making in cancer patients**

The identification of individual patients most likely to benefit from a metabolic therapy may speed up the entrance of these drugs into clinical practice, but the majority of metabolic therapies lack reliable biomarkers (Faubert et al., 2020). An exception to this is IDH1/2 inhibitors. As mentioned before, mutations in *IDH1/2* genes lead to neomorphic activities that convert  $\alpha$ -ketoglutarate ( $\alpha$ -KG) to 2-hydroxyglutarate (2-HG). The detection of this oncometabolite represents not only a potential biomarker of *IDH* mutation status and a surrogate marker of treatment in gliomas (Sim et al., 2019) but also a sensitive biomarker of residual leukemic cells after induction chemotherapy and measurable residual disease in AML (DiNardo et al., 2013).

The knowledge of the metabolic programs and adaptations in cancer cells allowed the identification of potential prognostic cancer biomarkers. The high expression of LDHA has been associated with poor prognosis in neuroblastoma (Dorneburg et al., 2018), medulloblastoma (Valvona and Fillmore, 2018), and MM (Fujiwara et al., 2013). The high expression of HKII was associated with shorter overall survival in HCC, GC, and CRC (Liu et al., 2016). In addition to these enzymes, GLUTs were also found to have prognostic value in oral squamous cell carcinoma (Botha et al., 2021), HCC (Gao et al., 2020), BC (Zeng et al., 2020), and locally advanced GC (Yin et al., 2020). The prognostic value of GLSs was also investigated in a multiomic analyses. Saha *et al.* found that overexpression of kidney-type glutaminase was associated with poor prognosis in breast, esophagus, head and neck, and blood cancers, and liver-type glutaminase overexpression was associated with shorter overall survival in colon, blood, ovarian, and thymoma cancers (Saha et al., 2019). Besides these prognostic biomarkers, the metabolic abnormalities may also lead to the identification of drug response biomarkers and contribute to a more personalized and precision medicine.

Positron emission tomography coupled to computed tomography (PET-CT) is certainly the best example of how tumor metabolism can be assessed and harnessed for cancer diagnosis, staging, and monitoring therapy response.  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) PET-CT imaging is indeed widely used, as a non-invasive technique in cancer patients, for the evaluation of both metabolic and anatomic characteristics of the disease. Despite the tremendous promise and use of  $^{18}\text{F}$ -FDG PET-CT, a noticeable portion of the tumors are still  $^{18}\text{F}$ -FDG PET-negative, thereby highlighting the high metabolic plasticity and flexibility within tumors, besides glucose utilization. This has led to the development of other metabolic PET imaging agents, and several radiolabeled AA have been thus developed and are now under investigation to assess their potential for clinical use. Alternative tracers such as  $^{11}\text{C}$ -labelled methionine, acetate and choline, and  $^{18}\text{F}$ -fluoroglutamine have been, for instance, clinically validated as promising tumor biomarkers in several different cancer types, including prostate cancer, MM, and glioma (Lapa et al., 2017; Michaud et al., 2020; Spick et al., 2016; Venneti et al., 2015). Labeled AA analogs such as the  $^{18}\text{F}$ -3,4-dihydroxyphenylalanine ( $^{18}\text{F}$ -DOPA) have also been developed and used for PET imaging of brain tumors (Somme et al., 2020). The short half-life of  $^{11}\text{C}$  limits the use of some metabolic tracers to nuclear medicine departments equipped with an onsite cyclotron.

In the last decade, the use of stable isotope-based metabolic analysis, directly in cancer patients, has brought important new insights into tumor cell metabolism, particularly on the fate of distinct bioenergetic substrates (*e.g.*, glucose, glutamine, and lactate) during disease

progression. For a variety of cancers, human patients have been indeed intraoperatively infused with  $^{13}\text{C}$ -labeled stable tracers (*e.g.*, isotopically labeled glucose, glutamine, lactate, and acetate) before surgical tumor resection and  $^{13}\text{C}$ -Nuclear Magnetic Resonance (NMR) or mass spectrometry imaging (MSI) analysis to assess isotope enrichment in downstream metabolites within the tumor tissues (Fernández-García et al., 2020). Infusion of [ $^{13}\text{C}$ ]glucose in patients revealed distinct metabolic fates depending on the tumor type. A recent study has reported that pediatric solid tumors use both glycolysis and the TCA cycle *in vivo*, with subtype-specific differences observed in glucose handling (Johnston et al., 2021).

Moreover, other tumors, such as clear cell RCC, have been reported as highly glycolytic, with a preferential conversion of pyruvate into lactate rather than oxidizing through the mitochondrial TCA cycle (Courtney et al., 2018). In contrast, infusion of [ $^{13}\text{C}$ ]glucose in patients has revealed that multiple cancer types, including glioma, NSCLC, and brain metastases, mostly rely on glucose-derived pyruvate oxidation through mitochondrial metabolism (Davidson et al., 2016; Fan et al., 2009; Hensley et al., 2016; Maher et al., 2012; Sellers et al., 2015). Importantly, these studies have shown enhanced glucose oxidation in FDG-PET-positive brain and lung tumors, thereby highlighting an uncoupling between high rates of glucose uptake and reduced glucose oxidation, suggesting that aggressive tumors can rely on the TCA cycle to produce energy via oxidative metabolism (Hensley et al., 2016; Sellers et al., 2015). Moreover, a limited proportion of the acetyl-CoA pool (< 50%) has been found to derive from blood-borne glucose in human brain tumors (Maher et al., 2012), suggesting that alternative substrates contribute to tumor metabolism. Some studies have identified glutamine, acetate, and lactate as additional respiratory fuels to complement glucose oxidation to support biosynthetic and bioenergetic needs within tumors (Faubert et al., 2017; Hensley et al., 2016; Hui et al., 2017; Mashimo et al., 2014). Although the stable isotope-based metabolic analysis in human cancer patients shows intrinsic limitations (*e.g.*, presence of stromal cells in collected tumor fragments, metabolic perturbation upon pre-surgical arterial occlusion), this method can potentially identify metabolic alterations in advanced tumors. These alterations may lead to novel metabolism-interfering therapeutic strategies that prevent and/or overcome resistance to conventional anticancer treatments.

The recent developments in the isolation and metabolic characterization of tumor interstitial fluid (TIF) allowed the finding that TIF metabolite composition could be different from the plasma (Ho et al., 2015; Sullivan et al., 2019). Since they represent an average level of metabolites found in the tumor extracellular fluid, these measurements do not allow to spatially capture the metabolic heterogeneity within tumor cell compartments. Nevertheless,

metabolomics analysis of TIF has been shown to pinpoint important changes in the absolute concentrations of metabolites upon a dietary alteration (Sullivan et al., 2019), thereby adding further credit to the clinical implementation of metabolomics.

MSI-based metabolomics has emerged as a very promising technique to visualize the spatially resolved metabolic preferences in heterogeneous tumor types and identify vulnerabilities that can be targeted for cancer therapy. Two recent studies have revealed a profound reprogramming of carnitine metabolism, at both metabolite and enzyme levels, in BC tissues from human patients and PDX models of GB (Randall et al., 2020; Sun et al., 2020). MSI-based metabolomics analysis in tissues from esophageal cancer patients has also shown spatially resolved alterations in several metabolic pathways, including biosynthesis of proline, polyamine, and FAs, as well as the metabolism of glutamine, uridine, and histidine (Sun et al., 2019a). Multi-isotope imaging MSI has also been used to document a high degree of metabolic heterogeneity at the single-cell level in various tumor types (Zhang et al., 2020b). Notably, the authors have identified a correlation between the heterogeneous utilization of glucose and glutamine, tumor cell proliferation, and (non)response to therapies. Recent studies have reported that metabolic acidosis can also be exploited for tumor imaging to enable early detection, localization, and monitoring of response to therapy and guide treatment decisions in cancer patients. Acidosis-based release of  $^{64}\text{Cu}$  radiotracer via pH-dependent polymers combined with PET imaging has been described as a non-invasive imaging technique with high resolution for the brain, head and neck, and breast tumors in mouse models (Huang et al., 2020a). Importantly, this strategy has been shown to outcompete conventional FDG-based PET imaging by showing clear detection of occult malignant in tumor-bearing mice while reducing false positive detection rates of inflammation in non-cancerous mouse models. Similar observations have been made with a pH-dependent peptide pHLIP that allows the specific release of the  $^{64}\text{Cu}$  radiotracer in acidic (tumor) tissues and the detection of primary and metastatic lesions in mouse models of CRC (Hao et al., 2021). In this study, the authors have also reported that this approach can monitor the therapeutic response to 5-FU, a standard chemotherapy for CRC. Further, intravenous administration of ONM-100, a fluorescent reporter of acidosis, has been reported as a useful tool for fluorescence-guided surgery to assess tumor margins in a variety of tumor types, including head and neck, CRC, and BC (Voskuil et al., 2020), thereby highlighting the need to integrate and exploit TME in clinical decision-making during and post-surgery or anticancer treatment.

Finally, the implementation of tumor metabolic profiling for clinical decision-making in cancer patients will undoubtedly benefit from the development of machine learning methods (*e.g.*,

artificial intelligence (AI)-based predictive analysis) to analyze multi-OMICs data, including large-scale metabolomics datasets (**Figure 4**). A recent study has shown that integration of metabolomics data, together with genomics and transcriptomics data, from a wide TCGA panel of radiation-sensitive and -resistant patient tumors, provides an accurate prediction of tumor metabolism and can identify diagnostic and therapeutic biomarkers for radiation response (Lewis and Kemp, 2021). Another study has also reported the use of machine learning algorithms to identify a set of metabolic biomarkers able to distinguish early-stage lung adenocarcinoma from controls (Huang et al., 2020b). High-quality metabolic datasets are still scarce and a collective effort is warranted to enable the metabolism field to take full advantage of AI. Nevertheless, such genome-scale metabolic modeling might be applied to various tumor types and anticancer therapies and position AI-based predictive analysis as one of the most promising methods to provide cancer patients and clinicians with predictive and prognostic metabolic markers to complement the oncogene-driven personalized/precision medicine (Vander Linden and Corbet, 2020).

## **7. Conclusion and Future perspectives**

The reprogramming of energy metabolism by tumor cells is currently considered one of the hallmarks of cancer (Hanahan and Weinberg, 2011) and metabolic rewiring is regarded as a novel and important mechanism of adaptive resistance (Zaal and Berkers, 2018). The mechanisms involved in therapy resistance are multifactorial. They are often interconnected and typically also involved in tumor progression, and most have been recognized as being either associated with the cancer hallmarks or associated with interactions between the TME and tumor cells (Assaraf et al., 2019). Besides tumor and TME characteristics, host-related factors are one of the significant effects that determine the activity of the antitumor drug, influencing drug absorption, distribution, metabolism, and excretion (pharmacokinetics), leading to the “Pharmacokinetic Resistance” concept (Alfarouk et al., 2015). Further, metabolic plasticity and flexibility, enabling tumor cells to adapt TME modifications and to evade therapy-induced stress, highlight the need to understand the complex metabolic phenotypes of therapy resistance, and the development of new therapeutic combinations with several metabolic drugs to overcome metabolic plasticity (and metabolic synthetic lethality) and to enhance overall antitumor effects, in order to improve patient management. The widespread use of  $^{18}\text{F}$ -FDG highlights the importance of cancer metabolism in diagnosis, treatment, and prognosis. The development of alternative tracers, as  $^{11}\text{C}$ -labelled methionine, acetate, choline and essentially of  $^{18}\text{F}$ -fluoroglutamine and  $^{18}\text{F}$ -3,4-dihydroxyphenylalanine, could further

improve the use of these techniques and in a more targeted and specific way, depending on the cancer type.

Although metabolic inhibitors such as antimetabolites (e.g., 5-FU and methotrexate) have been used for decades to treat cancers, several current lines of research are exploring the altered metabolism of cancer cells to find novel targets for therapy. This knowledge led to the development of compounds that specifically target the unique metabolism of cancers, some of which are already in clinical practice.

In this review, we have discussed specific metabolic programs and adaptations in therapy-resistant tumors, how these adaptations depend on the treatment and tumor origin and how they contribute to therapy resistance. These studies make it clear that combinational treatments with metabolic drugs and/or dietary approaches hold great promise to enhance drug efficacy for many first-line chemotherapeutic agents. Moreover, a better understanding of the altered metabolism in different therapy-resistant cancers is essential to further improve cancer therapy. Such understanding will provide insights into the molecular mechanisms underlying drug resistance to identify novel metabolic targets (through genome-scale metabolic modeling using artificial intelligence (AI)-based predictive analysis) that can be used for (combinational) therapy and/or circumvent therapy resistance. Finally, this knowledge may also lead to the identification of new prognostic biomarkers and therapy response, which could advance current therapy by predicting therapy response based on the metabolic state of a tumor in a specific patient and, thereby, contribute to a more efficacious precision medicine.

#### **Declaration of Competing Interest**

The authors have no conflict of interest to disclose.

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## Figure Legends

**Figure 1. Molecular mechanisms underlying cancer drug resistance.** Tumor heterogeneity is represented by cells with different colors. Cancer stem-like cells are represented in red. EV, extracellular vesicles; DDR, DNA damage response; TME, tumor microenvironment.

**Figure 2: Microenvironment-driven tumor metabolic heterogeneity and therapy resistance.** Besides the tumor genetic background, TME peculiarities can determine tumor metabolic adaptability and resistance to anticancer treatments via the (co-)existence of different metabolic "scenarios". Intratumor metabolic heterogeneity relies not only on high capacities of flexibility and plasticity but also on the capacities of distinct tumor cell populations (*e.g.*, normoxic vs. hypoxic cancer cells) to cooperate together or with stromal cells, such as cancer-associated fibroblasts and adipocytes. Tumor cells can also compete with immune cells for specific bioenergetic substrates, thereby impairing efficient immune response. Horizontal transfer of mitochondria or mtDNA, via tunneling nanotubes or extracellular vesicles, is another example of metabolic cooperation between cancer cells and stromal cells that may support therapy resistance.

**Figure 3. The interplay between cell signaling pathways and metabolism.** In cancer cells, the metabolism shift into glycolysis is often regulated by PI3K/AKT and RAS/RAF/ERK pathways. AKT activates mTOR, which activates HIF-1 $\alpha$  resulting in the induction of GLUT, glycolytic enzymes, and PDK, inhibiting the pyruvate flux to the TCA cycle. MYC enhances glycolysis by increasing the transcription of glycolytic enzymes and is also involved in glutaminolysis. Also, mutant IDH produces 2HG, an inhibitor of TET and JHDM families, among other enzymes. TME produces several ligands (GF/cytokines) that activate cancer cell signaling and metabolism. 2HG, 2-hydroxyglutarate; AKT, Protein kinase B; BCL2, B-cell lymphoma protein 2; BCL-XL, B-cell lymphoma-extra-large; ERK, Extracellular signal-regulated kinases; G6P, glucose-6-phosphate; G6PD, glucose-6-phosphate dehydrogenase; GF, growth factor; GLUT, glucose transporter; GST, glutathione S-transferase; HIF, hypoxia-inducible factor; HK, hexokinase; HO-1, heme oxygenase-1; IDH, isocitrate dehydrogenase; IKK, IKB kinase; IKB, inhibitor of NF-kB; JHDM, JmjC domain-containing histone demethylation protein; KEAP1, kelch-like ECH-associated protein 1; LDH, lactate dehydrogenase; mTOR, mammalian target of rapamycin; MYC, Myc proto-oncogene protein; MRP1, multidrug resistance related protein 1; NF-kB,

Nuclear factor kappa B; NQO1, NAD(P)H quinone oxidoreductase; NRF2, Nuclear factor erythroid 2-related factor 2; P, phosphate; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PFK, phosphofructokinase; PI3K, phosphoinositide 3-kinase; PKM, pyruvate kinase; PRDX1, peroxiredoxin-1; RAF, Raf proto-oncogene, serine/threonine kinase; RAS, Rat sarcoma protein; ROS, reactive oxygen species; RTK, receptor tyrosine kinase; TCA, tricarboxylic acid; TET, ten-eleven translocation; TXNRD1, thioredoxin reductase 1;  $\alpha$ -KG,  $\alpha$ -ketoglutarate; TME, tumor microenvironment.

**Figure 4. Strategies to implement tumor metabolic profiling in clinical decision-making for cancer patients.** Metabolic profiling in cancer patients may complement the genomic, transcriptomic, and histological analyses, already used in the clinics, to identify new predictive and prognostic biomarkers. Metabolic tumor imaging and isotope tracing can also help tumor detection, therapy response monitoring, and identification of metabolic vulnerabilities. The overall integration of multiomic data, including metabolomics data with clinical information in machine learning and AI-based analyses, may enable patient clustering and prediction of clinical outcomes

Table 1. OXPHOS dependence in therapy-resistant cancers and associated metabolism-interfering therapeutic modalities.

Cancer	Subtype	Biological model	Therapy resistance	Metabolic rewiring	Metabolism-interfering therapeutic modalities	Ref	
AML	/	PDTX + human AML cell lines	cytarabine	-OXPHOS gene signature -increased FAO, ROS levels, mito mass	-mito protein synthesis inhib (tigecycline, ethidium bromide) -ETC complex activity inhib (rotenone, phenformin and metformin for complex I; antimycin A and atovaquone for complex III) -CPT1 inhib (etomoxir)	(Farge et al., 2017)	
	Relapsed/refractory AML	Human primary AML samples; PDTX and cell lines	standard-of-care treatment in AML	-High OXPHOS	-complex I inhib (IACS-010759)	(Molina et al., 2018)	
	<i>IDH</i> mutation	Human cell lines; PDTX	Ivosidenib; enasidenib	-High OXPHOS -FAO activity and increased PGC1 $\alpha$ phosphorylation PI3K-Akt mediated	-ETC complex I inhib (metformin, IACS-010759, ATVQ)	(Stuani et al., 2021)	
AML/CML	Sca-1 <sup>+</sup> /Lin <sup>-</sup> stem cells	Murine model of blast crisis CML; human primary bcCML and AML samples; xenografts	cytarabine, doxorubicin, etoposide, SN-38, irinotecan, dasatinib	-Increased FAO and CD36 expression	-CPT1 inhib (etomoxir) -CD36 inhib (SSO) -Glycolysis inhib (2-DG) -complex I inhib (rotenone)	(Ye et al., 2016)	
CML	Stem cell-enriched CD34 <sup>+</sup> cells	Human primary CML samples	imatinib (TKI)	-Increased FAO, pyruvate carboxylase activity and mito respiration	-inhib of mito protein synthesis (tigecycline) -complex I inhib (phenformin)	(Kuntz et al., 2017)	
Breast cancer	/	Py2T cell line from <i>MMTV-PyMT</i> transgenic mouse breast cancer model	antiangiogenics (nintedanib)	-Lactate-based metabolic symbiosis (increased GLUT1 and MCT4 expression in hypoxic tumor areas)	-glycolysis inhib (PFKFB3 inhib. 3PO) -MCT4 genetic knockout	(Pisarsky et al., 2016)	
	TNBC	Human cell lines and xenografts	PI3K/mTOR targeted therapies	-ERR $\alpha$ -dependent lactate metabolism (+ glutamine metab)	-ERR $\alpha$ antagonists (cpd 29 + XCT790) -complex I inhib (metformin) -MPC inhib (UK5099)	(Park et al., 2016)	
	TNBC	Neoadjuvant chemotherapy (AC)	Patient derived xenografts; biopsies	paclitaxel	-High OXPHOS	-ETC complex I inhib (IACS-010759)	(Echeverri et al., 2019)
	CD44 <sup>+</sup> /CD24 <sup>-</sup> stem cells (TNBC)	Human cell lines + <i>MMTV-PyMT</i> mice	paclitaxel	-JAK/STAT3-induced FAO	CPT1 inhib (etomoxir, perhexiline)	(Wang et al., 2018b)	
	ALDH <sup>+</sup> stem cells (TNBC)	Human primary tumor samples + cell lines	paclitaxel	-co-amplification of <i>MYC</i> and <i>MCL1</i> genes -MYC-dependent mito biogenesis -increased mito respiration (FAO) and ROS levels	-complex I inhib (metformin) -CPT1 inhib (etomoxir) -HIF1 $\alpha$ translation inhib (digoxin)	(Lee et al., 2017)	
	CD44 <sup>+</sup> /CD24 <sup>-</sup> stem cells (TNBC)	Human cell lines; xenografts; human breast cancer tissues	Doxorubicin-docetaxel combination therapy	Doxorubicin-docetaxel combination therapy	High ROS production; increased glucose metabolism and PPP	-CB-839, G6PD inhib; lonidamine -in combination with doxorubicin and docetaxel therapies	(Goldman et al., 2019)
/	Human cell lines; xenografts	Doxorubicin; epirubicin	Doxorubicin; epirubicin	-High ROS production and glutamine for <i>de novo</i> glutathione synthesis -increased OXPHOS	-phenformin -buthionine sulfoximine (BSO)	(McGuirk et al., 2021)	

Pancreatic cancer	PanNET	RIP1Tag2 transgenic mice + mouse PanNET cell lines	antiangiogenics (sunitinib, axitinib)	Lactate-based metabolic symbiosis: -compartmentalized expression of MCT1 in normoxic tumor cells and MCT4 and GLUT1 in hypoxic tumor cells -Increased mTOR signaling	-lactate uptake inhib (CHC, 7ACC2) -glutaminase and alanine aminotransferase inhib (DON, AOA) -mTOR signaling inhib (rapamycin)	(Allen et al., 2016)
	<i>KRAS</i> <sup>G12D</sup> -driven PDAC; CD133 <sup>+</sup> /CD44 <sup>high</sup> stem cells	inducible mouse model of <i>KRAS</i> <sup>G12D</sup> ; PDX	MEK inhib. (AZD8330); PI3K/mTOR inhib (BEZ235)	-Increased OXPHOS gene signature -Increased mito activity (FAO)	ATP synthase inhib (oligomycin) CPT1 inhib. (etomoxir)	(Viale et al., 2014)
	CD133 <sup>+</sup> cancer stem cells	PDX	/	-High mitochondrial respiration and biogenesis in a MYC/PGC1alpha-dependent manner	-complex I inhib (metformin, rotenone) -mito ROS induction (menadione) -ATP synthase inhib (resveratrol)	(Sancho et al., 2015)
	/	Human cell lines; human patient-derived cell lines	Gemcitabine	-SLC1A5 variant expression	-SLC1A5_var knockdown -Glycolysis inhib 2-DG treatment	(Yoo et al., 2020)
	AR transcription factor driven tumorigenesis	Human prostate cancer cell lines; human cancer specimens	AR signaling pathway inhibition hormone therapies	-MPC2 mRNA upregulation and locus amplification	-MPC targeting molecule (MSCDC0160)	(Bader et al., 2019)
Ovarian cancer	High-grade serous	Human ovarian cancer cell lines; xenografts; cohorts of ovarian cancer patients	Taxane and platinum salts	-High glutamine- and FAO-fuelled OXPHOS -Chronic oxidative stress	-ETC complex I inhib (Metformin)	(Gentric et al., 2019)
Renal cell carcinoma	/	PDX	antiangiogenics (sunitinib)	-Lactate-based metabolic symbiosis: - compartmentalized expression of MCT1 in normoxic tumor cells and MCT4 and GLUT1 in hypoxic tumor cells -Increased mTOR signaling	- mTOR signaling inhib (everolimus)	(Jiménez-Valerio et al., 2016)
NSCLC	MET- and EGFR-addicted tumours	Cell lines and xenografts + patient tumor samples	MET inhib (JNJ-605, crizotinib); EGFR inhib (erlotinib)	-Lactate-based symbiosis between tumor cells (increased GLUT1 and MCT4) and CAFs (HGF secretion)	-pharmacological and genetic inhibition of MCT1 (AZD3965) and LDH (NHI-Glc-2)	(Apicella et al., 2018)
Lung and breast tumours	/	Human cell lines + xenografts	Radiotherapy	-Tumor hypoxia	Papaverine	(Benej et al., 2018)
Melanoma	<i>BRAF</i> <sup>V600E</sup> -driven melanoma	Human cell lines + primary human melanoma specimens +xenografts	<i>BRAF</i> inhib (vemurafenib and PLX4720)	-Increased OXPHOS gene signature -Increased mito number (mito biogenesis)	-Mitochondrial uncoupling (DNP and CCCP) -OXPHOS inhib (oligomycin A, rotenone, TTFA)	(Haq et al., 2013)
	<i>BRAF</i> <sup>V600E</sup> -driven	Human cell lines, xenografts	<i>BRAF</i> inhib (PLX4720)	-Reliance on OXPHOS for cell growth	phenformin	(Yuan et al., 2013)

melanoma	and <i>BRAF</i> <sup>V600E</sup> / <i>PTEN</i> <sup>mut</sup> -driven mouse melanoma model				
<i>BRAF</i> <sup>V600E</sup> -driven melanoma	Human cell lines, human primary tumor specimens	BRAF inhib (RAF265, PLX4720) MEK inhib (PD0325901; AZD6244)	-High "MitoBiogenesis" gene signature -Increase in mtDNA, mito mass and ROS levels	-mito biogenesis inhib (gamitrinib) -complex I inhib (phenformin)	(Zhang et al., 2016)
BRAF mutation	Human cell lines; xenografts	Trametinib (MEK inhib)	-High OXPHOS	ETC complex I inhib (IACS-010759)	(Vashisht Gopal et al., 2019)

For different therapy-resistant cancers, the biological model(s) used in the study, the metabolic phenotype of resistant cancer cells and therapeutic strategies used to interfere with OXPHOS dependence are indicated; inhibitors are indicated in brackets. AML, acute myeloid leukemia; ETC, electron transport chain; inhib, inhibitor; MPC, mitochondrial pyruvate carrier; Mito, mitochondrial; NSCLC, non-small cell lung cancer; PanNET, pancreatic neuroendocrine tumours; PC, pyruvate carboxylase; PDTX, patient-derived tumor xenograft; TNBC, triple negative breast cancers; TKI, tyrosine kinase inhibitor.

Table 2. Amino acid metabolism in therapy-resistant cancers and associated metabolism-interfering therapeutic modalities.

Cancer	Subtype	Biological model	Therapy resistance	Metabolic rewiring	Metabolism-interfering therapeutic modalities	Ref
Breast cancer	ER $\alpha$ -positive	Human cell lines and xenografts	Endocrine therapy (tamoxifen, fulvestrant)	-Hypoxia-induced upregulation of SNAT2/SLC38A2, SLC1A1 and SLC7A5 -Increased glutamine metabolism	-SNAT2 knockout + (MeIAB) -SLC1A2 knock-down	(Morotti et al., 2019) (Bacci et al., 2019)
	ER $\alpha$ -positive	Human cell lines; PDTX and patient tumor samples	Endocrine therapy (tamoxifen, fulvestrant, letrozole)	-miR-23b-3p-dependent downregulation -decreased overall amino acid uptake -increased SLC1A2 expression and aspartate/glutamate uptake		
	Triple negative breast cancers (TNBC)	Human cell lines; purified tumor cells from patient pleural effusions	Paclitaxel Doxorubicin Carboplatin	-Glutamine auxotrophy -Increased expression -Enhanced cystine uptake	xCT -xCT (sulfasalazine)	(Timmerman et al., 2013)
Head and neck squamous cell carcinoma	CD44v-expressing tumours	Human cell lines and xenografts; patient tumor samples	Anti-EGFR therapy (cetuximab)	-Increased intracellular levels -Increased expression	GSH knockdown + (sulfasalazine) xCT	(Yoshikawa et al., 2013)
Pancreatic cancer	/	Human cell lines	Gemcitabine	-Increased expression -Enhanced cystine uptake	xCT -xCT inhib. (MSG)	(Lo et al., 2008)
	KRAS-driven PDAC	Human cell lines and xenografts, patient tumor samples, KPBC mouse PDAC allografts	Gemcitabine	-NRF2-induced glutamine dependence -Increased GLS1 expression	-GLS inhib. (BPTES, CB-839)	(Mukhopadhyay et al., 2020)
T-ALL	NOTCH1-driven leukaemia	Mouse models of T-ALL	Anti-NOTCH therapy (DBZ)	-Increased expression -Upregulated glutaminolysis	GLS -GLS inhib. (BPTES)	(Herranz et al., 2015)
Esophageal squamous cell carcinoma	Fbxo4-mutant or cyclin D1 overexpressing ESCC	Human cell lines and xenografts; mouse embryonic fibroblasts	Anti-CDK4/6 therapy (palbociclib)	-Increased glutamine uptake -Reduced OXPHOS	-GLS inhib. (CB-839)	(Qie et al., 2019)
Melanoma	BRAF-mutant cancers	Human cell lines and xenografts	BRAF inhib. (vemurafenib and PLX4720)	-Increased mito. mass and OXPHOS -Enhanced glutaminolysis	-GLS inhibition (BPTES)	(Baenke et al., 2016)
	BRAF-mutant cancers	Human cell lines and xenografts	BRAF inhib. (vemurafenib)	-Increased glutamine uptake and metabolism	-GLS inhibition (BPTES and DON)	(Hernandez-Davies et al., 2015)

For different therapy-resistant cancers, the biological model(s) used in the study, the metabolic phenotype of resistant cancer cells and therapeutic strategies used to interfere with amino acid metabolism are indicated; inhibitors are indicated between brackets. ALL acute lymphoblastic leukemia; DBZ, dibenzazepine; ER, estrogen receptor; GLS, glutaminase; MeIAB,  $\alpha$ (methylamino)isobutyric acid

MSG, monosodium glutamate; PDX, patient-derived tumor xenograft; SLC1A1, solute carrier family 1 member 1; SLC1A2, solute carrier family 1 member 2; SLC7A5, solute carrier family 7 member 5; SLC16A14, solute carrier family 16 member 14; SLC38A2, solute carrier family 38 member 2; SNAT2, sodium-coupled neutral amino acid transporter 2.

Table 3. Selected metabolic drugs approved and under research.

Drug	Class/mechanism of action	Stage and indication
ADI-PEG 20	Arginine deiminase replacements	Phase III: LC Phase II/III: Mesothelioma Phase II: AML; melanoma; NHL; SCLC; STS Phase I: Glioblastoma; HNC; NSCLC; PaC; solid tumours
AG 270	MAT2A protein inhibitors	Phase I: Lymphoma; solid tumours
AZD3965	Monocarboxylic acid transporter inhibitors	Phase I: Solid tumours
BAY-1436032	Isocitrate dehydrogenase 1 inhibitors	Phase I: AML; solid tumours
BAY872243	Hypoxia-inducible factor-1 alpha inhibitors	Preclinical: Solid tumours
Ciforadenant	Adenosine A2A receptor antagonists	Phase I/II: NSCLC; RCC Phase I: Cancer; MM
Devimistat	Ketoglutarate dehydrogenase complex inhibitors; Pyruvate dehydrogenase complex inhibitors	Phase III: AML; PaC Phase II: BCL; BL; MDS; SCLC; solid tumours Phase I/II: BiC; CRC; solid tumours;
Enasidenib	Isocitrate dehydrogenase 2 inhibitors	Approved: AML Phase III: MDS Phase II: Myelofibrosis; MPN Phase I/II: Solid tumours Phase I: CMML
Epacadostat	Indoleamine-pyrrole 2,3-dioxygenase inhibitors	Phase III: HNC; melanoma; NSCLC; RCC; UC Phase II: EC; FTC; GC; GIST; GB; OeC; OC; PaC; PeC; sarcoma; solid tumours Phase I/II: Solid tumours; CRC; PC Phase I: RC
IDH 305	Isocitrate dehydrogenase 1 inhibitors	Preclinical: AML; solid tumours
Ivosidenib	Isocitrate dehydrogenase 1 inhibitors	Approved: AML Preregistration: Cholangiocarcinoma Phase III: MDS Phase II: Glioma; solid tumours
L-asparaginase	Asparagine modulators	Approved: LM; NHL; PCLL
ND-646	Acetyl-CoA carboxylase inhibitors	Preclinical: BC; LC; NSCLC
Numidargistat	Arginase inhibitors	Phase I/II MM; solid tumours
NYH817100	Aldehyde dehydrogenase inhibitors; Cholestenone 5-alpha reductase inhibitors; Electron transport complex I inhibitors	Phase I: Solid tumours Preclinical: Haematological malignancies
Oleclumab	5-nucleotidase inhibitors; Antibody-dependent cell cytotoxicity	Phase II: BC; NSCLC; OC; sarcoma Phase I/II: CRC; PaC Phase I: BiC; Solid tumours
Olutasidenib	Isocitrate dehydrogenase 1 inhibitors	Phase I/II: AML; glioma; MDS; solid tumours
PEG-BCT-100	Arginase replacements	Phase II: AML; LC Phase I/II: Solid tumours
PFK 158	Glucose modulators; PFKFB3 protein inhibitors	Phase I: Solid tumours
Phenformin	Electron transport complex I inhibitors	Phase I: Melanoma
Telaglenastat (CB-839)	Glutaminase inhibitors	Phase II: BC; leukaemia; MDS; NSCLC Phase I/II: CRC; melanoma; PaC; Solid tumours Phase I: solid cancer; MM
TVB 2640	Fatty acid synthetase complex inhibitors; Vascular endothelial growth factors inhibitors	Phase II: Astrocytoma; BC; NSCLC Phase I: CRC; Solid tumours
Vorasidenib	Isocitrate dehydrogenase 1 inhibitors; Isocitrate dehydrogenase 2 inhibitors	Phase III: Glioma Phase I: Solid tumours

AML, acute myeloid leukemia; BC, breast cancer; BCL, B-cell lymphoma; BiC, biliary cancer; BL, Burkitt's lymphoma; BIC, bladder cancer; CMML, chronic myelomonocytic leukemia; CRC, colorectal cancer; EC, Endometrial cancer; FTC, fallopian tube cancer; GB, glioblastoma; GC, gastric cancer; GIST, gastrointestinal stromal tumours; HNC, head and neck cancer; LC, liver cancer; LM, lymphomatous meningitis; MDS, myelodysplastic syndromes; MM, multiple myeloma; MPN, myeloproliferative disorders; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer;

OC, ovarian cancer; OeC, esophageal cancer; PaC, pancreatic cancer; PCLL, Precursor cell lymphoblastic leukaemia/lymphoma; PeC, peritoneal cancer; RC, renal cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer; STS, soft tissue sarcoma; UC, Urogenital cancer. ClinicalTrials.gov and AdisInsight data accessed on 23<sup>rd</sup> July 2021.

## References

- Alfarouk, K.O., Stock, C.-M., Taylor, S., Walsh, M., Muddathir, A.K., Verduzco, D., et al., 2015. Resistance to cancer chemotherapy: failure in drug response from ADME to P-gp. *Cancer Cell Int.* 15, 71. <https://doi.org/10.1186/s12935-015-0221-1>
- Allen, E., Miéville, P., Warren, C.M., Saghafeinia, S., Li, L., Peng, M.-W., Hanahan, D., 2016. Metabolic symbiosis enables adaptive resistance to antiangiogenic therapy that is dependent on mTOR signaling. *Cell Reports.* 15, 11144-1160.
- Alves, R., Fonseca, A.R., Gonçalves, A.C., Ferreira-Teixeira, M., Lima, J., Abrantes, A.M., et al., 2015. Drug transporters play a key role in the complex process of Imatinib resistance in vitro. *Leuk Res.* 39, 355-360. <https://doi.org/10.1016/j.leukres.2014.12.008>
- Alves, R., Gonçalves, A. C., Jorge, J., Marques, G., Luís, D., Ribeiro, A. B., et al., 2019. MicroRNA signature refine response prediction in CML. *Sci Rep.* 9, 9666. <https://doi.org/10.1038/s41598-019-46132-9>
- Andreucci, E., Peppicelli, S., Ruzzolini, J., Bianchini, F., Biagioni, A., Papucci, L., et al., 2020. The acidic tumor microenvironment drives a stem-like phenotype in melanoma cells. *J Mol Med.* 98, 1431-1446. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7525286/#\\_\\_ffn\\_\\_sectitle](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7525286/#__ffn__sectitle)
- Antonia, S.J., Mirza, N., Fricke, I., Chiappori, A., Thompson, P., Williams, N., et al., 2006. Combination of p53 Cancer Vaccine with Chemotherapy in Patients with Extensive Stage Small Cell Lung Cancer. *Clin Cancer Res.* 12, 878-887. <https://doi.org/10.1158/1078-0432.CCR-05-2013>
- Apicella, M., Giannoni, E., Fiore, S., Ferrari, K.J., Fernández-Pérez, D., Isella, C., et al., 2018. Increased Lactate Secretion by Cancer Cells Sustains Non-cell-autonomous Adaptive Resistance to MET and EGFR Targeted Therapies. *Cell Metab.* 28, 848-865. <https://doi.org/10.1016/j.cmet.2018.08.006>
- Assaraf, Y.G., Brozovic, A., Gonçalves, A.C., Jurkovicova, D., Linê, A., Machuqueiro, M., et al., 2019. The multi-factorial nature of clinical multidrug resistance in cancer. *Drug Resist Updat.* 46, 100645. <https://doi.org/10.1016/j.drug.2019.100645>
- Avendaño, C., Menéndez, J.C., 2008. Chapter 2 - Antimetabolites. In: C. Avendaño and J.C. Menéndez, Editors, *Medicinal Chemistry of Anticancer Drugs*, Elsevier, Amsterdam. 9-52.
- Avnet, S., Lemma, S., Cortini, M., Pellegrini, P., Perut, F., Zini, N., et al., 2016. Altered pH gradient at the plasma membrane of osteosarcoma cells is a key mechanism of drug resistance. *Oncotarget.* 7, 63408-63423. <https://doi.org/10.18632/oncotarget.11503>
- Avolio, R., Matassa, D.S., Crisculo, D., Landriscina, M., Esposito, F., 2020. Modulation of Mitochondrial Metabolic Reprogramming and Oxidative Stress to Overcome Chemoresistance in Cancer. *Biomolecules.* 10, 135. <https://doi.org/10.3390/biom10010135>
- Bacci, M., Lorito, N., Ippolito, L., Ramazzotti, M., Luti, S., Romagnoli, S., et al., 2019. Reprogramming of Amino Acid Transporters to Support Aspartate and Glutamate Dependency Sustains Endocrine Resistance in Breast Cancer. *Cell Rep.* 28, 104-118. <https://doi.org/10.1016/j.celrep.2019.06.010>
- Bader, D.A., Hartig, S.M., Putluri, V., Foley, C., Hamilton, M.P., Smith, E.A., et al., 2019. Mitochondrial pyruvate import is a metabolic vulnerability in androgen receptor-driven prostate cancer. *Nat Metab.* 1, 70-85. <https://doi.org/10.1038/s42255-018-0002-y>

- Bader, J.E., Voss, K., Rathmell, J.C., 2020. Targeting Metabolism to Improve the Tumor Microenvironment for Cancer Immunotherapy. *Molecular Cell* 78 (2020), pp. 1019-1033. <https://doi.org/10.1016/j.molcel.2020.05.034>
- Baenke, F., Chaneton, B., Smith, M., Van Den Broek, N., Hogan, K., Tang, H., et al., 2016. Resistance to BRAF inhibitors induces glutamine dependency in melanoma cells. *Mol Oncol.* 10, 73-84. <https://doi.org/10.1016/j.molonc.2015.08.003>
- Bai, R., Chen, N., Li, L., Du, N., Bai, L., Lv, Z., et al., 2020. Mechanisms of Cancer Resistance to Immunotherapy. *Front Oncol.* 10, 1290. <https://doi.org/10.3389/fonc.2020.01290>
- Balça-Silva, J., Matias, D., Dubois, L.G., Carneiro, B., do Carmo, A., Girão, H., et al., 2017. The Expression of Connexins and SOX2 Reflects the Plasticity of Glioma Stem-Like Cells. *Transl Oncol.* 10, 555-569. <https://doi.org/10.1016/j.tranon.2017.04.005>
- Bång-Rudenstam, A., Cerezo-Magaña, M., Belting, M., 2019. Pro-metastatic functions of lipoproteins and extracellular vesicles in the acidic tumor microenvironment. *Cancer Metastasis Rev.* 38, 79-92. <https://doi.org/10.1007/s10555-019-09786-5>
- Barrera, G., Cucci, M.A., Grattarola, M., Dianzani, C., Muzio, G., Pizzimenti, S., 2021. Control of Oxidative Stress in Cancer Chemoresistance: Spotlight on Nrf2 Role. *Antioxidants (Basel).* 10, 510. <https://doi.org/10.3390/antiox10040510>
- Beckwitt, C.H., Brufsky, A., Oltvai, Z.N., Wells, A., 2018. Statin drugs to reduce breast cancer recurrence and mortality. *Breast Cancer Res.* 20, 144. <https://doi.org/10.1186/s13058-018-1066-z>
- Belisario, D.C., Akman, M., Godel, M., Campani, V., Patrizio, M.P., Scotti, L., et al., 2020a. ABCA1/ABCB1 Ratio Determines Chemo- and Immune-Sensitivity in Human Osteosarcoma. *Cells.* 9, 647. <https://doi.org/10.3390/cells9030647>
- Belisario, D.C., Kopecka, J., Pasino, M., Akman, M., De Smaele, E., Donadelli, M., et al., 2020b. Hypoxia Dictates Metabolic Rewiring of Tumors: Implications for Chemoresistance. *Cells.* 9, 2598. <https://doi.org/10.3390/cells9122598>
- Belouèche-Babari, M., Wantuch, S., Casals Galobart, T., Koniordou, M., Parkes, H.G., Arunan, V., et al., 2017. MCT1 Inhibitor AZD3965 Increases Mitochondrial Metabolism, Facilitating Combination Therapy and Noninvasive Magnetic Resonance Spectroscopy. *Cancer Res.* 77, 5913-5924. <https://doi.org/10.1158/0008-5472.CAN-16-2686>
- Benej, M., Hong, X., Vibhute, S., Scott, S., Wu, J., Graves, E., et al., 2018. Papaverine and its derivatives radiosensitize solid tumors by inhibiting mitochondrial metabolism. *Proc Natl Acad Sci USA.* 115, 10756-10761. <https://doi.org/10.1073/pnas.1808945115>
- Birsoy, K., Wang, T., Chen, W.W., Freinkman, E., Abu-Remaileh, M., Sabatini, D.M., 2015. An Essential Role of the Mitochondrial Electron Transport Chain in Cell Proliferation Is to Enable Aspartate Synthesis. *Cell.* 162, 540-551. <https://doi.org/10.1016/j.cell.2015.07.016>
- Boedtker, E., Pedersen, S.F., 2020. The Acidic Tumor Microenvironment as a Driver of Cancer. *Annu Rev Physiol.* 82, 103-126. <https://doi.org/10.1146/annurev-physiol-021119-034627>
- Bosc, C., Selak, M.A., Sarry, J.-E., 2017. Resistance Is Futile: Targeting Mitochondrial Energetics and Metabolism to Overcome Drug Resistance in Cancer Treatment. *Cell Metab.* 26, 705-707. <https://doi.org/10.1016/j.cmet.2017.10.013>

- Botha, H., Farah, C.S., Koo, K., Cirillo, N., McCullough, M., Paolini, et al., 2021. The Role of Glucose Transporters in Oral Squamous Cell Carcinoma. *Biomolecules*. 11, 1070. <https://doi.org/10.3390/biom11081070>
- Bougnoux, P., Hajjaji, N., Ferrasson, M.N., Giraudeau, B., Couet, C., Le Floch, O., 2009. Improving outcome of chemotherapy of metastatic breast cancer by docosahexaenoic acid: a phase II trial. *Br J Cancer*. 101, 1978-1985. <https://doi.org/10.1038/sj.bjc.6605441>
- Boumahdi, S., Sauvage, F.J., 2020. The great escape: tumor cell plasticity in resistance to targeted therapy. *Nat Rev Drug Disc*. 19, 39-56. <https://doi.org/10.1038/s41573-019-0044-1>
- Brachtendorf, S., Wanger, R.A., Birod, K., Thomas, D., Trautmann, S., Wegner, M.-S., et al., 2018. Chemosensitivity of human colon cancer cells is influenced by a p53-dependent enhancement of ceramide synthase 5 and induction of autophagy. *Biochim Biophys Acta Mol Cell Biol Lipids*. 1863, 1214-1227. <https://doi.org/10.1016/j.bbali.2018.07.011>
- Bu, L., Baba, H., Yasuda, T., Uchihara, T., Ishimoto, T., 2020. Functional diversity of cancer-associated fibroblasts in modulating drug resistance. *Cancer Sci*. 111, 3468-3477. <https://doi.org/10.1111/cas.14578>
- Burt, R., Dey, A., Aref, S., Aguiar, M., Akarca, A., Bailey, K., et al., 2019. Activated stromal cells transfer mitochondria to rescue acute lymphoblastic leukemia cells from oxidative stress. *Blood*. 134, 1415-1429. <https://doi.org/10.1182/blood.2019001398>
- Butler, M., van der Meer, L.T., van Leeuwen, F.N., 2021. Amino Acid Depletion Therapies: Starving Cancer Cells to Death. *Trends Endocrinol Metab*. 32, 367-381. <https://doi.org/10.1016/j.tem.2021.03.003>
- Cao, Y., 2019. Adipocyte and lipid metabolism in cancer drug resistance, *The Journal of Clinical Investigation* 129 (2019), pp. 3006-3017. <https://doi.org/10.1172/JCI127201>
- Carling, D., 2017. AMPK signaling in health and disease. *Curr Opin Cell Biol*. 45, 31-37. <https://doi.org/10.1016/j.ceb.2017.01.005>
- Caro, P., Kishan, A.U., Norberg, E., Stanley, I.A., Chapuy, B., Ficarro, S.B., et al., 2012. Metabolic Signatures Uncover Distinct Targets in Molecular Subsets of Diffuse Large B Cell Lymphoma. *Cancer Cell*. 22, 547-560. <https://doi.org/10.1016/j.ccr.2012.08.014>
- Cascone, T., McKenzie, J.A., Mbofung, R.M., Punt, S., Wang, Z., Xu, C., et al., 2018. Increased Tumor Glycolysis Characterizes Immune Resistance to Adoptive T Cell Therapy. *Cell Metab*. 27, 977-987. <https://doi.org/10.1016/j.cmet.2018.02.024>
- Catanzaro, D., Gaude, E., Orso, G., Giordano, C., Guzzo, G., Rasola, A., et al., 2015. Inhibition of glucose-6-phosphate dehydrogenase sensitizes cisplatin-resistant cells to death. *Oncotarget*. 6, 30102-30114. <https://doi.org/10.18632/oncotarget.4945>
- Celestino, A.T., Levy, D., Maria Ruiz, J.L., Bydlowski, S.P., 2015. ABCB1, ABCC1, and LRP gene expressions are altered by LDL, HDL, and serum deprivation in a human doxorubicin-resistant uterine sarcoma cell line. *Biochem Biophys Res Commun*. 457, 664-668. <https://doi.org/10.1016/j.bbrc.2015.01.045>
- Chai, Y., Wang, C., Liu, W., Fan, Y., Zhang, Y., 2019. MPC1 deletion is associated with poor prognosis and temozolomide resistance in glioblastoma. *J Neuro-Oncol*. 144, 293-301. <https://doi.org/10.1007/s11060-019-03226-8>

- Chakraborty, P.K., Mustafi, S.B., Xiong, X., Dwivedi, S.K.D., Nesin, V., Saha, S., et al., 2017. MICU1 drives glycolysis and chemoresistance in ovarian cancer. *Nat Commun.* 8, 14634. <https://doi.org/10.1038/ncomms14634>
- Chang, C.-H., Qiu, J., O'Sullivan, D., Buck, M.D., Noguchi, T., Curtis, J.D., et al., 2015. Metabolic Competition in the Tumor Microenvironment Is a Driver of Cancer Progression. *Cell.* 162, 1229-1241. <https://doi.org/10.1016/j.cell.2015.08.016>
- Chiappa, M., Guffanti, F., Bertoni, F., Colombo, I., Damia, G., 2021. Overcoming PARPi resistance: Preclinical and clinical evidence in ovarian cancer. *Drug resist update.* 55, 100744. <https://doi.org/10.1016/j.drug.2021.100744>
- Chun, K.-S., Kim, D.-H., Surh, Y.-J., 2021. Role of Reductive versus Oxidative Stress in Tumor Progression and Anticancer Drug Resistance. *Cells.* 10, 758. <https://doi.org/10.3390/cells10040758>
- Corbet, C., 2017. Stem Cell Metabolism in Cancer and Healthy Tissues: Pyruvate in the Limelight. *Front Pharmacol* 8, 958. <https://doi.org/10.3389/fphar.2017.00958>
- Corbet, C., Bastien, E., Draoui, N., Doix, B., Mignon, L., Jordan, B.F., et al., 2018. Interruption of lactate uptake by inhibiting mitochondrial pyruvate transport unravels direct antitumor and radiosensitizing effects. *Nat Commun.* 9, 1208. <https://doi.org/10.1038/s41467-018-03525-0>
- Corbet, C., Bastien, E., Santiago de Jesus, J.P., Dierge, E., Martherus, R., Vander Linden, C., et al., 2020. TGF $\beta$ 2-induced formation of lipid droplets supports acidosis-driven EMT and the metastatic spreading of cancer cells. *Nat Commun.* 11, 454. <https://doi.org/10.1038/s41467-019-14262-3>
- Corbet, C., Draoui, N., Polet, F., Pinto, A., Drozak, X., Riant, O., Feron, O., 2014. The SIRT1/HIF2 $\alpha$  Axis Drives Reductive Glutamine Metabolism under Chronic Acidosis and Alters Tumor Response to Therapy. *Cancer Res.* 74, 5507-5519. <https://doi.org/10.1158/0008-5472.CAN-14-0705>
- Corbet, C., Feron, O., 2017a. Emerging roles of lipid metabolism in cancer progression. *Curr Opin Clin Nutr Metab Care.* 20, 254-260. doi: 10.1097/MCO.0000000000000381
- Corbet, C., Feron, O., 2017b. Tumor acidosis: from the passenger to the driver's seat, *Nat Rev Cancer.* 17, 577-593. <https://doi.org/10.1038/nrc.2017.77>
- Corbet, C., Pinto, A., Martherus, R., Santiago de Jesus, J.P., Polet, F., Feron, O., 2016. Acidosis Drives the Reprogramming of Fatty Acid Metabolism in Cancer Cells through Changes in Mitochondrial and Histone Acetylation. *Cell Metab.* 24, 311-323. <https://doi.org/10.1016/j.cmet.2016.07.003>
- Cordani, M., Butera, G., Pacchiana, R., Masetto, F., Mullappilly, N., Riganti, C., et al., 2020. Mutant p53-Associated Molecular Mechanisms of ROS Regulation in Cancer Cells. *Biomolecules.* 10, 361. <https://doi.org/10.3390/biom10030361>
- Cotte, A.K., Aires, V., Fredon, M., Limagne, E., Derangère, V., Thibaudin, M., et al., 2018. Lysophosphatidylcholine acyltransferase 2-mediated lipid droplet production supports colorectal cancer chemoresistance. *Nat Commun.* 9, 322. <https://doi.org/10.1038/s41467-017-02732-5>
- Courtney, K.D., Bezwada, D., Mashimo, T., Pichumani, K., Vemireddy, V., Funk, A.M., et al., 2018. Isotope Tracing of Human Clear Cell Renal Cell Carcinomas Demonstrates Suppressed Glucose Oxidation *in vivo*. *Cell Metab.* 28, 793-800. <https://doi.org/10.1016/j.cmet.2018.07.020>
- Cruz-Bermúdez, A., Laza-Briviesca, R., Vicente-Blanco, R.J., García-Grande, A., Coronado, M.J., Laine-Menéndez, S., et al., 2019. Cisplatin resistance involves a metabolic reprogramming through ROS and

- PGC-1 $\alpha$  in NSCLC which can be overcome by OXPHOS inhibition. *Free Radic Biol Med.* 135, 167-181. <https://doi.org/10.1016/j.freeradbiomed.2019.03.009>
- Cui, J., Guo, Y., Wu, H., Xiong, J., Peng, T., 2021. Everolimus regulates the activity of gemcitabine-resistant pancreatic cancer cells by targeting the Warburg effect via PI3K/AKT/mTOR signaling. *Mol Med.* 27, 38. <https://doi.org/10.1186/s10020-021-00300-8>
- Cui, Q., Wang, J. Q., Assaraf, Y. G., Ren, L., Gupta, P., Wei, L., et al., 2018. Modulating ROS to overcome multidrug resistance in cancer. *Drug resist update.* 41, 1–25. <https://doi.org/10.1016/j.drug.2018.11.001>
- Dagogo-Jack, I., Shaw, A.T., 2018. Tumor heterogeneity and resistance to cancer therapies, *Nat Rev Clin Oncol.* 15, 81-94. <https://doi.org/10.1038/nrclinonc.2017.166>
- Dal Bo, M., De Mattia, E., Baboci, L., Mezzalana, S., Cecchin, E., Assaraf, Y. G., et al., 2020. New insights into the pharmacological, immunological, and CAR-T-cell approaches in the treatment of hepatocellular carcinoma. *Drug resist update.* 51, 100702. <https://doi.org/10.1016/j.drug.2020.100702>
- Dasari, S., Tchounwou, P.B., 2014. Cisplatin in cancer therapy: Molecular mechanisms of action. *Eur J Pharmacol.* 740, 364-378. <https://doi.org/10.1016/j.ejphar.2014.07.025>
- Davidson, S.M., Papagiannakopoulos, T., Olenchock, B.A., Heyman, J.E., Keibler, M.A., Luengo, A., et al., 2016. Environment Impacts the Metabolic Dependencies of Ras-Driven Non-Small Cell Lung Cancer. *Cell Metab.* 23, 517-528. <https://doi.org/10.1016/j.cmet.2016.01.007>
- De Angelis, M.L., La Torre, F., Zeuner, A., 2018. Stem Cell Plasticity and Dormancy in the Development of Cancer Therapy Resistance. *Front Oncol.* 9. <https://doi.org/10.3389/fonc.2019.00626>
- De Rosa, V., Iommelli, F., Monti, M., Fonti, R., Votta, G., Stoppelli, M.P., et al., 2015. Reversal of Warburg Effect and Reactivation of Oxidative Phosphorylation by Differential Inhibition of EGFR Signaling Pathways in Non-Small Cell Lung Cancer. *Clin Cancer Res.* 21, 5110-5120. <https://doi.org/10.1158/1078-0432.CCR-15-0375>
- DeBerardinis, R.J., Thompson, C.B., 2012. Cellular Metabolism and Disease: What Do Metabolic Outliers Teach Us?. *Cell.* 148, 1132-1144. <https://doi.org/10.1016/j.cell.2012.02.032>
- Demas, D.M., Demo, S., Fallah Y., Clarke R., Nephew K.P., Althouse S., et al., 2019. Glutamine Metabolism Drives Growth in Advanced Hormone Receptor Positive Breast Cancer. *Front. Oncol.* 9, 686. <https://doi.org/10.3389/fonc.2019.00686>
- Dey, P., Baddour, J., Muller, F., Wu, C.C., Wang, H., Liao, W.-T., et al., 2017. Genomic deletion of malic enzyme 2 confers collateral lethality in pancreatic cancer. *Nature.* 542, 119-123. <https://doi.org/10.1038/nature21052>
- Dierge, E., Debock, E., Guilbaud, C., Corbet, C., Mignolet, E., Mignard, L., et al., 2021. Peroxidation of n-3 and n-6 polyunsaturated fatty acids in the acidic tumor environment leads to ferroptosis-mediated anticancer effects. *Cell Metab.* 33, 1701-1715. <https://doi.org/10.1016/j.cmet.2021.05.016>
- Dietl, K., Renner, K., Dettmer, K., Timischl, B., Eberhart, K., Dorn, C., et al., 2010. Lactic Acid and Acidification Inhibit TNF Secretion and Glycolysis of Human Monocytes. *J Immunol.* 184, 1200-1209. <https://doi.org/10.4049/jimmunol.0902584>
- DiNardo, C.D., Pratz, K.W., Letai, A., Jonas, B.A., Wei, A.H., Thirman, M., et al., 2018a. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously

- untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. *Lancet Oncol.* 19, 216-228. [https://doi.org/10.1016/S1470-2045\(18\)30010-X](https://doi.org/10.1016/S1470-2045(18)30010-X)
- DiNardo, C.D., Propert, K.J., Loren, A.W., Paietta, E., Sun, Z., Levine, R.L., et al., 2013. Serum 2-hydroxyglutarate levels predict isocitrate dehydrogenase mutations and clinical outcome in acute myeloid leukemia. *Blood.* 121, 4917-4924. <https://doi.org/10.1182/blood-2013-03-493197>
- DiNardo, C.D., Stein, E.M., de Botton, S., Roboz, G.J., Altman, J.K., Mims, A.S., et al., 2018b. Durable Remissions with Ivosidenib in IDH1-Mutated Relapsed or Refractory AML. *N Eng J Med.* 378, 2386-2398. doi: 10.1056/NEJMoa1716984
- Doherty, J.R., Cleveland, J.L., 2013. Targeting lactate metabolism for cancer therapeutics. *J Clin Invest.* 123, 3685-3692. <https://doi.org/10.1172/JCI69741>
- Dong, J.-K., Lei, H.-M., Liang, Q., Tang, Y.-B., Zhou, Y., Wang, Y., et al., 2018. Overcoming erlotinib resistance in EGFR mutation-positive lung adenocarcinomas through repression of phosphoglycerate dehydrogenase. *Theranostics.* 8, 1808-1823. <https://www.thno.org/v08p1808.htm>
- Dorneburg, C., Fischer, M., Barth, T.F.E., Mueller-Klieser, W., Hero, B., Gecht, J., et al., 2018. LDHA in Neuroblastoma Is Associated with Poor Outcome and Its Depletion Decreases Neuroblastoma Growth Independent of Aerobic Glycolysis. *Clin Cancer Res.* 24, 5772-5783. <https://doi.org/10.1158/1078-0432.CCR-17-2578>
- Echeverria, G.V., Ge, Z., Seth, S., Zhang, X., Jeter-Jones, S., Zhou, X., et al., 2019. Resistance to neoadjuvant chemotherapy in triple-negative breast cancer mediated by a reversible drug-tolerant state. *Sci Transl Med.* 11, eaav0936. <https://doi.org/10.1126/scitranslmed.aav0936>
- El-Kenawi, A., Dominguez-Viqueira, W., Liu, M., Awasthi, S., Abraham-Miranda, J., Keske, A., et al., 2021. Macrophage-derived cholesterol contributes to therapeutic resistance in prostate cancer. *Cancer Res.* <https://doi.org/10.1158/0008-5472.CAN-20-4028>
- Elstrom, R.L., Bauer, D.E., Buzzai, M., Karnauskas, R., Harris, M.H., Plas, D.R., et al., 2004. Akt Stimulates Aerobic Glycolysis in Cancer Cells. *Cancer Res.* 64, 3892-3899. <https://doi.org/10.1158/0008-5472.CAN-03-2904>
- Emmings, E., Mullany, S., Chang, Z., Landen, C.N., Linder, S., Bazzaro, M., 2019. Targeting Mitochondria for Treatment of Chemoresistant Ovarian Cancer. *Int J Mol Sci.* 20, 229. <https://doi.org/10.3390/ijms20010229>
- Enriquez-Navas, P.M., Wojtkowiak, J.W., Gatenby, R.A., 2015. Application of Evolutionary Principles to Cancer Therapy. *Cancer Res.* 75, 4675-4680. <https://doi.org/10.1158/0008-5472.CAN-15-1337>
- Estañ, M.C., Calviño, E., Calvo, S., Guillén-Guío, B., Boyano-Adánez, M.d.C., de Blas, E., et al., 2014. Apoptotic Efficacy of Etomoxir in Human Acute Myeloid Leukemia Cells. Cooperation with Arsenic Trioxide and Glycolytic Inhibitors, and Regulation by Oxidative Stress and Protein Kinase Activities. *PLoS One.* 9, e115250. <https://doi.org/10.1371/journal.pone.0115250>
- Faheem, M.M., Seligson, N.D., Ahmad, S.M., Rasool, R.U., Gandhi, S.G., Bhagat, M., et al., 2020. Convergence of therapy-induced senescence (TIS) and EMT in multistep carcinogenesis: current opinions and emerging perspectives. *Cell Death Discov.* 6, 51. <https://doi.org/10.1038/s41420-020-0286-z>
- Fan, S., Niu, Y., Tan, N., Wu, Z., Wang, Y., You, H., et al., 2013. LASS2 enhances chemosensitivity of breast cancer by counteracting acidic tumor microenvironment through inhibiting activity of V-ATPase proton pump. *Oncogene.* 32, 1682-1690. <https://doi.org/10.1038/onc.2012.183>

- Fan, T.W.N., Lane, A.N., Higashi, R.M., Farag, M.A., Gao, H., Bousamra, M., et al., 2009. Altered regulation of metabolic pathways in human lung cancer discerned by <sup>13</sup>C stable isotope-resolved metabolomics (SIRM). *Mol Cancer*. 8, 41. <https://doi.org/10.1186/1476-4598-8-41>
- Farge, T., Saland, E., de Toni, F., Aroua, N., Hosseini, M., Perry, R., et al., 2017. Chemotherapy-Resistant Human Acute Myeloid Leukemia Cells Are Not Enriched for Leukemic Stem Cells but Require Oxidative Metabolism. *Cancer Discov*. 7, 716-735. <https://doi.org/10.1158/2159-8290.CD-16-0441>
- Faubert, B., Boily, G., Izreig, S., Griss, T., Samborska, B., Dong, Z., et al., 2013. AMPK Is a Negative Regulator of the Warburg Effect and Suppresses Tumor Growth in vivo. *Cell Metab*. 17, 113-124. <https://doi.org/10.1016/j.cmet.2012.12.001>
- Faubert, B., Li, K.Y., Cai, L., Hensley, C.T., Kim, J., Zacharias, L.G., et al., 2017. Lactate Metabolism in Human Lung Tumors. *Cell*. 171, 358-371. <https://doi.org/10.1016/j.cell.2017.09.019>
- Faubert, B., Solmonson, A., DeBerardinis, R.J., 2020. Metabolic reprogramming and cancer progression. *Science*. 368, eaaw5473. <https://doi.org/10.1126/science.aaw5473>
- Federici, C., Petrucci, F., Caimi, S., Cesolini, A., Logozzi, M., Borghi, M., et al., 2014. Exosome Release and Low pH Belong to a Framework of Resistance of Human Melanoma Cells to Cisplatin. *PLoS One*. 9, e88193. <https://doi.org/10.1371/journal.pone.0088193>
- Fendt, S.-M., Frezza, C., Erez, A., 2020. Targeting Metabolic Plasticity and Flexibility Dynamics for Cancer Therapy. *Cancer Discov*. 10, 1797-1807. <https://doi.org/10.1158/2159-8290.CD-20-0844>
- Fernández-García, J., Altea-Manzano, P., Pranzini, E., Fendt, S.-M., 2020. Stable Isotopes for Tracing Mammalian-Cell Metabolism in vivo. *Trends Biochem Sci*. 45, pp. 185-201. <https://doi.org/10.1016/j.tibs.2019.12.002>
- Filatova, A., Seidel, S., Böğürçü, N., Gräf, S., Garvalov, B.K., Acker, T., 2016. Acidosis Acts through HSP90 in a PHD/VHL-Independent Manner to Promote HIF Function and Stem Cell Maintenance in Glioma. *Cancer Res*. 76, 5845-5856. <https://doi.org/10.1158/0008-5472.CAN-15-2630>
- Fiorillo, M., Sotgia, F., Sisci, D., Cappello, A.R., Lisanti, M.P., 2017. Mitochondrial “power” drives tamoxifen resistance: NQO1 and GCLC are new therapeutic targets in breast cancer. *Oncotarget*. 8, 20309-20327. <https://doi.org/10.18632/oncotarget.15852>
- Fischer, K., Hoffmann, P., Voelkl, S., Meidenbauer, N., Ammer, J., Edinger, M., et al., 2007. Inhibitory effect of tumor cell-derived lactic acid on human T cells. *Blood*. 109, 3812-3819. <https://doi.org/10.1182/blood-2006-07-035972>
- Freitas, D.P., Teixeira, C.A., Santos-Silva, F., Vasconcelos, M.H., Almeida, G.M., 2014. Therapy-induced enrichment of putative lung cancer stem-like cells. *Int J Cancer*. 134, 1270-1278. <https://doi.org/10.1002/ijc.28478>
- Fu, S., Li, Z., Xiao, L., Hu, W., Zhang, L., Xie, B., et al., 2019. Glutamine Synthetase Promotes Radiation Resistance via Facilitating Nucleotide Metabolism and Subsequent DNA Damage Repair. *Cell Rep*. 28, 1136-1143. <https://doi.org/10.1016/j.celrep.2019.07.002>
- Fujiwara, S., Kawano, Y., Yuki, H., Okuno, Y., Nosaka, K., Mitsuya, H., et al., 2013. PDK1 inhibition is a novel therapeutic target in multiple myeloma. *Br J Cancer*. 108, 170-178. <https://doi.org/10.1038/bjc.2012.527>

- Fumarola, C., Petronini, p.G., Alfieri, R., 2018. Impairing energy metabolism in solid tumors through agents targeting oncogenic signaling pathways. *Biochem Pharmacol.* 151, 114-125. <https://doi.org/10.1016/j.bcp.2018.03.006>
- Furuta, E., Pai, S.K., Zhan, R., Bandyopadhyay, S., Watabe, M., Mo, Y.-Y., et al., 2008. Fatty Acid Synthase Gene Is Up-regulated by Hypoxia via Activation of Akt and Sterol Regulatory Element Binding Protein-1. *Cancer Res.* 68, 1003-1011. <https://doi.org/10.1158/0008-5472.CAN-07-2489>
- Gao, H., Hao, Y., Zhou, X., Li, H., Liu, F., Zhu, H., et al., 2020. Prognostic value of glucose transporter 3 expression in hepatocellular carcinoma. *Oncol Lett.* 19, 691-699. doi: 10.3892/ol.2019.11191
- Gao, R., Buechel, D., Kalathur, R.K.R., Morini, M.F., Coto-Llerena, M., Ercan, C., et al., 2021. USP29-mediated HIF1 $\alpha$  stabilization is associated with Sorafenib resistance of hepatocellular carcinoma cells by upregulating glycolysis. *Oncogenesis.* 10, 52. <https://doi.org/10.1038/s41389-021-00338-7>
- Gao, X., Sanderson, S.M., Dai, Z., Reid, M.A., Cooper, D.E., Lu, M., et al., 2019. Dietary methionine influences therapy in mouse cancer models and alters human metabolism. *Nature.* 572, 397-401. <https://doi.org/10.1038/s41586-019-1437-3>
- Garcia-Bermudez, J., Baudrier, L., La, K., Zhu, X.G., Fidelin, J., Sviderskiy, V.O., et al., 2018. Aspartate is a limiting metabolite for cancer cell proliferation under hypoxia and in tumours. *Nat Cell Biol.* 20, 775-781. <https://doi.org/10.1038/s41556-018-0118-z>
- Garnier-Suillerot, A., Marbeuf-Gueye, C., Salerno, M., Loetchutinat, C., Fokt, I., Krawczyk, M., et al., 2001. Analysis of drug transport kinetics in multidrug-resistant cells: implications for drug action. *Curr Med Chem.* 8, 51-64. <https://doi.org/10.2174/0929867013373967>
- Gatenby, R.A., Brown, J.S., 2020. Integrating evolutionary dynamics into cancer therapy. *Nat Rev Clin Oncol.* 17, 675-686. <https://doi.org/10.1038/s41571-020-0411-1>
- Gatenby, R.A., Gillies, R.J., 2008. A microenvironmental model of carcinogenesis. *Nat Rev Cancer.* 8, 56-61. <https://doi.org/10.1038/nrc2255>
- Gazzano, E., Lazzarato, L., Rolando, B., Kopecka, J., Guglielmo, S., Costamagna, C., et al., 2018. Mitochondrial Delivery of Phenol Substructure Triggers Mitochondrial Depolarization and Apoptosis of Cancer Cells. *Front Pharmacol.* 9, 580. <https://doi.org/10.3389/fphar.2018.00580>
- Gelsomino, G., Corsetto, P.A., Campia, I., Montorfano, G., Kopecka, J., Castella, B., et al., 2013. Omega 3 fatty acids chemosensitize multidrug resistant colon cancer cells by down-regulating cholesterol synthesis and altering detergent resistant membranes composition. *Mol Cancer.* 12, 137. <https://doi.org/10.1186/1476-4598-12-137>
- Gentric, G., Kieffer, Y., Mieulet, V., Goundiam, O., Bonneau, C., Nemat, F., et al., 2019. PML-Regulated Mitochondrial Metabolism Enhances Chemosensitivity in Human Ovarian Cancers. *Cell Metab.* 29, 156-173. <https://doi.org/10.1016/j.cmet.2018.09.002>
- Ghanbari Movahed, Z., Rastegari-Pouyani, M., Mohammadi, M.h., Mansouri, K., 2019. Cancer cells change their glucose metabolism to overcome increased ROS: One step from cancer cell to cancer stem cell? *Biomed Pharmacother.* 112, 108690. <https://doi.org/10.1016/j.biopha.2019.108690>
- Giddings, E.L., Champagne, D.P., Wu, M.-H., Laffin, J.M., Thornton, T.M., Valenca-Pereira, F., et al., 2021. Mitochondrial ATP fuels ABC transporter-mediated drug efflux in cancer chemoresistance. *Nat Commun.* 12, 2804. <https://doi.org/10.1038/s41467-021-23071-6>

- Gillies, R.J., Verduzco, D., Gatenby, R.A., 2012. Evolutionary dynamics of carcinogenesis and why targeted therapy does not work. *Nat Rev Cancer*. 12, 487-493. <https://doi.org/10.1038/nrc3298>
- Goldman, A., Khiste, S., Freinkman, E., Dhawan, A., Majumder, B., Mondal, J., et al., 2019. Targeting tumor phenotypic plasticity and metabolic remodeling in adaptive cross-drug tolerance. *Sci Signal*. 12, eaas8779. <https://doi.org/10.1126/scisignal.aas8779>
- Gonen, N., Assaraf, Y. G., 2012. Antifolates in cancer therapy: structure, activity and mechanisms of drug resistance. *Drug resist update*. 15, 183–210. <https://doi.org/10.1016/j.drug.2012.07.002>
- Gong, T., Cui, L., Wang, H., Wang, H., Han, N., 2018. Knockdown of KLF5 suppresses hypoxia-induced resistance to cisplatin in NSCLC cells by regulating HIF-1 $\alpha$ -dependent glycolysis through inactivation of the PI3K/Akt/mTOR pathway. *J Transl Med*. 16, 164. <https://doi.org/10.1186/s12967-018-1543-2>
- Gottfried, E., Kunz-Schughart, L.A., Ebner, S., Mueller-Klieser, W., Hoves, S., Andreesen, R., et al., 2006. Tumor-derived lactic acid modulates dendritic cell activation and antigen expression. *Blood*. 107, 2013-2021. <https://doi.org/10.1182/blood-2005-05-1795>
- Greife, A., Tukova, J., Steinhoff, C., Scott, S.D., Schulz, W.A., Hatina, J., 2015. Establishment and characterization of a bladder cancer cell line with enhanced doxorubicin resistance by mevalonate pathway activation. *Tumor Biol*. 36, 3293-3300. <https://doi.org/10.1007/s13277-014-2959-9>
- Gremke, N., Polo, P., Dort, A., Schneikert, J., Elmshäuser, S., Brehm, C., et al., 2020. mTOR-mediated cancer drug resistance suppresses autophagy and generates a druggable metabolic vulnerability. *Nat Commun*. 11, 4684. <https://doi.org/10.1038/s41467-020-18504-7>
- Grondona, P., Bucher, P., Schulze-Osthoff, K., Hailfinger, S., Schmitt, A., 2018. NF- $\kappa$ B Activation in Lymphoid Malignancies: Genetics, Signaling, and Targeted Therapy. *Biomedicines*. 6, 38. <https://doi.org/10.3390/biomedicines6020038>
- Gstalter, C., Ader, I., Cuvillier, O., 2016. FTY720 (Fingolimod) Inhibits HIF1 and HIF2 Signaling, Promotes Vascular Remodeling, and Chemosensitizes in Renal Cell Carcinoma Animal Model. *Mol Cancer Ther*. 15, 2465-2474. <https://doi.org/10.1158/1535-7163.MCT-16-0167>
- Guerra, F., Perrone, A.M., Kurelac, I., Santini, D., Ceccarelli, C., Cricca, M., et al., 2012. Mitochondrial DNA Mutation in Serous Ovarian Cancer: Implications for Mitochondria-Coded Genes in Chemoresistance. *J Clin Oncol*. 30, e373-e378. doi: 10.1200/JCO.2012.43.5933
- Guièze, R., Liu, V.M., Rosebrock, D., Jourdain, A.A., Hernández-Sánchez, M., Martínez Zurita, A., et al., 2019. Mitochondrial Reprogramming Underlies Resistance to BCL-2 Inhibition in Lymphoid Malignancies. *Cancer Cell*. 36, 369-384. <https://doi.org/10.1016/j.ccell.2019.08.005>
- Hagenbuchner, J., Kuznetsov, A.V., Obexer, P., Ausserlechner, M.J., 2013. BIRC5/Survivin enhances aerobic glycolysis and drug resistance by altered regulation of the mitochondrial fusion/fission machinery. *Oncogene*. 32, 4748-4757. <https://doi.org/10.1038/onc.2012.500>
- Halbrook, C.J., Thurston, G., McCarthy, A., Nelson, B.S., Sajjakulnukit, P., Krall, A.S., et al., 2020. Clonal Heterogeneity Supports Mitochondrial Metabolism in Pancreatic Cancer. *BioRxiv*. <https://doi.org/10.1101/2020.05.15.098368>
- Hanahan, D., Weinberg, R.A., 2011. Hallmarks of Cancer: The Next Generation. *Cell*. 144, 646-674. <https://doi.org/10.1016/j.cell.2011.02.013>
- Hao, L., Rohani, N., Zhao, R.T., Pulver, E.M., Mak, H., Kelada, O.J., et al., 2021. Microenvironment-triggered multimodal precision diagnostics. *Nat Mater*. <https://doi.org/10.1038/s41563-021-01042-y>

- Haq, R., Shoag, J., Andreu-Perez, P., Yokoyama, S., Edelman, H., Rowe, G.C., et al., 2013. Oncogenic BRAF Regulates Oxidative Metabolism via PGC1 $\alpha$  and MITF. *Cancer Cell*. 23, 302-315. <https://doi.org/10.1016/j.ccr.2013.02.003>
- Hardie, D.G., 2011. AMP-activated protein kinase: an energy sensor that regulates all aspects of cell function. *Genes Dev*. 25, 1895-908. doi: 10.1101/gad.17420111
- Hayes, J.D., Dinkova-Kostova, A.T., Tew, K.D., 2020. Oxidative Stress in Cancer. *Cancer Cell*. 38, 167-197. <https://doi.org/10.1016/j.ccell.2020.06.001>
- He, M., Jin, Q., Chen, C., Liu, Y., Ye, X., Jiang, Y., et al., 2019. The miR-186-3p/EREG axis orchestrates tamoxifen resistance and aerobic glycolysis in breast cancer cells. *Oncogene*. 38, 5551-5565. <https://doi.org/10.1038/s41388-019-0817-3>
- Hensley, C.T., Faubert, B., Yuan, Q., Lev-Cohain, N., Jin, E., Kim, J., et al., 2016. Metabolic Heterogeneity in Human Lung Tumors. *Cell*. 164, 681-694. <https://doi.org/10.1016/j.cell.2015.12.034>
- Hernandez-Davies, J.E., Tran, T.Q., Reid, M.A., Rosales, K.R., Lowman, X.H., Pan, M., et al., 2015. Vemurafenib resistance reprograms melanoma cells towards glutamine dependence. *J Transl Med*. 13, 210. <https://doi.org/10.1186/s12967-015-0581-2>
- Herranz, D., Ambesi-Impiombato, A., Sudderth, J., Sánchez-Martín, M., Belver, L., Tosello, V., et al., 2015. Metabolic reprogramming induces resistance to anti-NOTCH1 therapies in T cell acute lymphoblastic leukemia. *Nat Med*. 21, 1182-1189. <https://doi.org/10.1038/nm.3955>
- Hertweck, K.L., Dasgupta, S., 2017. The Landscape of mtDNA Modifications in Cancer: A Tale of Two Cities. *Front Oncol*. 7, 262. <https://doi.org/10.3389/fonc.2017.00262>
- Hirpara, J., Eu, J.Q., Tan, J.K.M., Wong, A.L., Clement, M.-V., Kong, L.R., et al., 2019. Metabolic reprogramming of oncogene-addicted cancer cells to OXPHOS as a mechanism of drug resistance. *Redox Biol*. 25, 101076. <https://doi.org/10.1016/j.redox.2018.101076>
- Hjelmeland, A.B., Wu, Q., Heddlestone, J.M., Choudhary, G.S., MacSwords, J., Lathia, J.D., et al., 2011. Acidic stress promotes a glioma stem cell phenotype. *Cell Death Differ*. 18, 829-840. <https://doi.org/10.1038/cdd.2010.150>
- Ho, P.-C., Bihuniak, J.D., Macintyre, A.N., Staron, M., Liu, X., Amezquita, R., et al., 2015. Phosphoenolpyruvate Is a Metabolic Checkpoint of Antitumor T Cell Responses. *Cell*. 162, 1217-1228. <https://doi.org/10.1016/j.cell.2015.08.012>
- Hoang-Minh, L.B., Siebzehnrubl, F.A., Yang, C., Suzuki-Hatano, S., Dajac, K., Loche, T., et al., 2018. Infiltrative and drug-resistant slow-cycling cells support metabolic heterogeneity in glioblastoma. *EMBO J*. 37, e98772. <https://doi.org/10.15252/embj.201798772>
- Holmgaard, R.B., Zamarin, D., Li, Y., Gasmir, B., Munn, D.H., Allison, J.P., et al., 2015. Tumor-Expressed IDO Recruits and Activates MDSCs in a Treg-Dependent Manner. *Cell Rep*. 13, 412-424. <https://doi.org/10.1016/j.celrep.2015.08.077>
- Hossian, A.K.M.N., Zahra, F.T., Poudel, S., Abshire, C.F., Polk, P., Garai, J., et al., 2021. Advanced bioinformatic analysis and pathway prediction of NSCLC cells upon cisplatin resistance. *Sci Rep*. 11, 6520. <https://doi.org/10.1038/s41598-021-85930-y>
- Huang, G., Zhao, T., Wang, C., Nham, K., Xiong, Y., Gao, X., et al., 2020a. PET imaging of occult tumours by temporal integration of tumor-acidosis signals from pH-sensitive <sup>64</sup>Cu-labelled polymers. *Nat Biomed Eng*. 4, 314-324. <https://doi.org/10.1038/s41551-019-0416-1>

- Huang, L., Wang, L., Hu, X., Chen, S., Tao, Y., Su, H., et al., 2020b. Machine learning of serum metabolic patterns encodes early-stage lung adenocarcinoma. *Nat Commun.* 11, 3556. <https://doi.org/10.1038/s41467-020-17347-6>
- Hui, S., Ghergurovich, J.M., Morscher, R.J., Jang, C., Teng, X., Lu, W., et al., 2017. Glucose feeds the TCA cycle via circulating lactate. *Nature.* 551, 115-118.
- Hulea, L., Gravel, S.-P., Morita, M., Cargnello, M., Uchenunu, O., Im, Y.K., et al., 2018. Translational and HIF-1 $\alpha$ -Dependent Metabolic Reprogramming Underpin Metabolic Plasticity and Responses to Kinase Inhibitors and Biguanides. *Cell Metab.* 28, 817-832. <https://doi.org/10.1016/j.cmet.2018.09.001>
- Hultsch, S., Kankainen, M., Paavolainen, L., Kovanen, R.-M., Ikonen, E., Kangaspeska, S., et al., 2018. Association of tamoxifen resistance and lipid reprogramming in breast cancer. *BMC Cancer.* 18, 850. <https://doi.org/10.1186/s12885-018-4757-z>
- Hutchinson, S.A., Websdale, A., Cioccoloni, G., Røberg-Larsen, H., Lianto, P., Kim, B., et al., 2021. Liver x receptor alpha drives chemoresistance in response to side-chain hydroxycholesterols in triple negative breast cancer. *Oncogene.* 40, 2872-2883. <https://doi.org/10.1038/s41388-021-01720-w>
- Iannelli, F., Roca, M.S., Lombardi, R., Ciardiello, C., Grumetti, L., De Rienzo, S., et al., 2020. Synergistic antitumor interaction of valproic acid and simvastatin sensitizes prostate cancer to docetaxel by targeting CSCs compartment via YAP inhibition. *J Exp Clin Cancer Res.* 39, 213. <https://doi.org/10.1186/s13046-020-01723-7>
- Intlekofer, A.M., Shih, A.H., Wang, B., Nazir, A., Rustenburg, A.S., Albanese, S.K., et al., 2018. Acquired resistance to IDH inhibition through trans or cis dimer-interface mutations. *Nature.* 559, 125-129. <https://doi.org/10.1038/s41586-018-0251-7>
- Ippolito, J.E., Brandenburg, M.W., Ge, X., Crowley, J.R., Kirmess, K.M., Som, A., et al., 2016. Extracellular pH Modulates Neuroendocrine Prostate Cancer Cell Metabolism and Susceptibility to the Mitochondrial Inhibitor Niclosamide. *PLoS One.* 11, e0159675. <https://doi.org/10.1371/journal.pone.0159675>
- Issaq, S.H., Heske, C.M., 2020. Targeting metabolic dependencies in pediatric cancer. *Curr Opin Pediatr.* 32, 26-34. doi: 10.1097/MOP.0000000000000853
- Iwamoto, H., Abe, M., Yang, Y., Cui, D., Seki, T., Nakamura, M., et al., 2018. Cancer Lipid Metabolism Confers Antiangiogenic Drug Resistance. *Cell Metab.* 28, 104-117. <https://doi.org/10.1016/j.cmet.2018.05.005>
- Jayaprakash, P., Ai, M., Liu, A., Budhani, P., Bartkowiak, T., Sheng, J., et al., 2018. Targeted hypoxia reduction restores T cell infiltration and sensitizes prostate cancer to immunotherapy. *J Clin Invest.* 128, 5137-5149. <https://doi.org/10.1172/JCI96268>
- Jensen, S.A., Calvert, A.E., Volpert, G., Kouri, F.M., Hurley, L.A., Luciano, J.P., et al., 2014. Bcl2L13 is a ceramide synthase inhibitor in glioblastoma. *Proc Natl Acad Sci USA.* 111, 5682-5687. <https://doi.org/10.1073/pnas.1316700111>
- Jiménez-Valerio, G., Martínez-Lozano, M., Bassani, N., Vidal, A., Ochoa-de-Olza, M., Suárez, C., et al., 2016. Resistance to Antiangiogenic Therapies by Metabolic Symbiosis in Renal Cell Carcinoma PDX Models and Patients. *Cell Rep.* 15, 1134-1143. <https://doi.org/10.1016/j.celrep.2016.04.015>
- Jin, L., Zhu, L.-Y., Pan, Y.-L., Fu, H.-Q., Zhang, J., 2021a. Prothymosin  $\alpha$  promotes colorectal carcinoma chemoresistance through inducing lipid droplet accumulation. *Mitochondrion.* 59, 123-134. <https://doi.org/10.1016/j.mito.2021.04.001>

- Jin, Z., Lu, Y., Wu, X., Pan, T., Yu, Z., Hou, J., et al., 2021b. The cross-talk between tumor cells and activated fibroblasts mediated by lactate/BDNF/TrkB signaling promotes acquired resistance to anlotinib in human gastric cancer. *Redox Biol.* 46, 102076. <https://doi.org/10.1016/j.redox.2021.102076>
- Johnston, K., Pachnis, P., Tasdogan, A., Faubert, B., Zacharias, L.G., Vu, H.S., et al., 2021. Isotope tracing reveals glycolysis and oxidative metabolism in childhood tumors of multiple histologies. *Med (N Y)*. 2, 395-410. doi: 10.1016/j.medj.2021.01.002
- Joyce, H., McCann, A., Clynes, M., Larkin, A., 2015. Influence of multidrug resistance and drug transport proteins on chemotherapy drug metabolism. *Expert Opin Drug Metab Toxicol.* 11, 795-809. <https://doi.org/10.1517/17425255.2015.1028356>
- Ju, Y.S., Alexandrov, L.B., Gerstung, M., Martincorena, I., Nik-Zainal, S., Ramakrishna, M., et al., 2014. Origins and functional consequences of somatic mitochondrial DNA mutations in human cancer. *eLife*. 3, e02935. <https://doi.org/10.7554/eLife.02935.001>
- Kadel, D., Zhang, Y., Sun, H.R., Zhao, Y., Dong, Q.Z., Qin, L. X., 2019. Current perspectives of cancer-associated fibroblast in therapeutic resistance: potential mechanism and future strategy. *Cell Bio Toxicol.* 35, 407-421. <https://doi.org/10.1007/s10565-019-09461-z>
- Kanarek, N., Keys, H.R., Cantor, J.R., Lewis, C.A., Chan, S.H., Kunchok, T., et al., 2018. Histidine catabolism is a major determinant of methotrexate sensitivity. *Nature*. 559, 632-636. <https://doi.org/10.1038/s41586-018-0316-7>
- Kant, S., Kumar, A., Singh, S.M., 2014. Tumor growth retardation and chemosensitizing action of fatty acid synthase inhibitor orlistat on T cell lymphoma: Implication of reconstituted tumor microenvironment and multidrug resistance phenotype. *Biochim Biophys Acta.* 1840, 294-302. <https://doi.org/10.1016/j.bbagen.2013.09.020>
- Kaoutari, A.E., Fraunhofer, N.A., Hoare, O., Teyssedou, C., Soubeyran, P., Gayet, O., et al., 2021. Metabolomic profiling of pancreatic adenocarcinoma reveals key features driving clinical outcome and drug resistance. *EBioMedicine.* 66, 103332. <https://doi.org/10.1016/j.ebiom.2021.103332>
- Kausar, S., Wang, F., Cui, H., 2020. The Role of Mitochondria in Reactive Oxygen Species Generation and Its Implications for Neurodegenerative Diseases. *Cells*. 7, 274.
- Kennedy, L., Sandhu, J.K., Harper, M.-E., Cuperlovic-Culf, M., 2020. Role of Glutathione in Cancer: From Mechanisms to Therapies. *Biomolecules.* 10, 1429. <https://doi.org/10.3390/biom10101429>
- Khacho, M., Tarabay, M., Patten, D., Khacho, P., MacLaurin, J.G., Guadagno, J., et al., 2014. Acidosis overrides oxygen deprivation to maintain mitochondrial function and cell survival. *Nat Commun.* 5, 3550. <https://doi.org/10.1038/ncomms4550>
- Kim, J.-w., Tchernyshyov, I., Semenza, G.L., Dang, C.V., 2006. HIF-1-mediated expression of pyruvate dehydrogenase kinase: A metabolic switch required for cellular adaptation to hypoxia. *Cell Metab.* 3, 177-185. <https://doi.org/10.1016/j.cmet.2006.02.002>
- Kim, M.-J., Choi, Y.-K., Park, S.Y., Jang, S.Y., Lee, J.Y., Ham, H.J., et al., 2017. PPAR $\delta$  Reprograms Glutamine Metabolism in Sorafenib-Resistant HCC. *Mol Cancer Res.* 15, 1230-1242. <https://doi.org/10.1158/1541-7786.MCR-17-0061>
- Kim, S., Lee, M., Dhanasekaran, D.N., Song, Y.S., 2018. Activation of LXRA/ $\beta$  by cholesterol in malignant ascites promotes chemoresistance in ovarian cancer. *BMC Cancer.* 18, 1232. <https://doi.org/10.1186/s12885-018-5152-5>

- Kim, S.J., Kim, H.S., Seo, Y.R., 2019. Understanding of ROS-Inducing Strategy in Anticancer Therapy. *Oxid Med Cell Longev.* 2019, 5381692. <https://doi.org/10.1155/2019/5381692>
- Kohler, C., Radpour, R., Barekati, Z., Asadollahi, R., Bitzer, J., Wight, E., et al., 2009. Levels of plasma circulating cell free nuclear and mitochondrial DNA as potential biomarkers for breast tumors. *Mol Cancer.* 8, 105. <https://doi.org/10.1186/1476-4598-8-105>
- Kolosenko, I., Avnet, S., Baldini, N., Viklund, J., De Milito, A., 2017. Therapeutic implications of tumor interstitial acidification. *Semin Cancer Biol.* 43, 119-133. <https://doi.org/10.1016/j.semcancer.2017.01.008>
- Komurov, K., Tseng, J.-T., Muller, M., Seviour, E.G., Moss, T.J., Yang, L., et al., 2012. The glucose-deprivation network counteracts lapatinib-induced toxicity in resistant ErbB2-positive breast cancer cells. *Mol Syst Biol.* 8, 596. <https://doi.org/10.1038/msb.2012.25>
- Kon, E., Benhar, I., 2019. Immune checkpoint inhibitor combinations: Current efforts and important aspects for success. *Drug resist update.* 45, 13–29. <https://doi.org/10.1016/j.drup.2019.07.004>
- Kopecka, J., Campia, I., Jacobs, A., Frei, A.P., Ghigo, D., Wollscheid, B., et al., 2015. Carbonic anhydrase XII is a new therapeutic target to overcome chemoresistance in cancer cells. *Oncotarget.* 6, 6776-6793. <https://doi.org/10.18632/oncotarget.2882>
- Kopecka, J., Campia, I., Olivero, P., Pescarmona, G., Ghigo, D., Bosia, A., et al., 2011. A LDL-masked liposomal-doxorubicin reverses drug resistance in human cancer cells. *J Control Release.* 149, 196-205. <https://doi.org/10.1016/j.jconrel.2010.10.003>
- Kopecka, J., Gazzano, E., Castella, B., Salaroglio, I.C., Mungo, E., Massaia, M., et al., 2020a. Mitochondrial metabolism: Inducer or therapeutic target in tumor immune-resistance? *Semin Cell Dev Biol.* 98, 80-89. <https://doi.org/10.1016/j.semcdb.2019.05.008>
- Kopecka, J., Porto, S., Lusa, S., Gazzano, E., Salzano, G., Pinzòn-Daza, M.L., et al., 2016. Zoledronic acid-encapsulating self-assembling nanoparticles and doxorubicin: a combinatorial approach to overcome simultaneously chemoresistance and immunoresistance in breast tumors. *Oncotarget.* 7, 20753-20772. <https://doi.org/10.18632/oncotarget.8012>
- Kopecka, J., Trouillas, P., Gašparović, A.Č., Gazzano, E., Assaraf, Y.G., Riganti, C., 2020b. Phospholipids and cholesterol: Inducers of cancer multidrug resistance and therapeutic targets. *Drug Resist Updat.* 49, 100670. <https://doi.org/10.1016/j.drup.2019.100670>
- Kuntz, E.M., Baquero, P., Michie, A.M., Dunn, K., Tardito, S., Holyoake, T.L., et al., 2017. Targeting mitochondrial oxidative phosphorylation eradicates therapy-resistant chronic myeloid leukemia stem cells. *Nat Med.* 23, 1234-1240. <https://doi.org/10.1038/nm.4399>
- Kuzu, O.F., Noory, M.A., Robertson, G.P., 2016. The Role of Cholesterol in Cancer. *Cancer Res.* 76, 2063-2070. <https://doi.org/10.1158/0008-5472.CAN-15-2613>
- Lagadinou, E.D., Sach, A., Callahan, K., Rossi, R.M., Neering, S.J., Minhajuddin, M., et al., 2013. BCL-2 Inhibition Targets Oxidative Phosphorylation and Selectively Eradicates Quiescent Human Leukemia Stem Cells. *Cell Stem Cell.* 12, 329-341. <https://doi.org/10.1016/j.stem.2012.12.013>
- LaMonte, G., Tang, X., Chen, J.L.-Y., Wu, J., Ding, C.-K.C., Keenan, M.M., et al., 2013. Acidosis induces reprogramming of cellular metabolism to mitigate oxidative stress. *Cancer Metab.* 1, 23. <https://doi.org/10.1186/2049-3002-1-23>

- Lapa, C., Garcia-Velloso, M.J., Lückcrath, K., Samnick, S., Schreder, M., Otero, P.R., et al., 2017. <sup>11</sup>C-Methionine-PET in Multiple Myeloma: A Combined Study from Two Different Institutions. *Theranostics*. 7, 2956-2964. <https://www.thno.org/v07p2956.htm>
- Lasfar, A., Balan, M., Cohen-Solal, K.A., Zloza, A., 2019. Editorial: Tumor Microenvironment and Resistance to Current Therapies. *Front Oncol*. 9, 1131. <https://doi.org/10.3389/fonc.2019.01131>
- Law, Z.J., Khoo, X.H., Lim, P.T., Goh, B.H., Ming, L.C., Lee, W.L., et al., 2021. Extracellular Vesicle-Mediated Chemoresistance in Oral Squamous Cell Carcinoma. *Front Mol Biosci*. 8, 629888. <https://doi.org/10.3389/fmolb.2021.629888>
- Lee, J.-H., Liu, R., Li, J., Wang, Y., Tan, L., Li, X.-J., et al., 2018. EGFR-Phosphorylated Platelet Isoform of Phosphofructokinase 1 Promotes PI3K Activation. *Mol Cell*. 70, 197-210. <https://doi.org/10.1016/j.molcel.2018.03.018>
- Lee, K.-m., Giltane, J.M., Balko, J.M., Schwarz, L.J., Guerrero-Zotano, A.L., Hutchinson, K.E., et al., 2017. MYC and MCL1 Cooperatively Promote Chemotherapy-Resistant Breast Cancer Stem Cells via Regulation of Mitochondrial Oxidative Phosphorylation. *Cell Metab*. 26, 633-647. <https://doi.org/10.1016/j.cmet.2017.09.009>
- Lehuédé, C., Li, X., Dauvillier, S., Vaysse, C., Franchet, C., Clement, E., et al., 2019. Adipocytes promote breast cancer resistance to chemotherapy, a process amplified by obesity: Role of the major vault protein (MVP). *Breast Cancer Res*. 21, 7. <https://doi.org/10.1186/s13058-018-1088-6>
- Lemos, H., Huang, L., Prendergast, G.C., Mellor, A.L., 2019. Immune control by amino acid catabolism during tumorigenesis and therapy. *Nat Rev Cancer*. 19, 162-175. <https://doi.org/10.1038/s41568-019-0106-z>
- Leonetti, A., Wever, B., Mazzaschi, G., Assaraf, Y. G., Rolfo, C., Quaini, et al., 2019. Molecular basis and rationale for combining immune checkpoint inhibitors with chemotherapy in non-small cell lung cancer. *Drug resist update*. 46, 100644. <https://doi.org/10.1016/j.drug.2019.100644>
- Levin, M., Stark, M., Berman, B., Assaraf, Y. G., 2019. Surmounting Cytarabine-resistance in acute myeloblastic leukemia cells and specimens with a synergistic combination of hydroxyurea and azidothymidine. *Cell Death Dis*. 10, 390. <https://doi.org/10.1038/s41419-019-1626-x>
- Lewis, J.E., Kemp, M.L., 2021. Integration of machine learning and genome-scale metabolic modeling identifies multi-omics biomarkers for radiation resistance. *Nat Commun*. 12, 2700. <https://doi.org/10.1038/s41467-021-22989-1>
- Li, W., Zhang, H., Assaraf, Y. G., Zhao, K., Xu, X., Xie, J., et al., 2016. Overcoming ABC transporter-mediated multidrug resistance: Molecular mechanisms and novel therapeutic drug strategies. *Drug resist update*. 27, 14–29. <https://doi.org/10.1016/j.drug.2016.05.001>
- Li, Y., Wang, Z., Ajani, J.A., Song, S., 2021. Drug resistance and Cancer stem cells. *Cell commun signal*. 19, 19. <https://doi.org/10.1186/s12964-020-00627-5>
- Liao, Y.-P., Schae, D., McBride, W.H., 2007. Modification of the tumor microenvironment to enhance immunity. *Front Biosci*. 12, 3576-3600. doi: 10.2741/2336
- Lièvre, A., Chapusot, C., Bouvier, A.-M., Zinzindohoué, F., Piard, F., Rognot, P., et al., 2005. Clinical Value of Mitochondrial Mutations in Colorectal Cancer. *J Clin Oncol*. 23, 3517-3525. DOI: 10.1200/JCO.2005.07.044

- Lima, R.T., Busacca, S., Almeida, G.M., Gaudino, G., Fennell, D.A., Vasconcelos, M.H., 2011. MicroRNA regulation of core apoptosis pathways in cancer. *Eur J cancer*. 47, 163-174. <https://doi.org/10.1016/j.ejca.2010.11.005>
- Lima, R.T., Martins, L.M., Guimarães, J.E., Sambade, C., Vasconcelos, M.H., 2004. Specific downregulation of bcl-2 and XIAP by RNAi enhances the effects of chemotherapeutic agents in MCF-7 human breast cancer cells. *Cancer Gene Ther*. 11, 309-316. <https://doi.org/10.1038/sj.cgt.7700706>
- Liu, J., Pan, C., Guo, L., Wu, M., Guo, J., Peng, S., et al., 2016. A new mechanism of trastuzumab resistance in gastric cancer: MACC1 promotes the Warburg effect via activation of the PI3K/AKT signaling pathway. *J Hematol Oncol*. 9, 76. <https://doi.org/10.1186/s13045-016-0302-1>
- Liu, R., Chen, Y., Liu, G., Li, C., Song, Y., Cao, Z., et al., 2020. PI3K/AKT pathway as a key link modulates the multidrug resistance of cancers. *Cell Death Dis*. 11, 797. <https://doi.org/10.1038/s41419-020-02998-6>
- Liu, T., Zhou, L., Li, D., Andl, T., Zhang, Y., 2019. Cancer-Associated Fibroblasts Build and Secure the Tumor Microenvironment. *Front Cell Dev Biol*. 7. <https://doi.org/10.3389/fcell.2019.00060>
- Lo, M., Ling, V., Wang, Y.Z., Gout, P.W., 2008. The xc<sup>-</sup> cystine/glutamate antiporter: a mediator of pancreatic cancer growth with a role in drug resistance. *Br J Cancer*. 99, 464-472. <https://doi.org/10.1038/sj.bjc.6604485>
- Loayza-Puch, F., Rooijers, K., Buil, L.C.M., Zijlstra, J., Oude Vrielink, J.F., Lopes, R., et al., 2016. Tumor-specific proline vulnerability uncovered by differential ribosome codon reading. *Nature*. 530, 490-494. <https://doi.org/10.1038/nature16982>
- Logozzi, M., Mizzone, D., Angelini, D.F., Di Raimo, R., Falchi, M., Battistini, L., Fais, S., 2018. Microenvironmental pH and Exosome Levels Interplay in Human Cancer Cell Lines of Different Histotypes. *Cancers*. 10, 370. <https://doi.org/10.3390/cancers10100370>
- Long, Y., Tao, H., Karachi, A., Grippin, A.J., Jin, L., Chang, Y., et al., 2020. Dysregulation of Glutamate Transport Enhances Treg Function That Promotes VEGF Blockade Resistance in Glioblastoma. *Cancer Res*. 80, 499-509. <https://doi.org/10.1158/0008-5472.CAN-19-1577>
- Lozupone, F., Borghi, M., Marzoli, F., Azzarito, T., Matarrese, P., et al., 2015. TM9SF4 is a novel V-ATPase-interacting protein that modulates tumor pH alterations associated with drug resistance and invasiveness of colon cancer cells. *Oncogene*. 34, 5163-5174. <https://doi.org/10.1038/onc.2014.437>
- Lu, C.-W., Lin, S.-C., Chen, K.-F., Lai, Y.-Y., Tsai, S.-J., 2008. Induction of Pyruvate Dehydrogenase Kinase-3 by Hypoxia-inducible Factor-1 Promotes Metabolic Switch and Drug Resistance. *J Biol Chem*. 283, 28106-28114. <https://doi.org/10.1074/jbc.M803508200>
- Lu, Y., Yang, Y., Liu, Y., Hao, Y., Zhang, Y., Hu, Y., et al., 2017. Upregulation of PAG1/Cbp contributes to adipose-derived mesenchymal stem cells promoted tumor progression and chemoresistance in breast cancer. *Biochem Biophys Res Commun*. 494, 719-727. <https://doi.org/10.1016/j.bbrc.2017.10.118>
- Luengo, A., Gui, D.Y., Vander Heiden, M.G., 2017. Targeting Metabolism for Cancer Therapy. *Cell Chem Biol*. 24, 1161-1180. <https://doi.org/10.1016/j.chembiol.2017.08.028>
- Maher, E.A., Marin-Valencia, I., Bachoo, R.M., Mashimo, T., Raisanen, J., Hatanpaa, K.J., et al., 2012. Metabolism of [U-13C]glucose in human brain tumors in vivo. *NMR Biomed*. 25, 1234-1244. <https://doi.org/10.1002/nbm.2794>

- Marchiq, I., Pouysségur, J., 2016. Hypoxia, cancer metabolism and the therapeutic benefit of targeting lactate/H(+) symporters. *J Mol Med.* 94, 155-171. doi: 10.1007/s00109-015-1307-x
- Marcucci, F., Rumio, C., 2021. Glycolysis-induced drug resistance in tumors—A response to danger signals? *Neoplasia.* 23, 234-245. <https://doi.org/10.1016/j.neo.2020.12.009>
- Marengo, B., Garbarino, O., Speciale, A., Monteleone, L., Traverso, N., Domenicotti, C., 2019. MYC Expression and Metabolic Redox Changes in Cancer Cells: A Synergy Able to Induce Chemoresistance. *Oxid Med Cell Longev.* 2019, 7346492. <https://doi.org/10.1155/2019/7346492>
- Marine, J.-C., Dawson, S.-J., Dawson, M.A., 2020. Non-genetic mechanisms of therapeutic resistance in cancer. *Nat Rev Cancer.* 20, 743-756. <https://doi.org/10.1038/s41568-020-00302-4>
- Marlein, C.R., Zaitseva, L., Piddock, R.E., Robinson, S.D., Edwards, D.R., Shafat, M.S., et al., 2017. NADPH oxidase-2 derived superoxide drives mitochondrial transfer from bone marrow stromal cells to leukemic blasts. *Blood.* 130, 1649-1660. <https://doi.org/10.1182/blood-2017-03-772939>
- Martinez-Outschoorn, U.E., Peiris-Pagés, M., Pestell, R.G., Sotgia, F., Lisanti, M.P., 2017. Cancer metabolism: a therapeutic perspective. *Nat Rev Clin Oncol.* 14, 11-31. <https://doi.org/10.1038/nrclinonc.2016.60>
- Masamha, C.P., LaFontaine, P., 2018. Molecular targeting of glutaminase sensitizes ovarian cancer cells to chemotherapy. *J Cell Biochem.* 119, 6136-6145. <https://doi.org/10.1002/jcb.26814>
- Mashimo, T., Pichumani, K., Vemireddy, V., Hatanpaa, K.J., Singh, D.K., Sirasanagandla, S., et al., 2014. Acetate Is a Bioenergetic Substrate for Human Glioblastoma and Brain Metastases. *Cell.* 159, 1603-1614. <https://doi.org/10.1016/j.cell.2014.11.025>
- Matassa, D.S., Amoroso, M.R., Lu, H., Avolio, R., Arzeni, D., et al., 2016. Oxidative metabolism drives inflammation-induced platinum resistance in human ovarian cancer. *Cell Death Differ.* 23, 1542-1554. <https://doi.org/10.1038/cdd.2016.39>
- Matés, J.M., Di Paola, F.J., Campos-Sandoval, J.A., Mazurek, S., Márquez, J., 2020. Therapeutic targeting of glutaminolysis as an essential strategy to combat cancer. *Semin Cell Dev Biol.* 98, 34-43. <https://doi.org/10.1016/j.semcdb.2019.05.012>
- Matula, Z., Mikala, G., Lukácsi, S., Matkó, J., Kovács, T., Monostori, É., et al., 2021. Stromal Cells Serve Drug Resistance for Multiple Myeloma via Mitochondrial Transfer: A Study on Primary Myeloma and Stromal Cells. *Cancers.* 13, 3461. <https://doi.org/10.3390/cancers13143461>
- Mavrakis, K.J., McDonald, E.R., Schlabach, M.R., Billy, E., Hoffman, G.R., deWeck, A., et al., 2016. Disordered methionine metabolism in MTAP/CDKN2A-deleted cancers leads to dependence on PRMT5. *Science.* 351, 1208-1213. <https://doi.org/10.1126/science.aad5944>
- McCann, C., Kerr, E.M., 2021. Metabolic Reprogramming: A Friend or Foe to Cancer Therapy? *Cancers.* 13, 3351. <https://doi.org/10.3390/cancers13133351>
- McGuirk, S., Audet-Delage, Y., Annis, M.G., Xue, Y., Vernier, M., Zhao, K., et al., 2021. Resistance to different anthracycline chemotherapeutics elicits distinct and actionable primary metabolic dependencies in breast cancer. *eLife.* 10, e65150. doi: 10.7554/eLife.65150
- McGuirk, S., Audet-Delage, Y., St-Pierre, J., 2020. Metabolic Fitness and Plasticity in Cancer Progression. *Trends Cancer.* 6, 49-61. <https://doi.org/10.1016/j.trecan.2019.11.009>

- Méndez-Lucas, A., Lin, W., Driscoll, P.C., Legrave, N., Novellasdemunt, L., Xie, C., et al., 2020. Identifying strategies to target the metabolic flexibility of tumours. *Nat Metab.* 2, 335-350. <https://doi.org/10.1038/s42255-020-0195-8>
- Mentoor, I., Engelbrecht, A.-M., van Jaarsveld, P.J., Nell, T., 2018. Chemoresistance: Intricate Interplay Between Breast Tumor Cells and Adipocytes in the Tumor Microenvironment. *Front Endocrinol.* 9, 758. <https://doi.org/10.3389/fendo.2018.00758>
- Michaud, L., Touijer, K.A., Manguen, A., Zelefsky, M.J., Morris, M.J., Lyashchenko, S.K., et al., 2020. <sup>11</sup>C-Choline PET/CT in Recurrent Prostate Cancer: Retrospective Analysis in a Large U.S. Patient Series. *J Nucl Med.* 61, 827-833. <https://doi.org/10.2967/jnumed.119.233098>
- Minami, K., Ueda, N., Ishimoto, K., Tsujiuchi, T., 2020. Lysophosphatidic acid receptor-2 (LPA2)-mediated signaling enhances chemoresistance in melanoma cells treated with anticancer drugs. *Mol Cell Biochem.* 469, 89-95. <https://doi.org/10.1007/s11010-020-03730-w>
- Minami, K., Ueda, N., Maeda, H., Ishimoto, K., Otagaki, S., Tsujiuchi, T., 2019. Modulation of chemoresistance by lysophosphatidic acid (LPA) signaling through LPA5 in melanoma cells treated with anticancer drugs. *Biochem Biophys Res Commun.* 517, 359-363. <https://doi.org/10.1016/j.bbrc.2019.07.092>
- Miraglia, E., Viarisio, D., Riganti, C., Costamagna, C., Ghigo, D., Bosia, A., 2005. Na<sup>+</sup>/H<sup>+</sup> exchanger activity is increased in doxorubicin-resistant human colon cancer cells and its modulation modifies the sensitivity of the cells to doxorubicin. *Int J Cancer.* 115, 924-929. <https://doi.org/10.1002/ijc.20959>
- Molina, J.R., Sun, Y., Protopopova, M., Gera, S., Bandi, M., Bristow, C., et al., 2018. An inhibitor of oxidative phosphorylation exploits cancer vulnerability. *Nat Med.* 24, 1036-1046. <https://doi.org/10.1038/s41591-018-0052-4>
- Momcilovic, M., Bailey, S.T., Lee, J.T., Fishbein, M.C., Braas, D., Go, J., et al., 2018. The GSK3 Signaling Axis Regulates Adaptive Glutamine Metabolism in Lung Squamous Cell Carcinoma. *Cancer Cell.* 33, 905-921. <https://doi.org/10.1016/j.ccell.2018.04.002>
- Mondal, S., Roy, D., Bhattacharya, S.S., Jin, L., Jung, D., Zhang, S., et al., 2019. Therapeutic targeting of PFKFB3 with a novel glycolytic inhibitor PFK158 promotes lipophagy and chemosensitivity in gynecologic cancers. *Int J Cancer.* 144, 178-189. <https://doi.org/10.1002/ijc.31868>
- Montrose, D.C., Saha, S., Foronda, M., McNally, E.M., Chen, J., Zhou, X.K., et al., 2021. Exogenous and Endogenous Sources of Serine Contribute to Colon Cancer Metabolism, Growth, and Resistance to 5-Fluorouracil. *Cancer Res.* 81, 2275-2288. <https://doi.org/10.1158/0008-5472.CAN-20-1541>
- Morotti, M., Bridges, E., Valli, A., Choudhry, H., Sheldon, H., Wigfield, S., et al., 2019. Hypoxia-induced switch in SNAT2/SLC38A2 regulation generates endocrine resistance in breast cancer. *Proc Natl Acad Sci USA.* 116, 12452-12461. <https://doi.org/10.1073/pnas.1818521116>
- Moschoi, R., Imbert, V., Nebout, M., Chiche, J., Mary, D., Prebet, T., et al., 2016. Protective mitochondrial transfer from bone marrow stromal cells to acute myeloid leukemic cells during chemotherapy. *Blood.* 128, 253-264. <https://doi.org/10.1182/blood-2015-07-655860>
- Mujumdar, P., Kopecka, J., Bua, S., Supuran, C.T., Riganti, C., Poulsen, S.-A., 2019. Carbonic Anhydrase XII Inhibitors Overcome Temozolomide Resistance in Glioblastoma. *J Med Chem.* 62, 4174-4192. <https://doi.org/10.1021/acs.jmedchem.9b00282>
- Mukhopadhyay, S., Goswami, D., Adisheshaiah, P.P., Burgan, W., Yi, M., Guerin, T.M., et al., 2020. Undermining Glutaminolysis Bolsters Chemotherapy While NRF2 Promotes Chemoresistance in KRAS-

- Driven Pancreatic Cancers. *Cancer Res.* 80, 1630-1643. <https://doi.org/10.1158/0008-5472.CAN-19-1363>
- Muller, F.L., Aquilanti, E.A., DePinho, R.A., 2015. Collateral Lethality: A new therapeutic strategy in oncology. *Trends Cancer.* 1, 161-173. doi: 10.1016/j.trecan.2015.10.002
- Muller, F.L., Colla, S., Aquilanti, E., Manzo, V.E., Genovese, G., Lee, J., et al., 2012. Passenger deletions generate therapeutic vulnerabilities in cancer. *Nature.* 488, 337-342. <https://doi.org/10.1038/nature11331>
- Murphy, R.A., Mourtzakis, M., Chu, Q.S.C., Baracos, V.E., Reiman, T., Mazurak, V.C., 2011. Supplementation with fish oil increases first-line chemotherapy efficacy in patients with advanced nonsmall cell lung cancer. *Cancer.* 117, 3774-3780. <https://doi.org/10.1002/cncr.25933>
- Najjar, Y.G., Menk, A.V., Sander, C., Rao, U., Karunamurthy, A., Bhatia, R., et al., 2019. Tumor cell oxidative metabolism as a barrier to PD-1 blockade immunotherapy in melanoma. *JCI Insight.* 4, e124989. <https://doi.org/10.1172/jci.insight.124989>
- Namee, N.M., O'Driscoll, L., 2018. Extracellular vesicles and anticancer drug resistance. *Biochim Biophys Acta Rev Cancer.* 1870, 123-136. <https://doi.org/10.1016/j.bbcan.2018.07.003>
- Ngoi, N.Y.L., Eu, J.Q., Hirpara, J., Wang, L., Lim, J.S.J., Lee, S.-C., et al., 2019. Targeting Cell Metabolism as Cancer Therapy. *Antioxid Redox Signal.* 32, 285-308. <https://doi.org/10.1089/ars.2019.7947>
- Noguchi, F., Inui, S., Fedele, C., Shackleton, M., Itami, S., 2017. Calcium-Dependent Enhancement by Extracellular Acidity of the Cytotoxicity of Mitochondrial Inhibitors against Melanoma. *Mol Cancer Ther.* 16, 936-947. <https://doi.org/10.1158/1535-7163.MCT-15-0235>
- Obriest, F., Michels, J., Durand, S., Chery, A., Pol, J., Levesque, S., et al., 2018. Metabolic vulnerability of cisplatin-resistant cancers. *EMBO J.* 37, e98597. <https://doi.org/10.15252/embj.201798597>
- Olivier, C., Oliver, L., Lalier, L., Vallette, F.M., 2021. Drug Resistance in Glioblastoma: The Two Faces of Oxidative Stress. *Front Mol Biosci.* 7, 620677. <https://doi.org/10.3389/fmolb.2020.620677>
- Ordway, B., Tomaszewski, M., Byrne, S., Abrahams, D., Swietach, P., Gillies, R.J., et al., 2021. Targeting of Evolutionarily Acquired Cancer Cell Phenotype by Exploiting pH-Metabolic Vulnerabilities. *Cancers.* 13, 64. <https://doi.org/10.3390/cancers13010064>
- Oshima, N., Ishida, R., Kishimoto, S., Beebe, K., Brender, J.R., Yamamoto, K., et al., 2020. Dynamic Imaging of LDH Inhibition in Tumors Reveals Rapid *In Vivo* Metabolic Rewiring and Vulnerability to Combination Therapy. *Cell Rep.* 30, 1798-1810. <https://doi.org/10.1016/j.celrep.2020.01.039>
- Osswald, M., Jung, E., Sahm, F., Solecki, G., Venkataramani, V., Blaes, J., et al., 2015. Brain tumor cells interconnect to a functional and resistant network. *Nature.* 528, 93-98. <https://doi.org/10.1038/nature16071>
- Ozyerli-Goknar, E., Bagci-Onder, T., 2021. Epigenetic Deregulation of Apoptosis in Cancers. *Cancers (Basel).* 13, 3210. <https://doi.org/10.3390/cancers13133210>
- Papaevangelou, E., Almeida, G.S., Box, C., deSouza, N.M., Chung, Y.-L., 2018. The effect of FASN inhibition on the growth and metabolism of a cisplatin-resistant ovarian carcinoma model. *Int J Cancer.* 143, 992-1002. <https://doi.org/10.1002/ijc.31392>

- Park, S., Chang, C.-Y., Safi, R., Liu, X., Baldi, R., Jasper, J.S., et al., 2016. ERR $\alpha$ -Regulated Lactate Metabolism Contributes to Resistance to Targeted Therapies in Breast Cancer. *Cell Rep.* 15, 323-335. <https://doi.org/10.1016/j.celrep.2016.03.026>
- Pasquier, J., Guerrouahen, B.S., Al Thawadi, H., Ghiabi, P., Maleki, M., Abu-Kaoud, N., et al., 2013. Preferential transfer of mitochondria from endothelial to cancer cells through tunneling nanotubes modulates chemoresistance. *J Transl Med.* 11, 94. <https://doi.org/10.1186/1479-5876-11-94>
- Pathak, R.K., Marrache, S., Harn, D.A., Dhar, S., 2014. Mito-DCA: A Mitochondria Targeted Molecular Scaffold for Efficacious Delivery of Metabolic Modulator Dichloroacetate. *ACS Chem Biol.* 9, 1178-1187. <https://doi.org/10.1021/cb400944y>
- Pellegrini, P., Dyczynski, M., Sbrana, F.V., Karlgren, M., Buoncervello, M., Hägg-Olofsson, M., et al., 2016. Tumor acidosis enhances cytotoxic effects and autophagy inhibition by salinomycin on cancer cell lines and cancer stem cells. *Oncotarget.* 7, 35703-35723. <https://doi.org/10.18632/oncotarget.9601>
- Pepe, F., Pagotto, S., Soliman, S., Rossi, C., Lanuti, P., Braconi, C., et al., 2017. Regulation of miR-483-3p by the O-linked N-acetylglucosamine transferase links chemosensitivity to glucose metabolism in liver cancer cells. *Oncogenesis.* 6, e328-e328. <https://doi.org/10.1038/oncsis.2017.35>
- Pérez-Ruiz, E., Melero, I., Kopecka, J., Sarmiento-Ribeiro, A.B., García-Aranda, M., De Las Rivas, J., 2020. Cancer immunotherapy resistance based on immune checkpoints inhibitors: Targets, biomarkers, and remedies. *Drug Resist Updat.* 53, 100718. <https://doi.org/10.1016/j.drup.2020.100718>
- Pillai, S.R., Damaghi, M., Marunaka, Y., Spugnini, E.P., Fais, S., Gillies, R.J., 2019. Causes, consequences, and therapy of tumors acidosis. *Cancer Metastasis Rev.* 38, 205-222. <https://doi.org/10.1007/s10555-019-09792-7>
- Pisarsky, L., Bill, R., Fagiani, E., Dimeloe, S., Goosen, R.W., Hagmann, J., et al., 2016. Targeting Metabolic Symbiosis to Overcome Resistance to Antiangiogenic Therapy. *Cell Rep.* 15, 1161-1174. <https://doi.org/10.1016/j.celrep.2016.04.028>
- Polimeni, M., Voena, C., Kopecka, J., Riganti, C., Pescarmona, G., Bosia, A., et al., 2011. Modulation of doxorubicin resistance by the glucose-6-phosphate dehydrogenase activity. *Biochem J.* 439, 141-149. <https://doi.org/10.1042/BJ20102016>
- Qie, S., Yoshida, A., Parnham, S., Oleinik, N., Beeson, G.C., Beeson, C.C., et al., 2019. Targeting glutamine-addiction and overcoming CDK4/6 inhibitor resistance in human esophageal squamous cell carcinoma. *Nat Commun.* 10, 1296. <https://doi.org/10.1038/s41467-019-09179-w>
- Rahman, M., Hasan, M.R., 2015. Cancer Metabolism and Drug Resistance. *Metabolites.* 5, 571-600. <https://doi.org/10.3390/metabo5040571>
- Ralph, A.C.L., Valadão, I.C., Cardoso, E.C., Martins, V.R., Oliveira, L.M.S., Bevilacqua, E.M.A.F., et al., 2020. Environmental control of mammary carcinoma cell expansion by acidification and spheroid formation in vitro. *Sci Rep.* 10, 21959. <https://doi.org/10.1038/s41598-020-78989-6>
- Ramakrishnan, R., Assudani, D., Nagaraj, S., Hunter, T., Cho, H.-I., Antonia, S., et al., 2010. Chemotherapy enhances tumor cell susceptibility to CTL-mediated killing during cancer immunotherapy in mice. *J Clin Invest.* 120, 1111-1124. <https://doi.org/10.1172/JCI40269>
- Randall, E.C., Lopez, B.G.C., Peng, S., Regan, M.S., Abdelmoula, W.M., Basu, S.S., et al., 2020. Localized Metabolomic Gradients in Patient-Derived Xenograft Models of Glioblastoma. *Cancer Res.* 80, 1258-1267. <https://doi.org/10.1158/0008-5472.CAN-19-0638>

- Rashmi, R., Huang, X., Floberg, J.M., Elhammali, A.E., McCormick, M.L., Patti, G.J., et al., 2018. Radioresistant Cervical Cancers Are Sensitive to Inhibition of Glycolysis and Redox Metabolism. *Cancer Res.* 78, 1392-1403. <https://doi.org/10.1158/0008-5472.CAN-17-2367>
- Riganti, C., Kopecka, J., Panada, E., Barak, S., Rubinstein, M., et al., 2015. The role of C/EBP- $\beta$  LIP in multidrug resistance. *J Natl Cancer Inst.* 107, djv046. <https://doi.org/10.1093/jnci/djv046>
- Roberts, A.W., Davids, M.S., Pagel, J.M., Kahl, B.S., Puvvada, S.D., Gerecitano, J.F., et al., 2015. Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. *N Engl J Med.* 374, 311-322. doi: 10.1056/NEJMoa1513257
- Rojo de la Vega, M., Chapman, E., Zhang, D.D., 2018. NRF2 and the Hallmarks of Cancer. *Cancer Cell.* 34, 21-43. <https://doi.org/10.1016/j.ccell.2018.03.022>
- Roma-Rodrigues, C., Mendes, R., Baptista, P.V., Fernandes, A.R., 2019. Targeting Tumor Microenvironment for Cancer Therapy. *Int J Mol Sci.* 20, 840. <https://doi.org/10.3390/ijms20040840>
- Ross, K.C., Andrews, A.J., Marion, C.D., Yen, T.J., Bhattacharjee, V., 2017. Identification of the Serine Biosynthesis Pathway as a Critical Component of BRAF Inhibitor Resistance of Melanoma, Pancreatic, and Non-Small Cell Lung Cancer Cells. *Mol Cancer Ther.* 16, 1596-1609. <https://doi.org/10.1158/1535-7163.MCT-16-0798>
- Rubiño M. G., Carrillo E., Alcalá G. R., Domínguez-Martín A., Marchal J. A., Houria Boulaiz., 2019. Phenformin as an Anticancer Agent: Challenges and Prospects. *Int J Mol Sci.* 20 (13), 3316, 1-17. <https://doi.org/10.3390/ijms20133316>
- Ruprecht, B., Zaal, E.A., Zecha, J., Wu, W., Berkers, C.R., Kuster, B., Lemeer, S., 2017. Lapatinib Resistance in Breast Cancer Cells Is Accompanied by Phosphorylation-Mediated Reprogramming of Glycolysis. *Cancer Res.* 77, 1842-1853. <https://doi.org/10.1158/0008-5472.CAN-16-2976>
- Saha, S.K., Islam, S.M.R., Abdullah-AL-Wadud, M., Islam, S., Ali, F., Park, K.S., 2019. Multiomics Analysis Reveals that GLS and GLS2 Differentially Modulate the Clinical Outcomes of Cancer. *J Clin Med.* 8, 355. <https://doi.org/10.3390/jcm8030355>
- Salaroglio, I.C., Mujumdar, P., Annovazzi, L., Kopecka, J., Mellai, M., Schiffer, D., et al., 2018. Carbonic Anhydrase XII Inhibitors Overcome P-Glycoprotein-Mediated Resistance to Temozolomide in Glioblastoma. *Mol Cancer Ther.* 17, 2598-2609. <https://doi.org/10.1158/1535-7163.MCT-18-0533>
- Salaud, C., Alvarez-Arenas, A., Geraldo, F., Belmonte-Beitia, J., Calvo, G.F., Gratas, C., et al., 2020. Mitochondria transfer from tumor-activated stromal cells (TASC) to primary Glioblastoma cells. *Biochem Biophys Res Commun.* 533, 139-147. <https://doi.org/10.1016/j.bbrc.2020.08.101>
- Sanchez, W.Y., McGee, S.L., Connor, T., Mottram, B., Wilkinson, A., Whitehead, J.P., et al., 2013. Dichloroacetate inhibits aerobic glycolysis in multiple myeloma cells and increases sensitivity to bortezomib. *Br J Cancer.* 108, 1624-1633. <https://doi.org/10.1038/bjc.2013.120>
- Sancho, P., Burgos-Ramos, E., Tavera, A., Bou Kheir, T., Jagust, P., Schoenhals, M., et al., 2015. MYC/PGC-1 $\alpha$  Balance Determines the Metabolic Phenotype and Plasticity of Pancreatic Cancer Stem Cells. *Cell Metab.* 22, 590-605. <https://doi.org/10.1016/j.cmet.2015.08.015>
- Sansone, P., Savini, C., Kurelac, I., Chang, Q., Amato, L.B., Strillacci, A., et al., 2017. Packaging and transfer of mitochondrial DNA via exosomes regulate escape from dormancy in hormonal therapy-resistant breast cancer. *Proc Natl Acad Sci USA.* 114, E9066-E9075. <https://doi.org/10.1073/pnas.1704862114>

- Saraei, P., Asadi, I., Kakar, M.A., Moradi-Kor N., 2019. The beneficial effects of metformin on cancer prevention and therapy: a comprehensive review of recent advances. *Cancer Manag Res.* 11, 3295-3313. <https://doi.org/10.2147/CMAR.S200059>
- Sarmiento-Ribeiro, A.B., Proença, M.T., Sousa, I., Pereira, A., Guedes, F., et al., 2012. A possible role for oxidation stress in lymphoid leukaemias and therapeutic failure. *Leuk Res.* 36, 1041-1048. <https://doi.org/10.1016/j.leukres.2012.03.015>
- Sarmiento-Ribeiro, A.B., Scorilas, A., Gonçalves, A.C., Efferth, T., Trougakos, I.P., 2019. The emergence of drug resistance to targeted cancer therapies: Clinical evidence. *Drug Resist Updat.* 47, 100646. <https://doi.org/10.1016/j.drug.2019.100646>
- Sauvant, C., Nowak, M., Wirth, C., Schneider, B., Riemann, A., Gekle, M., Thews, O., 2008. Acidosis induces multi-drug resistance in rat prostate cancer cells (AT1) in vitro and in vivo by increasing the activity of the p-glycoprotein via activation of p38. *Int J Cancer.* 123, 2532-2542. <https://doi.org/10.1002/ijc.23818>
- Scalcon, V., Bindoli, A., Rigobello, M.P., 2018. Significance of the mitochondrial thioredoxin reductase in cancer cells: An update on role, targets and inhibitors. *Free Radic Biol Med.* 127, 62-79. <https://doi.org/10.1016/j.freeradbiomed.2018.03.043>
- Schell, J.C., Olson, K.A., Jiang, L., Hawkins, A.J., Van Vranken, J.G., Xie, J., et al., 2014. A Role for the Mitochondrial Pyruvate Carrier as a Repressor of the Warburg Effect and Colon Cancer Cell Growth. *Mol Cell.* 56, 400-413. <https://doi.org/10.1016/j.molcel.2014.09.026>
- Schlaepfer, I.R., Hitz, C.A., Gijón, M.A., Bergman, B.C., Eckel, R.H., Jacobsen, B.M., 2012. Progesterin modulates the lipid profile and sensitivity of breast cancer cells to docetaxel. *Mol Cell Endocrinol.* 363, 111-121. <https://doi.org/10.1016/j.mce.2012.08.005>
- Schoenfeld, A.J., Hellmann, M.D., 2020. Acquired Resistance to Immune Checkpoint Inhibitors. *Cancer Cell.* 37, 443-455. <https://doi.org/10.1016/j.ccell.2020.03.017>
- Sellers, K., Fox, M.P., Bousamra, M., Slone, S.P., Higashi, R.M., Miller, D.M., et al., 2015. Pyruvate carboxylase is critical for non-small-cell lung cancer proliferation. *J Clin Invest.* 125, 687-698. <https://doi.org/10.1172/JCI72873>
- Semenza, G.L., 2003. Targeting HIF-1 for cancer therapy. *Nat Rev Cancer.* 3, 721-732. <https://doi.org/10.1038/nrc1187>
- Sever, R., Brugge, J.S., 2015. Signal Transduction in Cancer. *Cold Spring Harb Perspect Med.* 5, a006098. doi: 10.1101/cshperspect.a006098
- Shah, R., Chen, S., 2020. Metabolic Signaling Cascades Prompted by Glutaminolysis in Cancer. *Cancers.* 12, 2624. <https://doi.org/10.3390/cancers12092624>
- Shanmugasundaram, K., Nayak, B.K., Friedrichs, W.E., Kaushik, D., Rodriguez, R., Block, K., 2017. NOX4 functions as a mitochondrial energetic sensor coupling cancer metabolic reprogramming to drug resistance. *Nat Commun.* 8, 997. <https://doi.org/10.1038/s41467-017-01106-1>
- Sharma, P., Hu-Lieskovan, S., Wargo, J.A., Ribas, A., 2017. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. *Cell.* 168, 707-723. <https://doi.org/10.1016/j.cell.2017.01.017>
- Sharon, D., Cathelin, S., Mirali, S., Di Trani, J.M., Yanofsky, D.J., Keon, K.A., et al., 2019. Inhibition of mitochondrial translation overcomes venetoclax resistance in AML through activation of the

- integrated stress response. *Sci Transl Med.* 11, eaax2863. <https://doi.org/10.1126/scitranslmed.aax2863>
- Shen, W., Xu, T., Chen, D., Tan, X., 2019. Targeting SREBP1 chemosensitizes colorectal cancer cells to gemcitabine by caspase-7 upregulation. *Bioengineered.* 10, 459-468. <https://doi.org/10.1080/21655979.2019.1676485>
- Shirai, Y., Chow, C.C.T., Kambe, G., Suwa, T., Kobayashi, M., Takahashi, I., et al., 2021. An Overview of the Recent Development of Anticancer Agents Targeting the HIF-1 Transcription Factor. *Cancers.* 13, 2813. <https://doi.org/10.3390/cancers13112813>
- Shojaei, S., Koleini, N., Samiei, E., Aghaei, M., Cole, L.K., Alizadeh, J., et al., 2020. Simvastatin increases temozolomide-induced cell death by targeting the fusion of autophagosomes and lysosomes. *FEBS J.* 287, 1005-1034. <https://doi.org/10.1111/febs.15069>
- Shukla, S.K., Purohit, V., Mehla, K., Gunda, V., Chaika, N.V., Vernucci, E., et al., 2017. MUC1 and HIF-1 $\alpha$  Signaling Crosstalk Induces Anabolic Glucose Metabolism to Impart Gemcitabine Resistance to Pancreatic Cancer. *Cancer Cell.* 32, 71-87. <https://doi.org/10.1016/j.ccell.2017.06.004>
- Sim, H.-W., Nejad, R., Zhang, W., Nassiri, F., Mason, W., Aldape, K.D., et al., 2019. Tissue 2-Hydroxyglutarate as a Biomarker for Isocitrate Dehydrogenase Mutations in Gliomas. *Clin Cancer Res.* 25, 3366-3373. <https://doi.org/10.1158/1078-0432.CCR-18-3205>
- Sinha, B.K., 2020. Role of Oxygen and Nitrogen Radicals in the Mechanism of Anticancer Drug Cytotoxicity. *J Cancer Sci Ther.* 12, 10-18.
- Sirois, I., Aguilar-Mahecha, A., Lafleur, J., Fowler, E., Vu, V., Scriver, M., et al., 2019. A Unique Morphological Phenotype in Chemoresistant Triple-Negative Breast Cancer Reveals Metabolic Reprogramming and PLIN4 Expression as a Molecular Vulnerability. *Mol Cancer Res.* 17, 2492-2507. <https://doi.org/10.1158/1541-7786.MCR-19-0264>
- Somme, F., Bender, L., Namer, I.J., Noël, G., Bund, C., 2020. Usefulness of <sup>18</sup>F-FDOPA PET for the management of primary brain tumors: a systematic review of the literature. *Cancer Imaging.* 20, 70. <https://doi.org/10.1186/s40644-020-00348-5>
- Song, I.S., Kim, H.K., Lee, S.R., Jeong, S.H., Kim, N., Ko, K.S., et al., 2013. Mitochondrial modulation decreases the bortezomib-resistance in multiple myeloma cells. *Int J Cancer.* 133, 1357-1367. <https://doi.org/10.1002/ijc.28149>
- Sonveaux, P., Végran, F., Schroeder, T., Wergin, M.C., Verrax, J., Rabbani, Z.N., et al., 2008. Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice. *J Clin Invest.* 118, 3930-3942. <https://doi.org/10.1172/JCI36843>
- Soriano, G.P., Besse, L., Li, N., Kraus, M., Besse, A., Meeuwenoord, N., et al., 2016. Proteasome inhibitor-adapted myeloma cells are largely independent from proteasome activity and show complex proteomic changes, in particular in redox and energy metabolism. *Leukemia.* 30, 2198-2207. <https://doi.org/10.1038/leu.2016.102>
- Sousa, C.M., Biancur, D.E., Wang, X., Halbrook, C.J., Sherman, M.H., Zhang, L., et al., 2016. Pancreatic stellate cells support tumor metabolism through autophagic alanine secretion. *Nature.* 536, 479-483. <https://doi.org/10.1038/nature19084>
- Sousa, D., Lima, R.T., Vasconcelos, M.H., 2015. Intercellular Transfer of Cancer Drug Resistance Traits by Extracellular Vesicles. *Trends Mol Med.* 21, 595-608. <https://doi.org/10.1016/j.molmed.2015.08.002>

- Spick, C., Herrmann, K., Czernin, J., 2016. Evaluation of Prostate Cancer with <sup>11</sup>C-Acetate PET/CT. *J Nucl Med.* 57, 30S-37S. <https://doi.org/10.2967/jnumed.115.169599>
- Stark, M., Silva, T., Levin, G., Machuqueiro, M., Assaraf, Y.G., 2020. The Lysosomotropic Activity of Hydrophobic Weak Base Drugs is Mediated via Their Intercalation into the Lysosomal Membrane. *Cells*, 9(5), 1082. <https://doi.org/10.3390/cells9051082>
- Stein, E.M., DiNardo, C.D., Pollyea, D.A., Fathi, A.T., Roboz, G.J., Altman, J.K., et al., 2017. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood.* 130, 722-731. <https://doi.org/10.1182/blood-2017-04-779405>
- Stewart, J.B., Alaei-Mahabadi, B., Sabarinathan, R., Samuelsson, T., Gorodkin, J., Gustafsson, C.M., et al., 2015. Simultaneous DNA and RNA Mapping of Somatic Mitochondrial Mutations across Diverse Human Cancers. *PLoS Genet.* 11, e1005333. <https://doi.org/10.1371/journal.pgen.1005333>
- Stuani, L., Sabatier, M., Saland, E., Cognet, G., Poupin, N., Bosc, C., et al., 2021. Mitochondrial metabolism supports resistance to IDH mutant inhibitors in acute myeloid leukemia. *J Exp Med.* 218, e20200924. <https://doi.org/10.1084/jem.20200924>
- Sullivan, E.J., Kurtoglu, M., Brenneman, R., Liu, H., Lampidis, T.J., 2014. Targeting cisplatin-resistant human tumor cells with metabolic inhibitors. *Cancer Chemother Pharmacol.* 73, 417-427. <https://doi.org/10.1007/s00280-013-2366-8>
- Sullivan, L.B., Luengo, A., Danai, L.V., Bush, L.N., Diehl, F.F., Hosios, A.M., et al., 2018. Aspartate is an endogenous metabolic limitation for tumor growth. *Nat Cell Biol.* 20, 782-788. <https://doi.org/10.1038/s41556-018-0125-0>
- Sullivan, M.R., Danai, L.V., Lewis, C.A., Chan, S.H., Gui, D.Y., Kunchok, T., et al., 2019. Quantification of microenvironmental metabolites in murine cancers reveals determinants of tumor nutrient availability. *eLife.* 8, e44235. doi: 10.7554/eLife.44235
- Sun, C., Li, T., Song, X., Huang, L., Zang, Q., Xu, J., et al., 2019a. Spatially resolved metabolomics to discover tumor-associated metabolic alterations. *Proc Natl Acad Sci USA.* 116, 52-57. <https://doi.org/10.1073/pnas.1808950116>
- Sun, J., Nagel, R., Zaal, E.A., Ugalde, A.P., Han, R., Proost, N., et al., 2019b. SLC1A3 contributes to L-asparaginase resistance in solid tumors. *EMBO J.* 38, e102147. <https://doi.org/10.15252/embj.2019102147>
- Sun, X., Sun, G., Huang, Y., Hao, Y., Tang, X., Zhang, N., et al., 2020. 3-Bromopyruvate regulates the status of glycolysis and BCNU sensitivity in human hepatocellular carcinoma cells. *Biochem Pharmacol.* 177, 113988. <https://doi.org/10.1016/j.bcp.2020.113988>
- Tabassum, D.P., Polyak, K., 2015. Tumorigenesis: it takes a village. *Nat Rev Cancer.* 15, 473-483. <https://doi.org/10.1038/nrc3971>
- Tadros, S., Shukla, S.K., King, R.J., Gunda, V., Vernucci, E., Abrego, J., et al., 2017. *De Novo* Lipid Synthesis Facilitates Gemcitabine Resistance through Endoplasmic Reticulum Stress in Pancreatic Cancer. *Cancer Res.* 77, 5503-5517. <https://doi.org/10.1158/0008-5472.CAN-16-3062>
- Takaoka, Y., Konno, M., Koseki, J., Colvin, H., Asai, A., Tamari, K., et al., 2019. Mitochondrial pyruvate carrier 1 expression controls cancer epithelial-mesenchymal transition and radioresistance. *Cancer Sci.* 110, 1331-1339. <https://doi.org/10.1111/cas.13980>

- Takehara, M., Sato, Y., Kimura, T., Noda, K., Miyamoto, H., Fujino, Y., et al., 2020. Cancer-associated adipocytes promote pancreatic cancer progression through SAA1 expression. *Cancer Sci.* 111, 2883–2894. <https://doi.org/10.1111/cas.14527>
- Tan, W., Zhong, Z., Carney, R.P., Men, Y., Li, J., Pan, T., Wang, Y., 2019. Deciphering the metabolic role of AMPK in cancer multi-drug resistance. *Semin Cancer Biol.* 56, 56-71. <https://doi.org/10.1016/j.semcancer.2018.09.005>
- Tanaka, K., Sasayama, T., Irino, Y., Takata, K., Nagashima, H., Satoh, N., et al., 2015. Compensatory glutamine metabolism promotes glioblastoma resistance to mTOR inhibitor treatment. *J Clin Invest.* 125, 1591-1602. <https://doi.org/10.1172/JCI78239>
- Taylor, S., Spugnini, E.P., Assaraf, Y.G., Azzarito, T., Rauch, C., Fais, S., 2015. Microenvironment acidity as a major determinant of tumor chemoresistance: Proton pump inhibitors (PPIs) as a novel therapeutic approach. *Drug Resist Updat.* 23, 69-78. <https://doi.org/10.1016/j.drug.2015.08.004>
- Thewes, V., Simon, R., Hlevnjak, M., Schlotter, M., Schroeter, P., Schmidt, K., et al., 2017. The branched-chain amino acid transaminase 1 sustains growth of antiestrogen-resistant and ER $\alpha$ -negative breast cancer. *Oncogene.* 36, 4124-4134. <https://doi.org/10.1038/onc.2017.32>
- Thompson, R.M., Dytfield, D., Reyes, L., Robinson, R.M., Smith, B., Manevich, Y., et al., 2017. Glutaminase inhibitor CB-839 synergizes with carfilzomib in resistant multiple myeloma cells. *Oncotarget.* 8, 35863-35876. <https://doi.org/10.18632/oncotarget.16262>
- Timmerman, L.A., Holton, T., Yuneva, M., Louie, R.J., Padró, M., Daemen, A., et al., 2013. Glutamine Sensitivity Analysis Identifies the xCT Antiporter as a Common Triple-Negative Breast Tumor Therapeutic Target. *Cancer Cell.* 24, 450-465. <https://doi.org/10.1016/j.ccr.2013.08.020>
- Trempelec, N., Degavre, C., Doix, B., Brusa, D., Corbet, C., Feron, O., 2020. Acidosis-Induced TGF- $\beta$ 2 Production Promotes Lipid Droplet Formation in Dendritic Cells and Alters Their Potential to Support Anti-Mesothelioma T Cell Response. *Cancers.* 12, 1284. <https://doi.org/10.3390/cancers12051284>
- Tucci, J., Chen, T., Margulis, K., Orgel, E., Paszkiewicz, R.L., Cohen, M.D., et al., 2021. Adipocytes Provide Fatty Acids to Acute Lymphoblastic Leukemia Cells. *Front Oncol.* 11, 665763. doi: 10.3389/fonc.2021.665763
- Twomey, J.D., Zhang, B., 2021. Cancer Immunotherapy Update: FDA-Approved Checkpoint Inhibitors and Companion Diagnostics. *AAPS J.* 23, 39. <https://doi.org/10.1208/s12248-021-00574-0>
- ValvonaC.J., Fillmore, H.L., 2018. Oxamate, but Not Selective Targeting of LDH-A, Inhibits Medulloblastoma Cell Glycolysis, Growth and Motility. *Brain Sci.* 8, 56. <https://doi.org/10.3390/brainsci8040056>
- van Gastel, N., Spinelli, J.B., Sharda, A., Schajnovitz, A., Baryawno, N., Rhee, C., et al., 2020. Induction of a Timed Metabolic Collapse to Overcome Cancer Chemoresistance. *Cell Metab.* 32, 391-403. <https://doi.org/10.1016/j.cmet.2020.07.009>
- Vander Linden, C., Corbet, C., 2019. Therapeutic Targeting of Cancer Stem Cells: Integrating and Exploiting the Acidic Niche. *Front Oncol.* 9, 159. <https://doi.org/10.3389/fonc.2019.00159>
- Vander Linden, C., Corbet, C., 2020. Reconciling environment-mediated metabolic heterogeneity with the oncogene-driven cancer paradigm in precision oncology. *Semin Cell Dev Biol.* 98, 202-210. <https://doi.org/10.1016/j.semcdb.2019.05.016>

- Vander Linden, C., Corbet, C., Bastien, E., Martherus, R., Guilbaud, C., Petit, L., et al., 2021. Therapy-induced DNA methylation inactivates MCT1 and renders tumor cells vulnerable to MCT4 inhibition. *Cell Rep.* 35, 109202. <https://doi.org/10.1016/j.celrep.2021.109202>
- Vara-Ciruelos, D., Russell, F.M., Hardie, D.G., 2019. The strange case of AMPK and cancer: Dr Jekyll or Mr Hyde? *Open Biol.* 9, 190099. <https://doi.org/10.1098/rsob.190099>
- Vasan, N., Baselga, J., Hyman, D.M., 2019. A view on drug resistance in cancer. *Nature.* 575, 299-309. <https://doi.org/10.1038/s41586-019-1730-1>
- Vashisht Gopal, Y.N., Gammon, S., Prasad, R., Knighton, B., Pisaneschi, F., Roszik, J., et al., 2019. A Novel Mitochondrial Inhibitor Blocks MAPK Pathway and Overcomes MAPK Inhibitor Resistance in Melanoma. *Clin Cancer Res.* 25, 6429-6442. <https://doi.org/10.1158/1078-0432.CCR-19-0836>
- Vazquez, F., Lim, J.-H., Chim, H., Bhalla, K., Girnun, G., Pierce, K., et al., 2013. PGC1 $\alpha$  Expression Defines a Subset of Human Melanoma Tumors with Increased Mitochondrial Capacity and Resistance to Oxidative Stress. *Cancer Cell.* 23, 287-301. <https://doi.org/10.1016/j.ccr.2012.11.020>
- Vellinga, T.T., Borovski, T., de Boer, V.C.J., Fatrai, S., van Schelven, S., Trumpi, K., et al., 2015. SIRT1/PGC1 $\alpha$ -Dependent Increase in Oxidative Phosphorylation Supports Chemotherapy Resistance of Colon Cancer. *Clin Cancer Res.* 21, 2870-2879. <https://doi.org/10.1158/1078-0432.CCR-14-2290>
- Venkatraman, G., Benesch, M.G.K., Tang, X., Dewald, J., McMullen, T.P.W., Brindley, D.N., 2015. Lysophosphatidate signaling stabilizes Nrf2 and increases the expression of genes involved in drug resistance and oxidative stress responses: implications for cancer treatment. *FASEB J.* 29, 772-785. <https://doi.org/10.1096/fj.14-262659>
- Venneti, S., Dunphy, M.P., Zhang, H., Pitter, K.L., Zanzonico, P., Campos, C. et al., 2015. Glutamine-based PET imaging facilitates enhanced metabolic evaluation of gliomas in vivo. *Sci Transl Med.* 7, 274ra217. <https://doi.org/10.1126/scitranslmed.aaa1009>
- Vernieri, C., Casola, S., Foiani, M., Pietrantonio, F., de Braud, F., Longo, V., 2016. Targeting Cancer Metabolism: Dietary and Pharmacologic Interventions. *Cancer Discov.* 6, 1315-1333. <https://doi.org/10.1158/2159-8290.CD-16-0615>
- Viale, A., Pettazoni, P., Lyssiotis, C.A., Ying, H., Sánchez, N., Marchesini, M., et al., 2014. Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function. *Nature.* 514, 628-632. <https://doi.org/10.1038/nature13611>
- Visioli, F., Wang, Y., Alam, G.N., Ning, Y., Rados, P.V., Nör, J.E., Polverini, P.J., 2014. Glucose-Regulated Protein 78 (Grp78) Confers Chemoresistance to Tumor Endothelial Cells under Acidic Stress. *PLoS One.* 9, e101053. <https://doi.org/10.1371/journal.pone.0101053>
- Viswanathan, V.S., Ryan, M.J., Dhruv, H.D., Gill, S., Eichhoff, O.M., Seashore-Ludlow, B., et al., 2017. Dependency of a therapy-resistant state of cancer cells on a lipid peroxidase pathway. *Nature.* 547, 453-457. <https://doi.org/10.1038/nature23007>
- von Neubeck, B., Gondi, G., Riganti, C., Pan, C., Parra Damas, A., Scherb, H., et al., 2018. An inhibitory antibody targeting carbonic anhydrase XII abrogates chemoresistance and significantly reduces lung metastases in an orthotopic breast cancer model in vivo. *Int J Cancer.* 143, 2065-2075. <https://doi.org/10.1002/ijc.31607>
- Voskuil, F.J., Steinkamp, P.J., Zhao, T., van der Vegt, B., Koller, M., Doff, J.J., et al., 2020. Exploiting metabolic acidosis in solid cancers using a tumor-agnostic pH-activatable nanoprobe for fluorescence-guided surgery. *Nat Commun.* 11, 3257. <https://doi.org/10.1038/s41467-020-16814-4>

- Wang, F., Morita, K., DiNardo, C. D., Furudate, K., Tanaka, T., Yan, Y., et al., 2021. Leukemia stemness and co-occurring mutations drive resistance to IDH inhibitors in acute myeloid leukemia. *Nat Commun.* 12, 2607. <https://doi.org/10.1038/s41467-021-22874-x>
- Wang, H., Zuo, Y., Ding, M., Ke, C., Yan, R., Zhan, H., et al., 2017. LASS2 inhibits growth and invasion of bladder cancer by regulating ATPase activity. *Oncol Lett.* 13, 661-668. doi: 10.3892/ol.2016.5514
- Wang, J., Liu, X., Qiu, Y., Shi, Y., Cai, J., Wang, B., et al., 2018a. Cell adhesion-mediated mitochondria transfer contributes to mesenchymal stem cell-induced chemoresistance on T cell acute lymphoblastic leukemia cells. *J Hematol Oncol.* 11, 11. <https://doi.org/10.1186/s13045-018-0554-z>
- Wang, I., Xu, m., Qin, j., Lin, S.-C., Lee, H.-J., Tsai, S.Y., Tsai, M.-J., 2016a. MPC1, a key gene in cancer metabolism, is regulated by COUPTFII in human prostate cancer. *Oncotarget.* 7, 14673-14683. <https://doi.org/10.18632/oncotarget.7405>
- Wang, L., Zhao, X., Fu, J., Xu, W., Yuan, J., 2021. The Role of Tumor Metabolism in Cisplatin Resistance. *Front Mol Biosci.* 8, 691795. <https://doi.org/10.3389/fmolb.2021.691795>
- Wang, S.-Y., Wei, Y.-H., Shieh, D.-B., Lin, L.-L., Cheng, S.-P., Wang, P.-W., Chuang, J.-H., 2015. 2-Deoxy-d-Glucose Can Complement Doxorubicin and Sorafenib to Suppress the Growth of Papillary Thyroid Carcinoma Cells. *PLoS One.* 10, e0130959. <https://doi.org/10.1371/journal.pone.0130959>
- Wang, S., Wang, Z., Yu, G., Zhou, Z., Jacobson, O., Liu, Y., et al., 2019a. Tumor-Specific Drug Release and Reactive Oxygen Species Generation for Cancer Chemo/Chemodynamic Combination Therapy. *Adv Sci (Weinh).* 6, 1801986. doi: 10.1002/advs.201801986
- Wang, T., Fahrman, J.F., Lee, H., Li, Y.-J., Tripathi, S.C., Yue, C., et al., 2018b. JAK/STAT3-Regulated Fatty Acid  $\beta$ -Oxidation Is Critical for Breast Cancer Stem Cell Self-Renewal and Chemoresistance. *Cell Metab.* 27, 136-150. <https://doi.org/10.1016/j.cmet.2017.11.001>
- Wang, X., Zhang, H., Chen, X., 2019b. Drug resistance and combating drug resistance in cancer. *Cancer Drug Resist.* 2, 141-160. doi: 10.20517/cdr.2019.10
- Wang, Y., Zhang, J., Ren, S., Sun, D., Huang, H.-Y., Wang, H., et al., 2019c. Branched-Chain Amino Acid Metabolic Reprogramming Orchestrates Drug Resistance to EGFR Tyrosine Kinase Inhibitors. *Cell Rep.* 28, 512-525. <https://doi.org/10.1016/j.celrep.2019.06.026>
- Wang, Z., Liu, P., Chen, Q., Deng, S., Liu, X., Situ, H., et al., 2016b. Targeting AMPK Signaling Pathway to Overcome Drug Resistance for Cancer Therapy. *Curr Drug Targets.* 17, 853-864. doi: 10.2174/1389450116666150316223655
- Wang, Z., Yip, L.Y., Lee, J.H.J., Wu, Z., Chew, H.Y., Chong, P.K.W., et al., 2019d. Methionine is a metabolic dependency of tumor-initiating cells. *Nat Med.* 25, 825-837. <https://doi.org/10.1038/s41591-019-0423-5>
- Wangpaichitr, M., Wu, C., Li, Y.Y., Nguyen, D.J.M., Kandemir, H., Shah, S., et al., 2017. Exploiting ROS and metabolic differences to kill cisplatin resistant lung cancer. *Oncotarget.* 8, 49275-49292. <https://doi.org/10.18632/oncotarget.17568>
- Weerts, M.J.A., Hollestelle, A., Sieuwerts, A.M., Foekens, J.A., Sleijfer, S., Martens, J.W.M., 2017. Low Tumor Mitochondrial DNA Content Is Associated with Better Outcome in Breast Cancer Patients Receiving Anthracycline-Based Chemotherapy. *Clin Cancer Res.* 23, 4735-4743. <https://doi.org/10.1158/1078-0432.CCR-17-0032>

- Wegner, M.-S., Gruber, L., Mattjus, P., Geisslinger, G., Grösch, S., 2018. The UDP-glucose ceramide glycosyltransferase (UGCG) and the link to multidrug resistance protein 1 (MDR1). *BMC Cancer*. 18, 153. <https://doi.org/10.1186/s12885-018-4084-4>
- Wei, L., Lee, D., Law, C.-T., Zhang, M.S., Shen, J., Chin, D.W.-C., et al., 2019. Genome-wide CRISPR/Cas9 library screening identified PHGDH as a critical driver for Sorafenib resistance in HCC. *Nat Commun*. 10, 4681. <https://doi.org/10.1038/s41467-019-12606-7>
- Wei, T.-T., Lin, Y.-T., Tang, S.-P., Luo, C.-K., Tsai, C.-T., Shun, C.-T., ET AL., 2020. Metabolic targeting of HIF-1 $\alpha$  potentiates the therapeutic efficacy of oxaliplatin in colorectal cancer. *Oncogene*. 39, 414-427. <https://doi.org/10.1038/s41388-019-0999-8>
- Weng, C.-Y., Kao, C.-X., Chang, T.-S., Huang, Y.-H., 2021. Immuno-Metabolism: The Role of Cancer Niche in Immune Checkpoint Inhibitor Resistance. *Int J Mol Sci*. 22, 1258. <https://doi.org/10.3390/ijms22031258>
- Wijdeven, R. H., Pang, B., Assaraf, Y. G., Neefjes, J., 2016. Old drugs, novel ways out: Drug resistance toward cytotoxic chemotherapeutics. *Drug resist update*. 28, 65–81. <https://doi.org/10.1016/j.drug.2016.07.001>
- Williams, R.T., Guarecuco, R., Gates, L.A., Barrows, D., Passarelli, M.C., Carey, B., et al., 2020. ZBTB1 Regulates Asparagine Synthesis and Leukemia Cell Response to L-Asparaginase. *Cell Metab*. 31, 852-861. <https://doi.org/10.1016/j.cmet.2020.03.008>
- Wilson, W.R., Hay, M.P., 2011. Targeting hypoxia in cancer therapy. *Nat Rev Cancer*. 11, 393-410. <https://doi.org/10.1038/nrc3064>
- Wu, Y., Si, R., Tang, H., He, Z., Zhu, H., Wang, L., et al., 2015. Cholesterol reduces the sensitivity to platinum-based chemotherapy via upregulating ABCG2 in lung adenocarcinoma. *Biochem Biophys Res Commun*. 457, 614-620. <https://doi.org/10.1016/j.bbrc.2015.01.035>
- Xavier, C., Castro, I., Caires, H.R., Ferreira, D., Cavadas, B., Pereira, L., et al., 2021. Chitinase 3-like-1 and fibronectin in the cargo of extracellular vesicles shed by human macrophages influence pancreatic cancer cellular response to gemcitabine. *Cancer Lett*, 501, 210-223. <https://doi.org/10.1016/j.canlet.2020.11.013>
- Xu, K., He, Z., Chen, M., Wang, N., Zhang, D., Yang, L., et al., 2020. HIF-1 $\alpha$  regulates cellular metabolism, and Imatinib resistance by targeting phosphogluconate dehydrogenase in gastrointestinal stromal tumors. *Cell Death Dis*. 11, 586.
- Yang, H., Villani, R.M., Wang, H., Simpson, M.J., Roberts, M.S., Tang, M., Liang, X., 2018. The role of cellular reactive oxygen species in cancer chemotherapy, *Journal of Experimental & Clinical Cancer Research* 37 (2018), p. 266. <https://doi.org/10.1038/s41419-020-02768-4>
- Ye, H., Adane, B., Khan, N., Sullivan, T., Minhajuddin, M., Gasparetto, M., et al., 2016. Leukemic Stem Cells Evade Chemotherapy by Metabolic Adaptation to an Adipose Tissue Niche. *Cell Stem Cell*. 19, 23-37. <https://doi.org/10.1016/j.stem.2016.06.001>
- Yeon, A., You, S., Kim, M., Gupta, A., Park, M.H., Weisenberger, D.J. et al., 2018. Rewiring of cisplatin-resistant bladder cancer cells through epigenetic regulation of genes involved in amino acid metabolism. *Theranostics*. 8, 4520-4534. <https://www.thno.org/v08p4520.htm>
- Yin, C., Gao, B., Yang, J., Wu, J., 2020. Glucose Transporter-1 (GLUT-1) Expression is Associated with Tumor Size and Poor Prognosis in Locally Advanced Gastric Cancer. *Med Sci Monit Basic Res*. 26, e920778. doi: 10.12659/MSMBR.920778

- Yoo, H.C., Park, S.J., Nam, M., Kang, J., Kim, K., Yeo, J.H., et al., 2020. A Variant of SLC1A5 Is a Mitochondrial Glutamine Transporter for Metabolic Reprogramming in Cancer Cells. *Cell Metab.* 31, 267-283. <https://doi.org/10.1016/j.cmet.2019.11.020>
- Yoshikawa, M., Tsuchihashi, K., Ishimoto, T., Yae, T., Motohara, T., Sugihara, E., et al., 2013. xCT Inhibition Depletes CD44v-Expressing Tumor Cells That Are Resistant to EGFR-Targeted Therapy in Head and Neck Squamous Cell Carcinoma. *Cancer Res.* 73, 1855-1866. <https://doi.org/10.1158/0008-5472.CAN-12-3609-T>
- Yu, D., Liu, Y., Zhou, Y., Ruiz-Rodado, V., Larion, M., Xu, G., et al., 2020. Triptolide suppresses IDH1-mutated malignancy via Nrf2-driven glutathione metabolism. *Proc Natl Acad Sci USA.* 117 (2020), pp. 9964-9972. <https://doi.org/10.1073/pnas.1913633117>
- Yu, T., Yang, G., Hou, Y., Tang, X., Wu, C., Wu, X.a., et al., 2017. Cytoplasmic GPER translocation in cancer-associated fibroblasts mediates cAMP/PKA/CREB/glycolytic axis to confer tumor cells with multidrug resistance. *Oncogene.* 36, 2131-2145. <https://doi.org/10.1038/onc.2016.370>
- Yuan, P., Ito, K., Perez-Lorenzo, R., Del Guzzo, C., Lee, J.H., Shen, C.H., et al., 2013. Phenformin enhances the therapeutic benefit of BRAF(V600E) inhibition in melanoma. *Proc Natl Acad Sci USA.* 110, 18226-18231. <https://doi.org/10.1073/pnas.1317577110>
- Zaal, E.A., Berkers, C.R., 2018. The Influence of Metabolism on Drug Response in Cancer. *Front Oncol.* 8, 500. <https://doi.org/10.3389/fonc.2018.00500>
- Zaal, E.A., Wu, W., Jansen, G., Zweegman, S., Cloos, J., Berkers, C.R., 2017. Bortezomib resistance in multiple myeloma is associated with increased serine synthesis. *Cancer Metab.* 5, 7. <https://doi.org/10.1186/s40170-017-0169-9>
- Zadra, G., Ribeiro, C.F., Chetta, P., Ho, Y., Cacciatore, S., Gao, X., et al., 2019. Inhibition of de novo lipogenesis targets androgen receptor signaling in castration-resistant prostate cancer. *Proc Natl Acad Sci USA.* 116, 631-640. <https://doi.org/10.1073/pnas.1808834116>
- Zandberg, D.P., Menk, A.V., Velez, M., Normolle, D., DePeaux, K., Liu, A., et al., 2021. Tumor hypoxia is associated with resistance to PD-1 blockade in squamous cell carcinoma of the head and neck. *J Immunother Cancer.* 9, e002088. doi: 10.1136/jitc-2020-002088
- Zecchini, V., Frezza, C., 2017. Metabolic synthetic lethality in cancer therapy. *Biochim Biophys Acta Bioenerg.* 1858, 723-731. <https://doi.org/10.1016/j.bbabi.2016.12.003>
- Zeng, K., Ju, G., Wang, H., Huang, J., 2020. GLUT1/3/4 as novel biomarkers for the prognosis of human breast cancer. *Transl Cancer Res.* 9, 2363-2377. doi: 10.21037/tcr.2020.03.50
- Zervantonakis, I.K., Poskus, M.D., Scott, A.L., Selfors, L.M., Lin, J.-R., Dillon, D.A., et al., 2020. Fibroblast-tumor cell signaling limits HER2 kinase therapy response via activation of MTOR and antiapoptotic pathways. *Proc Natl Acad Sci USA.* 117, 6500-16508. <https://doi.org/10.1073/pnas.2000648117>
- Zhang, G., Frederick, D.T., Wu, L., Wei, Z., Krepler, C., Srinivasan, S., et al., 2016. Targeting mitochondrial biogenesis to overcome drug resistance to MAPK inhibitors. *J Clin Invest.* 126, 1834-1856. <https://doi.org/10.1172/JCI82661>.
- Zhang, L., Yao, Y., Zhang, S., Liu, Y., Guo, H., Ahmed, M., et al., 2019. Metabolic reprogramming toward oxidative phosphorylation identifies a therapeutic target for mantle cell lymphoma. *Sci Transl Med.* 11, eaau1167. <https://doi.org/10.1126/scitranslmed.aau1167>

- Zhang, Q., Huang, R., Hu, H., Yu, L., Tang, Q., Tao, Y., et al., 2020a. Integrative Analysis of Hypoxia-Associated Signature in Pan-Cancer. *iScience*. 23, 101460. <https://doi.org/10.1016/j.isci.2020.101460>
- Zhang, X., Ai, Z., Chen, J., Yi, J., Liu, Z., Zhao, H., Wei, H., 2017a. Glycometabolic adaptation mediates the insensitivity of drug-resistant K562/ADM leukaemia cells to adriamycin via the AKT-mTOR/c-Myc signalling pathway. *Mol Med Rep*. 15, 1869-1876. <https://doi.org/10.3892/mmr.2017.6189>
- Zhang, X., Chen, J., Ai, Z., Zhang, Z., Lin, L., Wei, H., 2018. Targeting glycometabolic reprogramming to restore the sensitivity of leukemia drug-resistant K562/ADM cells to adriamycin. *Life Sci*. 215, 1-10. <https://doi.org/10.1016/j.lfs.2018.10.050>
- Zhang, Y., Guillemier, C., De Raedt, T., Cox, A.G., Maertens, O., Yimlamai, D., et al., 2020b. Imaging Mass Spectrometry Reveals Tumor Metabolic Heterogeneity. *iScience*. 23, 101355. <https://doi.org/10.1016/j.isci.2020.101355>
- Zhang, Y., Kwok-Shing Ng, P., Kucherlapati, M., Chen, F., Liu, Y., Tsang, Y.H., et al., 2017b. A Pan-Cancer Proteogenomic Atlas of PI3K/AKT/mTOR Pathway Alterations. *Cancer Cell*. 31, 820-832. <https://doi.org/10.1016/j.ccell.2017.04.013>
- Zhang, Z., Tan, X., Luo, J., Yao, H., Si Z., Tong, J.-S., 2020c. The miR-30a-5p/CLCF1 axis regulates sorafenib resistance and aerobic glycolysis in hepatocellular carcinoma. *Cell Death Dis*. 11, 902. <https://doi.org/10.1038/s41419-020-03123-3>
- Zhao, Y., Liu, H., Liu, Z., Ding, Y., LeDoux, S.P., Wilson, G.L., et al., 2011. Overcoming Trastuzumab Resistance in Breast Cancer by Targeting Dysregulated Glucose Metabolism. *Cancer Res*. 71, 4585-4597. <https://doi.org/10.1158/0008-5472.CAN-11-0127>
- Zheng, X., Carstens, J.L., Kim, J., Scheible, M., Kaye, J., Sugimoto, H., et al., 2015. Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer. *Nature*. 527, 525-530. <https://doi.org/10.1038/nature16064>
- Zhitomirsky, B., Assaraf, Y.G., 2014. Lysosomal sequestration of hydrophobic weak base chemotherapeutics triggers lysosomal biogenesis and lysosome-dependent cancer multidrug resistance. *Oncotarget*. 6, 1143-1156.
- Zhitomirsky, B., Assaraf, Y.G., 2016. Lysosomes as mediators of drug resistance in cancer, *Drug Resistance Updates* 24 (2016), pp. 23-33. <https://doi.org/10.18632/oncotarget.2732>
- Zhitomirsky, B., Yunaev, A., Kreiserman, R., Kaplan, A., Stark, M., Assaraf, Y.G., 2018. Lysosomotropic drugs activate TFEB via lysosomal membrane fluidization and consequent inhibition of mTORC1 activity. *Cell Death Dis*. 9, 1191. <https://doi.org/10.1038/s41419-018-1227-0>
- Zhong, Y., Li, X., Yu, D., Li, X., Li, Y., Long, Y., et al., 2015. Application of mitochondrial pyruvate carrier blocker UK5099 creates metabolic reprogram and greater stem-like properties in LnCap prostate cancer cells in vitro. *Oncotarget*. 6, 37758-37769. <https://doi.org/10.18632/oncotarget.5386>
- Zhou, C., Li, J., Du, J., Jiang, X., Xu, X., Liu, Y., et al., 2021. HMGCS1 drives drug-resistance in acute myeloid leukemia through endoplasmic reticulum-UPR-mitochondria axis. *Biomed Pharmacother*. 137, 111378. <https://doi.org/10.1016/j.biopha.2021.111378>
- Zielonka, J., Joseph, J., Sikora, A., Hardy, M., Ouari, O., Vasquez-Vivar, J., et al., 2017. Mitochondria-Targeted Triphenylphosphonium-Based Compounds: Syntheses, Mechanisms of Action, and Therapeutic and Diagnostic Applications. *Chem Rev*. 117, 10043-10120. <https://doi.org/10.1021/acs.chemrev.7b00042>

