Cytokine and Growth Factor Reviews 73 (2023) 150–162

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

The role of Extracellular Vesicles in glycolytic and lipid metabolic reprogramming of cancer cells: Consequences for drug resistance

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ARTICLE INFO

Keywords:
Cancer
Metabolic Reprogramming
Drug Resistance
Extracellular Vesicles
Intercellular Communication

ABSTRACT

In order to adapt to a higher proliferative rate and an increased demand for energy sources, cancer cells rewire their metabolic pathways, a process currently recognized as a hallmark of cancer. Even though the metabolism of glucose is perhaps the most discussed metabolic shift in cancer, lipid metabolic alterations have been recently recognized as relevant players in the growth and proliferation of cancer cells. Importantly, some of these metabolic alterations are reported to induce a drug resistant phenotype in cancer cells. The acquisition of drug resistance traits severely hinders cancer treatment, being currently considered one of the major challenges of the oncological field. Evidence suggests that Extracellular Vesicles (EVs), which play a crucial role in intercellular communication, may act as facilitators of tumour progression, survival and drug resistance by modulating several aspects involved in the metabolism of cancer cells. This review aims to gather and discuss relevant data regarding metabolic reprograming in cancer, particularly involving the glycolytic and lipid alterations, focusing on its influence on drug resistance and highlighting the relevance of EVs as intercellular mediators of this process.

1. Introduction

The rewiring of cancer cells metabolism is one of the emerging hallmarks of cancer [1]. As rapid proliferative cells, cancer cells are characterized by an increased demand for energy sources and biosynthetic macromolecules [2]. Thus, in order to meet these needs, several metabolic and biosynthetic pathways, including glucose, lipids and amino acids metabolism are deregulated [3]. Glycolysis and oxidative phosphorylation (OXPHOS) are the two main metabolic pathways through which cells generate the necessary energy for all biological processes in the form of adenosine triphosphate (ATP) [4,5]. OXPHOS is the metabolic pathway preferentially used by normal cells, under non-proliferating conditions. Since it requires oxygen, it is also known as aerobic respiration and is responsible for the conversion of the glycolytic product pyruvate into acetyl coenzyme A (acetyl-CoA), which is then redirected to the tricarboxylic acid cycle (TCA) and to the electron transport chain (ETC). This process takes place in the mitochondria and presents a net gain of 36 ATP molecules per each glucose molecule [6]. On the other hand, glycolysis, commonly referred to as anaerobic respiration due to its lack of dependence on oxygen, occurs in the cytosol and results in the conversion of pyruvate into lactate. In this process, only 2 ATP molecules are produced. Although glycolysis presents a lower efficiency when compared to OXPHOS, the ATP is produced at a faster rate. Thus, generally, glycolysis is used to sustain the basic cell's needs, keeping cells alive during stressful conditions and/or hypoxia [6].

In the 1920 s, Otto Warburg documented for the first time that, unlike normal cells, the majority of tumour cells use glycolysis as their primary source of ATP, presenting a higher intake of glucose than normal cells [7]. Even in the presence of significant amounts of oxygen, this metabolic pathway is preferred by cancer cells, being therefore known as "aerobic glycolysis" [8]. This metabolic shift that occurs in cancer cells, is commonly referred to as the "Warburg effect" [8,9], and is currently considered one of the hallmarks of cancer [1].

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https://doi.org/10.1016/j.cytogfr.2023.05.001
Received 30 April 2023; Received in revised form 10 May 2023; Accepted 12 May 2023
Available online 14 May 2023

Knowing that glycolysis is a much less energy efficient pathway, the Warburg effect may seem counterintuitive, raising the question of "Why would cancer cells prefer glycolysis?". The first hypothesis relied on the possible dysfunction of mitochondria in tumour cells [8,9]. However, this theory was rejected, as there is considerable evidence showing that cancer cells are able to maintain functional mitochondrial activity [10,11]. Importantly, it is well known that one of the advantages of glycolysis in tumours is the continuous and accelerated production of ATP, and consequently an improved biosynthesis of macromolecules, including nucleotides, lipids, amino acids, NAD^+, NADPH and H^+ co-factors, all essential building blocks and redox cofactors to meet the requirements of rapidly proliferating cells [12,13]. Moreover, carbon dioxide and reactive oxygen species (ROS), such as superoxide and hydrogen peroxide, are released as subproducts of the OXPHOS pathway. Released ROS can lead to a variety of cellular processes, including DNA damage that leads to cell death, being harmful to cancer cells [5]. Therefore, the shift from OXPHOS to glycolysis pathway is a benefit to tumour cells, as the production of ROS is decreased, avoiding DNA damage and consequent apoptosis [14,15].

Even though the metabolism of glucose is perhaps the most recognized metabolic shift of cancer cells, other relevant metabolic alterations occur in tumours, particularly in lipids metabolism. Lipids play an important biological role in all cells as additional energy suppliers, membrane building blocks, hormones and second messengers in cellular signalling processes [16]. Interestingly, lipid composition differs between normal and cancer cells, being dependent on tumour type [17]. The majority of cell membrane lipids are phospholipids, sterols and sphingolipids. All these molecules are synthetized from acetyl-CoA and most of them contain fatty acids (FAs). In normal cells, the FAs building blocks are generally obtained directly from exogenous sources. On the other hand, tumour cells exhibit a shift towards *de novo* synthesis of FAs. The upregulation of FAs biosynthesis confers cancer cells the ability to meet their increased needs for cholesterol and lipids [18]. In fact, several enzymes involved in FAs synthesis are upregulated in different types of tumours, such as FA synthase (FAS), acetyl-CoA carboxylase (ACC) and ATP-citrate lyase (ACLY). Notably, it is known that FAs synthesis inhibition supresses tumour growth [19,20], indicating that FAs and complex lipids as essential components for tumour growth. Moreover, FAs and their by-products are being studied for other oncogenic roles, such as their capacity to remodel membrane structure and fluidity, their role as pro-tumorigenic signalling molecules and their impact on the tumour microenvironment (TME) [21]. On the other hand, FA oxidation (FAO) occurring in the mitochondria is upregulated in different cancer types and promotes the survival and proliferation of tumours, by functioning as an extra energy source when glucose is limited [22]. Additionally, NADH produced in this process may protect cancer cells from oxidative stress [23]. In addition to FAs metabolism, also cholesterol and isoprenoids biosynthesis via mevalonate pathway are altered in cancer cells. Moreover, mevalonate pathway activity is essential for the survival of several cancer cell lines, highlighting its crucial role in tumour growth and progression [24].

The metabolism of amino acids, including glutamine, is also known to be upregulated in cancer. Glutamine functions as a major substrate for energy production and its metabolism produces several intermediates, such as α-ketoglutarate and TCA cycle interveners, which serve as additional energy sources for cancer cells [25]. Thus, glutamine metabolism is increased in cancer cells in order to adapt to the alterations in glycolytic pathway [26]. Furthermore, several oncogenic signalling pathways are affected by glutamine metabolism, including the overexpression by tumour cells of the proto-oncogene MYC, which promotes an upregulated expression of glutamine transporters, glutaminase and glutamine synthetase [27,28].

Interestingly, alterations in the tumour metabolism have been recently associated with the development of therapy resistance in cancer [4,12,29–31]. Additionally, the possibility of targeting altered metabolic pathways for the development of new therapeutic strategies against cancer has also been discussed [6,30]. In fact, resistance of cancer cells to treatment is one of the major challenges in oncology nowadays. Resistance may be intrinsic, i.e. from diagnosis, or acquired, if developed throughout drug treatment [32,33]. There are several mechanisms behind the development of cancer drug resistance (Fig. 1), which are generally associated either with host factors, the TME or with tumour factors [33–35]. Host factors include genetic variations, mutations in the drug targets (point mutations or target gene amplification) and drug-drug interactions [36–38]; TME factors arise from the communication between the tumour and surrounding cells, such as fibroblasts and macrophages [39–41]; tumour cells may contribute to drug resistance by enhancing mechanisms to evade cell death [42,43], exacerbating DNA damage response and repair mechanisms [44], altering the expression of several microRNAs (miRNAs) [45,46] and increasing the expression of the multidrug resistant (MDR) ATP-binding cassette (ABC) transporter superfamily, leading to a higher drug efflux and a consequent reduction in the intracellular drug concentration to subtherapeutic levels, causing drug resistance [47,48]. Importantly, another tumour factor consists in the metabolic reprogramming of cancer cells, which may result in an important adaptative mechanism driving drug resistance [4,12,49].

Cell-cell communication via Extracellular Vesicles (EVs) is another mechanism that induces drug resistance, determining a spreading of host factors from resistant to sensitive cells. The cargo of EVs released by cells may contain proteins, lipids, DNA, RNA, among other components, that reflects the intracellular status of the cell of origin [50–53]. Since EVs play an important role in the intercellular communication, mediating the horizontal transfer of their biological cargo, they may facilitate the dissemination of metabolic alterations to recipient cells (Fig. 2). However, the mechanisms behind this process are not yet fully understood. This review will focus on the metabolic reprograming in cancer affecting drug resistance, mainly the glycolytic and lipid reprogramming, and on the intercellular transfer of these traits by EVs.

2. Metabolic reprogramming in cancer affects drug resistance

2.1. Glucose metabolic reprogramming

Several studies performed in well-established cancer cell lines demonstrated a relationship between increased glucose uptake and enhanced aerobic glycolysis with the development of chemoresistance. For instance, Rui-Hua Xu et al. suggested that an inhibition of glycolysis could be a strategy to overcome MDR in lymphoma and colon cancer cells, by promoting ATP depletion and activating pro-apoptotic signalling molecules, leading to cell death, especially in cancer cells presenting mitochondrial dysfunction [54]. Furthermore, there is evidence that gastric cancer cells that rely mainly on aerobic glycolysis and present an enhanced glucose uptake are also resistant to chemotherapy with cisplatin [55]. Another study performed in the breast cancer cell line MCF7 shows that higher concentrations of glucose reduce the cells sensitivity to tamoxifen treatment. This effect is a result of the direct glucose modulation of the signalling molecule connective tissue growth factor and its ability to promote interleukine-8 (IL-8) release by adipocytes. In fact, the inhibition of this interleukin was previously found to reverse drug resistance [56]. Moreover, a correlation between higher glycolytic rates and resistance to glucocorticoids was found in leukaemia models [57]. Interestingly, pyruvate, which is the final product of aerobic glycolysis, may modulate the expression of the ABC transporter P-glycoprotein (P-gp) in tumour spheroids derived from multiple cell lines models, thus contributing to drug efflux and the development of drug resistance [58].

Furthermore, a link between high levels of lactate, resulting from increased glycolysis, and the development of cancer drug resistance has been suggested in several studies. Wagner et al. showed the ability of increased levels of lactate to reinforce DNA damage repair mechanisms, leading to cisplatin-resistance in cervical carcinoma cells [59].

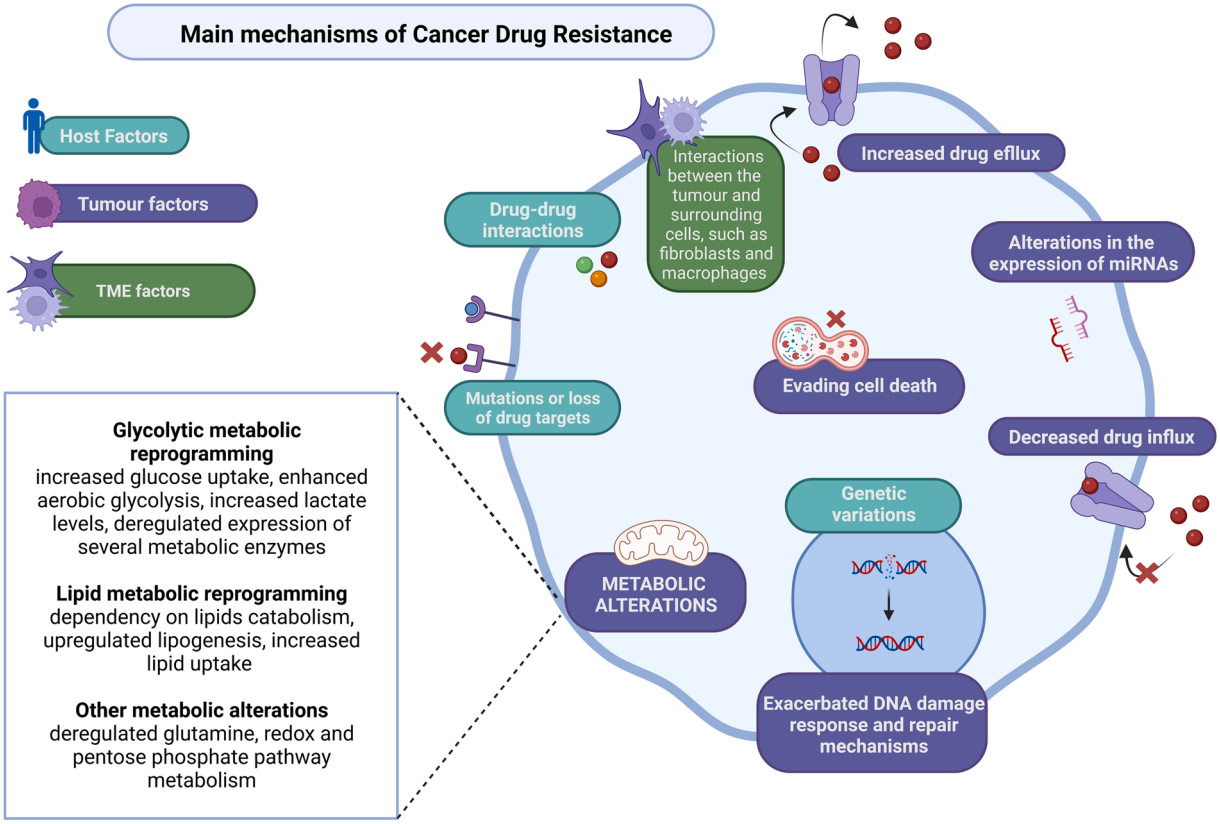

Fig. 1. Main mechanisms of drug resistance in cancer. The main drivers of cancer drug resistance are related either with the host, the tumour cells or with the tumour microenvironment (TME). Figure created with Biorender.com.

Importantly, the Warburg effect, with a consequent increase in lactate levels, is also linked to the development of resistance to melphalan, in multiple myeloma cells. In this study, the authors report that lactate functions as a signalling molecule that upregulates the secretion of IL-8 and the vascular endothelial growth factor (VEGF), both mediators of survival and proliferation, in resistant cells [60]. Interestingly, given this oncogenic potential, the monocarboxylate family of transporters, which are involved in lactate transport, are being considered as therapeutic targets for cancer treatments [61]. For instance, the expression of the monocarboxylate transporter 4 (MCT4) is currently considered of prognostic value in different types of cancer [62–64]. The enzyme Lactate dehydrogenase-A (LDHA) is responsible for the conversion of pyruvate to lactate during glycolysis, playing a major role in glucose metabolism. This isoform is predominantly expressed in breast tissue, having an increased expression in taxol-resistant human breast cancer cell lines, when compared to their sensitive counterparts. The down-regulation of this enzyme was found to re-sensitize taxol-resistant breast cancer cells [65]. Moreover, LDHA inhibition has shown to be a potentially useful strategy against trastuzumab resistance in ErbB2-positive breast cancer cells [66]. Similarly, inhibition of LDHA restores the sensitivity to bortezomib in multiple myeloma cell lines [67].

Other enzymes involved in glycolysis regulation are also known to be involved in the development of drug resistance in cancer. For instance, hexokinase 2 (HK2) is a rate limiting enzyme responsible for the first reaction in glycolysis, which may be associated with drug resistance due to its major role in the regulation of ATP production. Increased ATP levels in cancer cells are known to contribute to drug efflux through ABC transporters [68] and to activate the hypoxia inducible factor-1α (HIF-1α) transcription factor [69,70], both strongly contributing to the emergence of drug resistance. Interestingly, using HK2 inhibitors, such as 3-bromopyruvate, it was possible to reduce ATP levels, leading to the reversion of chemoresistance in liver cancer models [71,72]. In a study comparing ERBB2-overexpressing breast cancer cells with their lapatinib resistant counterparts, it was shown that the resistant cells were more sensitive to treatment with 2-deoxyglucose, a competitive HK2 inhibitor [73]. In another study using cisplatin-resistant lung and ovarian cancer cell lines, lower levels of HK2 were correlated with an increased sensitivity to treatment with the glycolytic inhibitor 2-deoxyglucose [74]. Moreover, HK2 was found upregulated in resistant neuroblastoma metastatic cells, playing a significant role in disease progression [75]. Also, pancreatic cancer cell lines resistance to gemcitabine presented higher levels of HK2. The knockdown of this enzyme increased the pancreatic cancer cells sensitivity to drug treatment, promoted apoptosis and decreased cell proliferation [76].

Also 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3, a rate limiting glycolytic enzyme, was associated with drug resistance since its inhibition increased the response of chronic myeloid leukaemia resistant cells to treatment with tyrosine kinase inhibitors [77]. Moreover, pyruvate kinase M2 (PKM2) is a key glycolytic enzyme that, when down-regulated in the lung cancer cell line A549 and in human lung cancer xenografts in mice, is associated with an increased sensitivity to docetaxel treatment [78]. Also, PKM2 silencing in doxorubicin-resistant cancer cell lines depleted the energy supply for ABC transporters, increasing the intracellular doxorubicin accumulation, and leading to cell starvation and mitochondrial apoptosis, synergistically contributing to the anticancer drug effect [79]. Moreover, the inhibition of PKM2 enhanced the anti-tumour activity of cisplatin in the A549 human lung cancer xenograft model [80]. Upregulated levels of PKM2 were also found in the tamoxifen resistant breast cancer cells MCF-7/TAMR, and its decreased expression re-sensitized the cells to treatment with 4-hydroxytamoxifen [81]. On the other hand, other authors reported conflicting results regarding this enzyme. For instance, Yoo et al. reported a decrease in the levels of PKM2 in cisplatin-resistant human

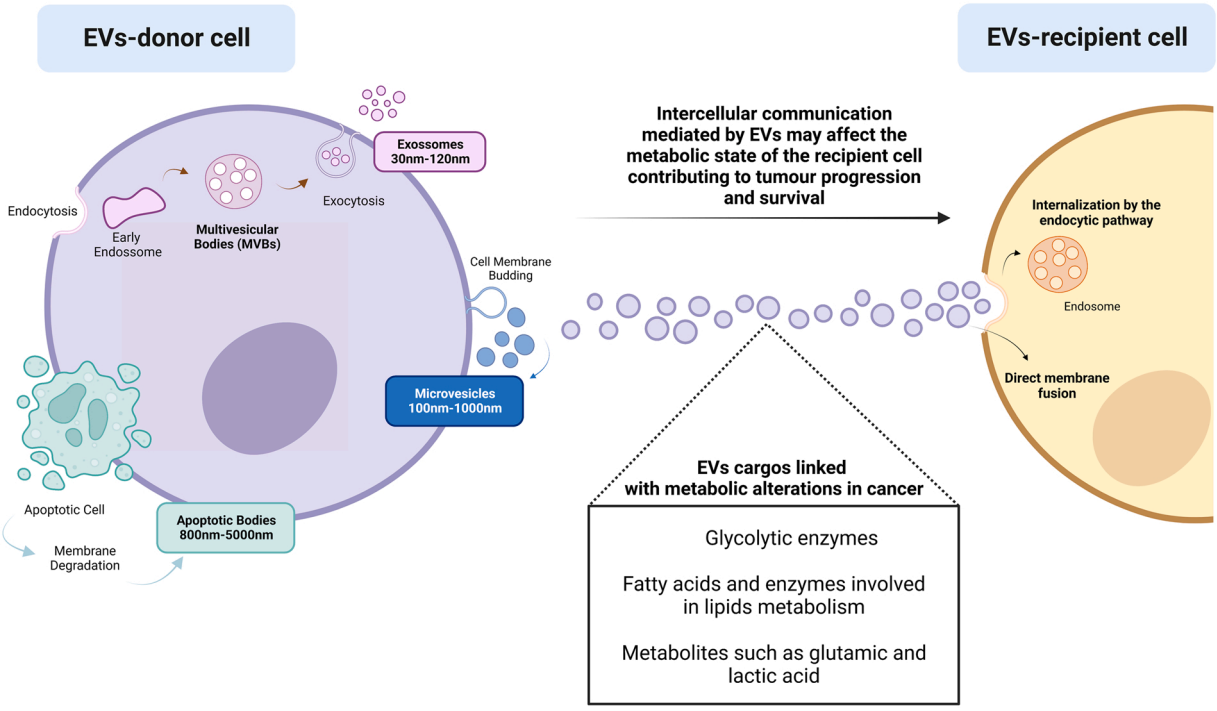

Fig. 2. Release and uptake of Extracellular Vesicles (EVs) and their role in the intercellular transfer of metabolic alterations. EVs are classified into different subtypes according to their biogenesis, physical properties and molecular composition. EVs derived from the inward budding of early endosomes are known as exosomes and their size varies between 30 nm and 120 nm, being the most heterogenous class of EVs; particles that arise from the shedding of the plasma membrane are classified as microvesicles (MVs), also known as ectosomes or microparticles, and their size ranges between 100 nm and 1000 nm; lastly, apoptotic bodies are EVs that are formed as a consequence of the degradation of the cell membrane of apoptotic cells and present a size ranging from 800 nm to 5000 nm. The recipient cell may internalize EVs by the endocytic pathway or by direct membrane fusion. EVs are important mediators of intercellular communication and allow the dissemination of metabolic alterations among cells. Figure created with Biorender.com.

gastric carcinoma cell lines [82], and Martinez-Balibrea et al., using a proteomic approach, found an association between decreased levels of PKM2 and oxaliplatin resistance in patients with colorectal cancer and in human cell lines [83].

2.2. Lipid metabolic reprogramming

Several lipid metabolism regulators have been considered important players in the development of drug resistance in cancer. A dependency on lipids catabolism, upregulated lipogenesis and increased lipid uptake are some of the factors sustaining the emergence of resistant phenotypes in tumour cells [84]. For instance, the overexpression of FAS is known to induce resistance to several anticancer drugs, such as BRAF inhibitors in melanoma cells [85], gemcitabine in pancreatic cancer cells [86,87], cisplatin in ovarian cancer cells [88], mitoxantrone and adriamycin in breast cancer cells [89], tyrosine kinase inhibitors in lung adenocarcinoma cells [90] and to radiotherapy in squamous cell carcinoma [91] and lung cancer cells [92]. Interestingly, not only the synthesis but also the composition of fatty acyl chains found in membrane phospholipids may confer drug resistance. In fact, enrichment of membrane lipids with oleic acid causes resistance to docetaxel in breast cancer [93]. In addition, the ceramide transport protein and the sphingosine Kinase 1 and 2 isoenzymes, necessary for the assembly of sphingolipids, are other regulators of lipid's metabolism whose increased expression has been correlated with resistance to cisplatin, paclitaxel and tamoxifen in ovarian cancer [94–96]. Moreover, Sylvia Faict et al. have reported a deregulation of the sphingolipid metabolism in multiple myeloma cells, characterized by an upregulation of several ceramides and down-regulation of sphingomyelin. This indicates an increase in sphingomyelinase, the enzyme responsible for the conversion of sphingomyelin to ceramide, which is also associated with a tumour protective role and the development of a drug resistant phenotype [97]. Of note, sphingosine and ceramide metabolism deregulations may cause overexpression of ABC transporters such as P-gp, MDR related proteins (MRPs), and breast cancer resistance protein (BCRP) [98,99]. Drug resistance may be also mediated by higher activity of the mevalonate pathway responsible for production of isoprenoids and sterols [100]. Isoprenoids are necessary for the activity of Ras and Rho proteins, well-known oncogenes [101], and activators of the respective downstream kinases (ERK1/2 and RhoAK) that stabilize HIF-1α and increase the transcription of its target genes, including ABC transporters [102,103]. Cholesterol instead regulates cell membrane permeability and fluidity, which directly and indirectly influences anti-cancer drugs uptake and efflux. Indeed, drug resistant tumours have higher membrane cholesterol content which favours the activity of ABC transporters such as P-gp [100,104].

2.3. Other altered metabolic pathways

The reprogramming of glutamine metabolism has been linked with the development of drug resistance to several drugs in a variety of cancer types [105]. In a study using mutant melanoma cells with acquired resistance to BRAF inhibitors, an increased uptake of glutamine and an upregulation of glutaminase was observed, compared with their sensitive counterpart cells. The authors suggest that the shift towards glutamine metabolism promotes survival and proliferation of resistant cells [106]. Similarly, an increased glutamine uptake and increased sensitivity to glutamine starvation was observed in melanoma cells with acquired resistance to the MAPK pathway inhibitor vemurafenib, compared to their sensitive counterparts [107]. Moreover, human platinum resistant ovarian cancer cells revealed glutamine dependency and an upregulation of glutamine transporters and glutaminase. Interestingly, the knockdown of glutaminase re-sensitized the resistant cells to drug treatment [108,109]. The combination of the FAS inhibitor

orlistat with cisplatin also improved sensitivity of cisplatin-resistant ovarian cancer cells, by decreasing glutamine metabolism and directing glutamine towards a reductive pathway of FAs resynthesis instead of nucleotides and glutathione synthesis [88], two key metabolites for cell proliferation and protection from oxidative stress induced by cisplatin. In a study using the MCF7 breast cancer cell line, glutamine was linked with tamoxifen-resistance by cooperation with cancer associated fibroblasts (CAFs). Ammonia, produced in the glutaminolysis pathway, induces autophagy in CAFs, which leads to the release of several catabolites (including glutamine) that are taken up by cancer cells. A metabolic loop that protects breast cancer cells from the tamoxifen-induced apoptosis is created since glutamine upregulates the glycolysis and apoptosis regulator TIGAR (an enzyme also commonly known as fructose-2,6-bisphosphatase), and consequently decreases apoptosis, autophagy and oxidative stress in the cancer cells [110]. The compensatory upregulation of glutamine metabolism was also demonstrated in glioblastoma cell lines and xenografts, triggering resistance to mTOR kinase inhibitors [111]. In a study with multiple myeloma resistant cells, the glutaminase inhibitor CB-839 enhanced the activity of several proteasome inhibitors, particularly carfilzomib [112]. Additionally, lung cancer cells resistant to cisplatin present a higher sensitivity to glutamine deprivation, when compared to drug-sensitive cells. When treated with riluzole, an approved drug for amyotrophic lateral sclerosis, cisplatin resistant cells were selectively killed through blockage of the cystine-glutamate antiporter xCT, which leads to a decrease in glutamate flux [113]. Gemcitabine resistance in pancreatic cancer cells may also be solved by disruption of glutamine metabolic pathways. It was suggested that the glutamine analogue 6-diazo-5-oxo-L-norleucine may synergize with the currently used therapeutic options (such as gemcitabine) and sensitize chemoresistant cells to treatment by modulating ROS homeostasis and downregulating EGFR, Akt, and MAPK dependent pathways [114].

Several chemotherapeutic drugs can interfere with the redox metabolism by increasing ROS and DNA damage, ultimately leading to cell death. Thus, alterations in the redox buffering system may contribute to the development of drug resistance. For instance, in lung cancer, cisplatin-resistant cells presented upregulated levels of glutathione and Glutamate-Cysteine Ligase Catalytic Subunit (GCLC), the first rate-limiting enzyme in glutathione synthesis, allowing cells to neutralise the ROS production induced by cisplatin [115,116]. Furthermore, it was reported that cisplatin-resistant lung cancer cells have higher sensitivity to elesclomol, a drug known to increase ROS [117]. This drug also induced cell death of vemurafenib-resistant melanoma cells [118], by the same mechanism. Moreover, the apoptotic rate of colorectal cancer cisplatin-resistant cells also increases by ROS accumulation [119]. In a study using multiple cervical cancer cell lines, radioresistant cells showed sensitivity to redox metabolism inhibition [120]. In addition, multiple myeloma cells resistant to bortezomib presented higher expression of the mitochondrial enzyme superoxide dismutase 2, which is involved in the superoxide radical's detoxification process [121]. In line with this tendency of resistant cells to present an increased antioxidant activity, higher levels of glutathione were also detected in proteasome inhibitor-resistant multiple myeloma cells [122]. Furthermore, in tamoxifen-resistant breast cancer cells, two enzymes involved in oxidative stress defence, NADPH dehydrogenase 1 and GCLC, were found to be upregulated. Interestingly, an inhibition of NADPH dehydrogenase 1 was able to restore sensitivity of these cells to tamoxifen [123].

A higher activity of the serine synthesis and pentose phosphate pathways has been linked with an increased antioxidant capacity in different multiple myeloma cell lines resistant to bortezomib [124]. One of the enzymes involved in the serine pathway synthesis is the phosphoserine aminotransferase 1 (PSAT1), which is known to be overexpressed in colorectal cancer cells and to confer resistance to oxaliplatin treatment [125]. In another study, it was found that an inhibition of this enzyme in colorectal cancer cells and removal of serine from mouse diet contributed to an increase in the antitumor efficacy of 5-fluorouracil in vivo [126]. Similarly, in oesophageal squamous cell carcinoma, expression of PSAT1 was found increased and associated with poor prognosis [127]. Moreover, in melanoma cells resistant to BRAF inhibitors, several enzymes involved in serine biosynthesis were found overexpressed, and depletion of phosphoglycerate dehydrogenase re-sensitized these cells to drug treatment [128].

3. Extracellular Vesicles are modulators of metabolic reprogramming in cancer

3.1. Effect on tumour progression and survival

Several authors have described the presence of glycolytic enzymes in EVs cargo. For example, the enzyme PKM2 has been identified in the cargo of EVs released by primary prostate cancer cells and its transfer to bone marrow stromal cells was found to promote a bone premetastatic niche, a characteristic feature of the metastatic process in prostate cancer [129]. The enzymes aldolase A and aldehyde dehydrogenase 3A1, also involved in the glycolytic pathway, can be transferred by EVs isolated from the lung cancer A549 and NCI-H446 irradiated cell lines to unirradiated cells, promoting glycolysis on the recipient cells and enhancing their motility [130]. EVs also carry miRNAs linked with the glucose metabolism. For instance, it was reported that EVs derived from cells infected with KSHV, the etiological agent of Kaposi's sarcoma, carry several miRNAs responsible for the induction of aerobic glycolysis and decreased mitochondria biogenesis to surrounding non-infected cells, leading to increased angiogenesis and migration [131]. Moreover, miR-155 and miR-210 were found in the cargo of melanoma-derived EVs, playing a pivotal role in the metabolic reprogramming of normal fibroblasts, enhancing the glycolytic pathway and supressing the OXPHOS pathway. Importantly, this metabolic alteration in the stroma fibroblasts contributes to a pre-metastatic microenvironment [132]. In addition, the miR-122 contained within EVs isolated from breast cancer cell lines downregulated the expression of the glycolytic enzyme PKM2, supressing glucose uptake in premetastatic niche cells, promoting metastasis and disease progression [133].

Moreover, FAs and enzymes involved in lipid metabolism have been found in EVs [134]. The lipidomic profiles of EVs from non-tumourigenic, tumourigenic and metastatic cell lines are significantly different, highlighting the potential significance of the EV's lipids both as causal agents of cancer progression and as potentially useful biomarkers of diagnosis or staging [135]. Interestingly, EVs released by adipocytes and containing proteins involved in FAO were able to upregulate this pathway in the recipient cells, generating energy supplies that favour migration, invasion and metastasis of melanoma cells [136]. EVs were found to play a critical role in mediating this metabolic cooperation between adipocytes and melanoma cells, providing them both with the enzymes and FAs that are needed for FAO [137]. Furthermore, the hormone adrenomedullin was shown to be upregulated in EVs from the plasma of pancreatic cancer patients and to induce lipolysis in the adipose tissue, when compared to plasma of healthy controls. This finding may be of relevance to the early detection of pancreatic cancer, using adrenomedullin as a biomarker [138]. EVs containing miRNAs and other non-coding RNAs can also interfere with lipids metabolism. A study using EVs isolated from breast cancer cells showed that exosomal miR-155 directly downregulated the receptor PPARγ, inducing the beige/brown differentiation in adipocytes, thus promoting lipolysis and triggering tumour progression [139]. Of note, PPARγ can be regulated also by miR-122, miR-192, miR27a-3p and miR27b-3p [140], which are known to be carried by EVs. Moreover, in another study using EVs isolated from breast cancer cells, miRNA-126 and miRNA-144 were also associated with tumour progression by inducing beige/brown differentiation and lipolysis in adipocytes [141]. Interestingly, the circRNA_101093 found in EVs isolated from the plasma of lung adenocarcinoma patients is able to interact with the fatty

acid-binding protein 3, leading to a reduction in the levels of global arachidonic acid and preventing the incorporation of this molecule in the plasma membrane, ultimately resulting in a desensitization of lung adenocarcinoma cells to ferroptosis [142]. Besides modulating the amount of free arachidonic acid (thus impacting directly on membrane fluidity, the unsaturation degree of FAs and sensitivity to ferroptosis), EVs also carry arachidonic acid derivatives, such as prostaglandins PGE2α, PGE1 and PGE2, which are important mediators of inflammation in the TME [103,140].

Metabolites such as glutamic and lactic acid were found in the cargo of EVs derived from human mesenchymal stem/stromal cells. Interestingly, these EVs promoted breast tumour growth in immunodeficient mouse models and the authors suggested an influence of the referred metabolites in this process, concluding that glutamic acid may act as a provider of biosynthetic precursors for macromolecules needed for tumour growth, while lactic acid may contribute to tumour survival in hypoxic and nutrient deprived conditions [143].

Interestingly, EVs are also important mediators of metabolic reprogramming in CAFs, key elements of the TME and important players in the reverse Warburg Effect. For instance, it was reported that EVs released by triple negative breast cancer cells induced mitophagy and, consequently, glycolysis in CAFs. This can be explained by the ability of EVs to transfer Integrin beta 4 to CAFs, a protein frequently overexpressed in cancer cells and associated with cancer progression [144]. In a study using the same breast cancer cell lines, the authors reported that EVs containing miR-105 in their cargo were able to confer CAFs the ability to adapt their metabolic features to nutrients availability [145]. In this study it was shown that, in a nutrient sufficient environment, miR-105 reprogrammed CAFs to upregulate glucose and glutamine metabolism, contributing to the growth of cancer adjacent cells, but in a nutrient insufficiency environment, CAFs acted as metabolic waste detoxifiers, converting lactic acid and ammonium into energy-rich metabolites [145]. Moreover, EVs derived from colorectal cancer cells were also shown to modulate the metabolism of CAFs by upregulating GLUT1 transporter, the MCT4 lactate transporter and amino acid biosynthesis proteins [146]. Interestingly, it was reported that EVs carrying the Epstein-Barr virus encoded latent membrane protein 1 were able to support the reverse Warburg effect in CAFs in nasopharyngeal carcinoma cells [147]. The lipid metabolic reprogramming of CAFs in liver, mediated by colorectal cancer cell derived-EVs, was also reported to facilitate a pre-metastatic niche formation. Exosomal HSPC111 upregulated acetyl-CoA levels and altered lipid metabolism in CAFs by phosphorylating ATP citrate lyase, an important enzyme in FAs biosynthesis that was previously linked with cancer cell growth and metastasis [148].

3.2. Effect on cancer drug resistance

Besides the role of EVs as mediators of metabolic reprogramming, these particles have also been described by several authors as important mediators of the intercellular transfer of a drug resistant phenotype [149–151]. Indeed, when EVs shed by different models of drug-resistant cells are incorporated by their drug-sensitive counterpart cells, a shift in their drug response phenotype may occur, transforming drug-sensitive cells into drug resistant [150–153]. A vast number of modulators known to be associated with drug resistance have been found in the cargo of EVs shed by resistant cells and are known to be transferred to recipient drug-sensitive cells by these small particles. Some of these modulators include the drug efflux pumps from the ABC transporters superfamily, apoptotic modulators, miRNAs, long non-coding RNAs (lncRNAs), among others [154–156].

Most interestingly, it has been reported that MDR cancer cell lines, overexpressing P-gp, present a different metabolic phenotype from their drug-sensitive counterparts, including decreased pentose phosphate pathway and OXPHOS rates and increased glutathione metabolism and glycolysis, as well as alterations in the methionine/S-adenosylmethionine pathway. Moreover, EVs released by the MDR cells were able to stimulate a metabolic switch in the drug-sensitive counterpart cells, conferring these drug-sensitive cells a MDR phenotype [157]. Nevertheless, the mechanisms and the EVs cargo behind these interesting results were not elucidated yet.

In the following sections, EVs cargos already reported to be associated with the induction of drug resistance, by shifting the metabolic features of cancer cells, will be reviewed (Fig. 3 and Table 1).

3.2.1. Non-coding RNAs on EVs cargo

Non-coding RNAs, including miRNAs, lncRNAs and circular RNAs, are known to induce metabolic alterations and consequently drug resistance, in a process that may be mediated by EVs. For example, EVs derived from M2 macrophages were reported to present high levels of miR-3679–5p, being able to transfer this miRNA to lung cancer cells. This miRNA leads to a decrease in the expression of NEDD4L, an important regulator of the ubiquitination and degradation processes of the oncogene c-Myc, promoting its stability. In turn, c-Myc stability was associated with increased aerobic glycolysis, leading to cisplatin-resistance in the human A549 lung cancer cell line [158]. In another study, decreased levels of the enzyme pyruvate dehydrogenase E1 (PDHA1, a component of the pyruvate dehydrogenase complex that links glycolysis to the TCA cycle) and a significant increase in the levels of miR-21–5p were observed in the cisplatin resistant ovarian cancer cell line SVOK3 and in ovarian cancer tissues resistant to the same drug, when compared to controls [159]. Importantly, these authors also detected increased levels of miR-21–5p in EVs derived from the cisplatin resistant SKOV3 cells. The treatment of SVOK3 sensitive cells with EVs shed by the cisplatin resistant cells promoted glycolysis and chemoresistance in the parental (sensitive) cells, through inhibition of PDHA1 [159]. Interestingly, the lncRNA HISLA, carried by EVs from tumour-associated macrophages, promoted aerobic glycolysis and apoptosis resistance in breast cancer cells by stabilization of HIF-1α. In addition, clinical data associated the lncRNA HISLA with shorter survival of patients with breast cancer due to lack of treatment response. Moreover, in vivo results showed that blocking the EV-mediated transfer of HISLA caused inhibition of glycolysis and chemoresistance in breast cancer cells [160].

The presence of circular RNAs in EVs has also been described to mediate drug resistance by inducing metabolic alterations in cancer cells. An in vitro and in vivo study reported the ability of EVs shed by oxaliplatin-resistant colorectal cancer cells to deliver the circular RNA hsa_circ_0005963 (ciRS-122) to chemosensitive cells. The ciRS-122 was positively associated with drug resistance through upregulation of glycolysis and PKM2 expression. Additionally, in vivo results showed that silencing ciRS-122 improved drug response [161]. Furthermore, another study revealed that EVs derived from pancreatic cancer cells under hypoxic conditions were able to enhance gemcitabine resistance in normoxic cells. The authors proposed that the mechanism behind this effect involved the circular RNA circZNF91, which was increased in EVs derived from hypoxic cells [162]. Indeed, circZNF91 was positively correlated with the overexpression of glycolytic enzymes and, after treatment with hypoxic EVs containing circZNF91, normoxic cells presented higher mRNA and protein levels of GLUT1, lactate dehydrogenase A (LDHA), HK2 and PKM2. Moreover, these authors described the competitive binding of circZNF91 to miR-23b-3p, which was found to upregulate the expression of the deacetylase Sirtuin1. In turn, this protein increased deacetylation-dependent stability of HIF-1α protein, promoting glycolysis and gemcitabine resistance. Thus, the authors suggested that targeting circZNF91 and inhibiting HIF-1α or glycolysis enhanced chemosensitivity of pancreatic cancer cells to gemcitabine treatment [162]. Also, the circular RNA DLGAP4 (circDLGAP4) carried by EVs played an important role in neuroblastoma chemoresistance [163]. The authors of this study demonstrated that neuroblastoma cells resistant to doxorubicin expressed higher levels of HK2 as well as higher glycolytic rates. Moreover, exosomes derived from these cells carried

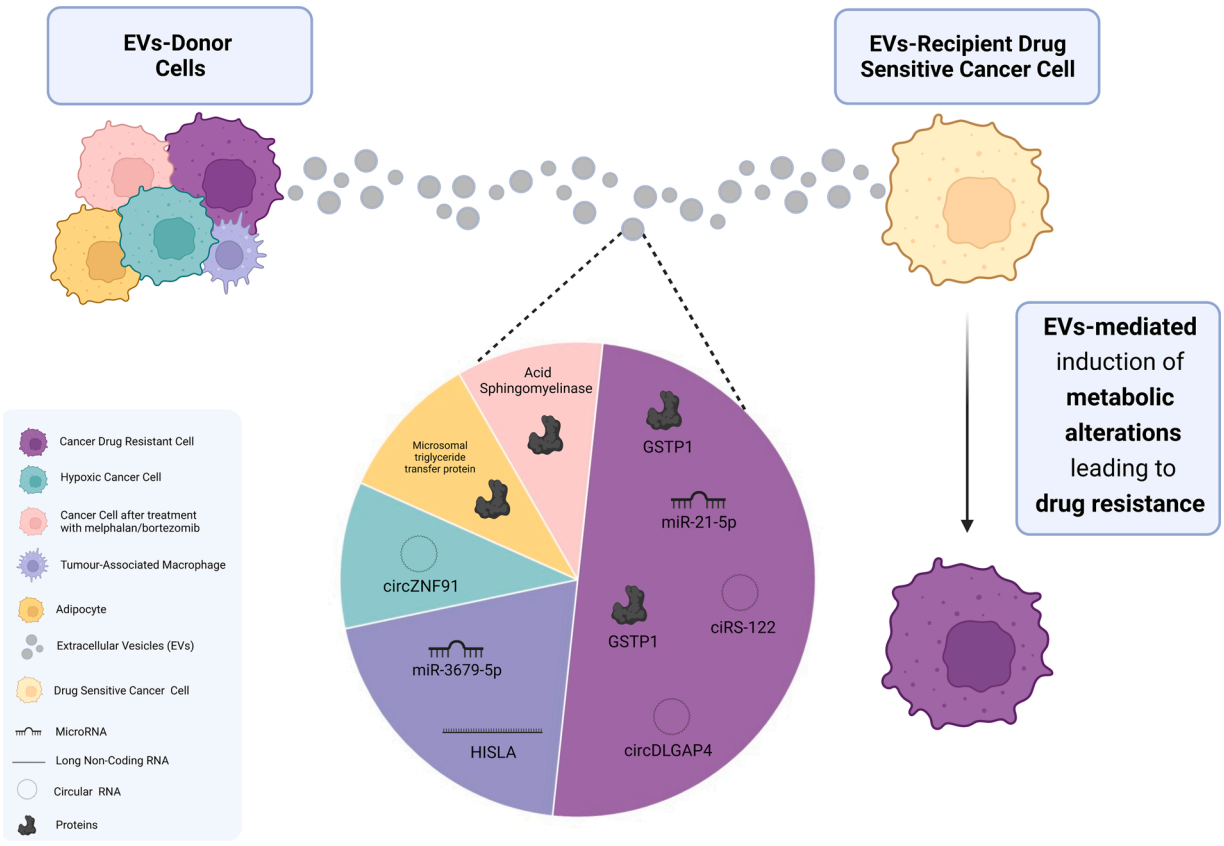

Fig. 3. Extracellular Vesicles (EVs) cargo released by different cancer and tumour microenvironment cells. This cargo has been reported to induce metabolic alterations in recipient cells, conferring them a drug resistant phenotype. Figure created with BioRender.com.

circDLGAP4 and delivered it to sensitive cells. This circular RNA functioned as a sponge for the HK2-targeting miR-143. Additionally, knockdown of circDLGAP4 reversed drug resistance in recipient cells. Thus, the authors suggested that exosome-delivered circDLGAP4 may enhance glycolysis and drug resistance in neuroblastoma cells via regulation of miR-143 and HK2 [163].

3.2.2. *Metabolic associated proteins on EVs cargo*

The direct regulation of metabolic enzymes, mediated by EVs, may also lead to drug resistance. Glutathione S-transferase P1 (GSTP1) is a phase II metabolic enzyme that belongs to the glutathione S-transferase family of proteins and is involved in the detoxification process of several drugs [164]. Increased expression of GSTP1 was found in adriamycin-resistant breast cancer cells and their EVs, when compared to sensitive control cells and respective EVs. Furthermore, this study also reported a shift to a drug resistant phenotype in the sensitive cells, following exposure to and internalization of GSTP1-containing EVs shed by adriamycin-resistant cells. Additionally, after treatment with GSTP1-siRNA, the apoptotic rates of adriamycin-resistant cells increased and resistance to adriamycin decreased. Thus, these authors suggested that there might be a positive correlation between GSTP1 levels and drug resistance in breast cancer cells [165].

In a study using EVs isolated from ovarian cancer cells incubated in low oxygen tension (hypoxia), the ability of these EVs to confer carboplatin resistance to previously sensitive ovarian cancer cells was reported. Moreover, these authors referred that the chemoresistant ovarian cells showed alterations in glycolysis and FAs synthesis. Supporting this information, several glycolysis associated proteins [such as PKM1/2, enolase 1 (ENO1) and fructose-bisphosphatase A] were identified in EVs isolated from the plasma of patients with ovarian cancer recurrence [166]. High levels of the glycolytic enzyme PKM2 were also found in the cargo of EVs released by hypoxic non-small cell lung cancer cells resistant to cisplatin. These EVs induced chemoresistance in previously sensitive cells through two different mechanisms. The first consisted in the direct transfer of PKM2 to sensitive cells, which may regulate glycolysis to produce reduced metabolites, decreasing ROS levels and inhibiting apoptosis in a PKM2-BCL2-dependent manner. The second involved the metabolic reprogramming of CAFs though PKM2, leading to pyruvate and lactate release, promoting tumor proliferation, invasion and chemoresistance [167].

The alteration in the metabolism of lipids, mediated by EVs, also has an impact in cancer drug resistance. For instance, in a study using multiple myeloma primary cells, an upregulation in the expression of acid sphingomyelinase (an enzyme involved in the metabolism of sphingomyelin to ceramide and phosphorylcholine) was found after treatment of these cells with melphalan or bortezomib. Moreover, EVs shed by these cells presented the same increase in acid sphingomyelinase. Interestingly, the authors reported that these EVs were able to transfer a drug-resistant phenotype to chemosensitive cells, suggesting a tumour protective role for the metabolic enzyme acid sphingomyelinase [97]. An increase in the expression of the microsomal triglyceride transfer protein (MTTP) was found in adipocyte derived EVs as well as in EVs from the plasma of colorectal cancer patients presenting a high body fat ratio. This protein was linked with ferroptosis inhibition and resistance to oxaliplatin in colorectal cancer, since it increases the ratio between saturated/unsaturated FAs in plasma membrane [168].

3.2.3. *Other modulators on EVs cargo*

Other modulators of the transfer of metabolic traits mediated by EVs, are growth factors and phosphorylated signalling proteins. For instance, EVs secreted by acute myeloid leukaemia cells were able to induce glycolysis in human umbilical vein endothelial cells (HUVECs), which in turn lead to vascular remodelling and chemoresistance in drug-sensitive cells. This effect was mediated by the presence of VEGF and VEGF

Table 1
Extracellular Vesicles (EVs) cargo and EVs mediated metabolic reprogramming leading to drug resistance in cancer cells.

Type of EVs cargo	Identified mediators of metabolic reprogramming	Cancer Type	Study Model Used	Observed Results	References
Not Described	Not Described	Lung Cancer and Acute Myeloid Leukaemia	Cell Lines	EVs released by the MDR cells stimulated a metabolic switch in the drug-sensitive counterpart cells, conferring them a MDR phenotype.	[157]
Non-Coding RNAs (miRNAs, lncRNAs, CircularRNAs)	miR-3679–5p	Lung Cancer	Cell Lines, Tumour xenografts in mice and Patient Tissues Samples	M2 macrophage-derived exosomes promoted cisplatin resistance in lung cancer cells by delivering miR-3679–5p, which downregulated NEDD4L. In turn, it promoted increased glycolysis and c-Myc stability, leading to chemoresistance.	[158]
	miR-21–5p	Ovarian Cancer	Cell Lines and Patient Tissues Samples	Exosomes derived from ovarian cancer cells resistant to cisplatin conferred sensitive cells an increased glycolytic rate and a chemoresistant phenotype, by delivering miR-21–5p and consequently targeting PDHA1.	[159]
	lncRNA HISLA	Breast Cancer	Cell lines, Tumour xenografts in mice, Patient Tissues Samples and Primary Culture	EVs from breast cancer tumor-associated macrophages delivered the lncRNA HISLA to breast cancer cells, promoting aerobic glycolysis, apoptosis resistance and chemoresistance, by stabilization of HIF-α. A correlation between HISLA and lack of treatment response in patients was also found.	[160]
	ciRS-122	Colorectal Cancer	Cell lines, Tumour xenografts in mice and Patient Tissues Samples	EVs-mediated transfer of ciRS-122 from oxiplatin-resistant colorectal cancer cells to sensitive cells increased glycolysis and PKM2 expression, inducing a drug resistant phenotype.	[161]
	circZNF91	Pancreatic Cancer	Cell lines, Tumour xenografts in mice,Patient Tissues and Blood samples	Exosomes derived from hypoxic pancreatic cancer cells promoted glycolysis and chemoresistance in normoxic cells through delivery of circZNF91, which acted as a miR-23b-3p sponge, upregulating SIRT1 expression and leading to HIF-1α protein stabilization.	[162]
	circDLGAP4	Neuroblastoma	Cell Lines	Exosome-delivered circDLGAP4 from doxorubicin resistant cells enhanced glycolysis and drug resistance in neuroblastoma sensitive cells via regulation of miR-143 and HK2.	[163]
Metabolic Enzymes	GSTP1	Breast Cancer	Cell lines, Patient Tissues and Blood samples	EVs-mediated transfer of GSTP1 from adriamycin-resistant breast cancer cells induced drug resistance in adriamycin sensitive breast cancer cells.	[165]
	PKM1/2, ENO1 and fructose-bisphosphate A	Ovarian Cancer	Cell lines and Patient blood samples	EVs shed by hypoxic ovarian cancer cells induced resistance to carboplatin in previously sensitive cells, accompanied by alterations in glycolysis and FAs synthesis. Additionally, metabolic proteins such as PKM1/2, ENO1 and fructose-bisphosphate A were identified in EVs from patient blood samples with ovarian cancer recurrence.	[166]
	PKM2	Lung Cancer	Cell Lines	EVs derived from cisplatin resistant non-small cell lung cancer cells presented a high level of PKM2 and were able to induce a chemoresistant phenotype in sensitive cells.	[167]
	Acid Sphingomyelinase	Multiple Myeloma	Cell Lines and Primary Culture	EVs shed by primary multiple myeloma cells presenting a high level of Acid Sphingomyelinase were able to induce chemoresistance in sensitive cells.	[97]
	Microsomal triglyceride transfer protein	Colorectal Cancer	Cell lines, Tumour xenografts in mice and Patient Tissues Samples	Microsomal triglyceride transfer protein was present in the cargo of adipocyte derived-EVs and was able to inhibit ferroptosis and promote chemoresistance to oxiplatin in colorectal cancer through the MTTP/PRAP1/ZEB1 axis.	[168]
Other Modulators	VEGF and VEGFR RNA	Acute Myeloid Leukaemia	Cell Lines	VEGF and VEGFR RNA carried by Acute Myeloid Leukaemia derived-EVs were able to promote vascular remodelling, glycolysis and drug resistance in HUVECs.	[169]
	p-ERK and p-AKT	Colorectal Cancer	Cell Lines and Patient Plasma Samples	p-ERK and p-AKT, delivered by EVs derived from normoxic colorectal cancer cells, activated HSCs, increasing the release of IL-6. In turn, IL-6 rewired lactate metabolism in hypoxic colorectal cancer cells, inducing drug resistance.	[170]

receptor (VEGFR) RNA in EVs, which were transferred to HUVECs, inducing glycolysis and chemoresistance in these cells [169]. In another study, EVs derived from normoxic colorectal cancer cells were able to activate hepatic stellate cells (HSCs) through the delivery of p-ERK and p-AKT, increasing the secretion of interleukin-6. In turn, interleukin-6 released by HSCs enhanced lactate metabolism of hypoxic colorectal cancer cells by upregulating the expression of monocarboxylate transporter 1, a lactate transporter, and lactate dehydrogenase B, an enzyme that catalyses the conversion of lactate into pyruvate. Rewiring of lactate metabolism lead to apoptosis inhibition in hypoxic colorectal tumour cells, thus conferring chemoresistance [170].

4. Discussion

Despite the scientific progress in the treatment of cancer, the acquisition of drug resistant traits by cancer cells remains one of the main causes of treatment failure. Given the fact that the metabolic reprogramming of cancer cells has been linked to the development of drug resistant traits, the disparity between the metabolic features of sensitive and resistant cells should be further studied to identify targets to overcome drug resistance. Nevertheless, the reprogramming of energy metabolism is highly variable due to intratumour (and intertumour) characteristics of cancer cells and their TME, making the study of the involved mechanisms a highly challenging research field. Importantly, the role of EVs as mediators of drug resistance in cancer is an already established fact among the scientific community. However, little is known regarding the ability of EVs released by drug resistant cells or by TME cells, to transfer metabolic features associated with drug resistance to drug-sensitive cancer cells. Further understanding of this intercellular communication network could contribute to the identification of novel biomarkers of drug response and/or therapeutic targets to overcome drug resistance.

Importantly, while the transfer of ncRNAs or proteins via EVs is widely described, surprisingly few evidence exists on the transfer of lipids that can induce a metabolic rewiring, triggering metastatic behaviour and/or drug resistance. Untargeted lipidome analyses of EVs from sensitive and resistant cells could help identifying a set of lipids characterizing good or poor response to chemotherapy in specific tumours. Based on this information, EVs enriched in specific lipids may be used to induce chemosensitization and/or prevent drug resistance caused by the horizontal transfer between resistant and sensitive cells. This exciting field is open to new investigations and may lead to an innovative approach in the prevention or overcoming of drug resistance.

EVs can be also manipulated in a reverse perspective, making them therapeutic tools. Indeed, the analysis of the cargos of EVs released by sensitive cells, in terms of miRNAs, proteins, metabolites and lipids, may be useful to treat resistant tumours with sensitive cell-derived EVs. This might induce a metabolic rewiring in the resistant cells (e.g. changes in plasma membrane lipid composition, shift from glycolytic to OXPHOS-based metabolism, transfer of chemosensitizing miRNAs and lncRNAs), thus reversing drug resistance in those cells. A better dissection of the role of each metabolite, protein or ncRNA in the EVs cargo could help to select the most effective EVs in inducing chemosensitization (as the ones most enriched in a specific sensitizing molecule).

Furthermore, as part of the continuous evolution of pharmaceutical biotechnology and discovery of advanced therapies, EVs from sensitive cells could also be exploited as carriers of chemotherapeutic drugs, small molecules acting as target therapy or immunotherapeutic agents. These engineered EVs could couple the benefits derived from the endogenous components of EVs, reflecting the protein, lipid composition and metabolism of donor sensitive cells, with the exogenous enrichment with anticancer agents, opening the possibility for a new multitarget approach that may be effective against the most aggressive and drug resistant tumours.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This article is based upon work from COST Action IG17104 – PANDORA, supported by COST (European Cooperation in Science and Technology), www.cost.eu. The Vasconcelos group is supported (in part) by project NORTE-01–0145-FEDER-072678 - Consórcio PORTO. CCC – Porto.Comprehensive Cancer Center, and by project NORTE-01–0145-FEDER-000051, supported by Norte Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF). Chiara Riganti and Joanna Kopecka acknowledge the Italiano Association for Cancer Research (AIRC; code: IG21408). Cristina P.R. Xavier is supported by the Fundação para a Ciência e a Tecnologia (FCT) and the Fundo Social Europeu (FSE), Portugal, through the postdoctoral grant SFRH/BPD/122871/2016. Bárbara Polónia is supported by FCT, through the PhD fellowship SFRH/BD/07661/2021.

References

[1] D. Hanahan Robert, Hallmarks of cancer: the next generation, Cell 144 (5) (2011) 646–674.
[2] R.J. DeBerardinis, N.S. Chandel, Fundamentals of cancer metabolism, Sci. Adv. 2 (5) (2016), e1600200.
[3] N.N. Pavlova, J. Zhu, C.B. Thompson, The hallmarks of cancer metabolism: Still emerging, Cell Metab. 34 (3) (2022) 355–377.
[4] B. Bhattacharya, M.F. Mohd Omar, R. Soong, The Warburg effect and drug resistance, Br. J. Pharm. 173 (6) (2016) 970–979.
[5] G. Solaini, G. Sgarbi, A. Baracca, Oxidative phosphorylation in cancer cells, Biochim Biophys. Acta 1807 (6) (2011) 534–542.
[6] J.D. Weyandt, C.B. Thompson, A.J. Giaccia, W.K. Rathmell, Metabolic alterations in cancer and their potential as therapeutic targets, Am. Soc. Clin. Oncol. Educ. Book 37 (2017) 825–832.
[7] O. Warburg, F. Wind, E. Negelein, The metabolism of tumors in the body, J. Gen. Physiol. 8 (6) (1927) 519–530.
[8] O. Warburg, On the origin of cancer cells, Science 123 (3191) (1956) 309–314.
[9] O. Warburg, On respiratory impairment in cancer cells, Science 124 (3215) (1956) 269–270.
[10] I. Martínez-Reyes, L.P. Diebold, H. Kong, M. Schieber, H. Huang, C.T. Hensley, M. M. Mehta, T. Wang, J.H. Santos, R. Woychik, E. Dufour, J.N. Spelbrink, S. E. Weinberg, Y. Zhao, R.J. DeBerardinis, N.S. Chandel, TCA cycle and mitochondrial membrane potential are necessary for diverse biological functions, Mol. Cell 61 (2) (2016) 199–209.
[11] D.C. Wallace, Mitochondria and cancer, Nat. Rev. Cancer 12 (10) (2012) 685–698.
[12] E.A. Zaal, C.R. Berkers, The influence of metabolism on drug response in cancer, Front. Oncol. 8 (2018).
[13] H. Lincet, P. Icard, How do glycolytic enzymes favour cancer cell proliferation by nonmetabolic functions? Oncogene 34 (29) (2015) 3751–3759.
[14] W.P. Roos, A.D. Thomas, B. Kaina, DNA damage and the balance between survival and death in cancer biology, Nat. Rev. Cancer 16 (1) (2016) 20–33.
[15] Y. He, Y. Luo, D. Zhang, X. Wang, P. Zhang, H. Li, S. Ejaz, S. Liang, PGK1-mediated cancer progression and drug resistance, Am. J. Cancer Res 9 (11) (2019) 2280–2302.
[16] L.P. Fernández, M. Gómez de Cedrón, A. Ramírez de Molina, Alterations of lipid metabolism in cancer: implications in prognosis and treatment, Front. Oncol. 10 (2144) (2020).
[17] S.R. Islam, S.K. Manna, Lipidomic analysis of cancer cell and tumor tissues, Methods Mol. Biol. 2019 (1928) 175–204.
[18] E. Currie, A. Schulze, R. Zechner, T.C. Walther, R.V. Farese Jr., Cellular fatty acid metabolism and cancer, Cell Metab. 18 (2) (2013) 153–161.
[19] V. Chajès, M. Cambot, K. Moreau, G.M. Lenoir, V. Joulin, Acetyl-CoA carboxylase alpha is essential to breast cancer cell survival, Cancer Res 66 (10) (2006) 5287–5294.
[20] T. Migita, T. Narita, K. Nomura, E. Miyagi, F. Inazuka, M. Matsuura, M. Ushijima, T. Mashima, H. Seimiya, Y. Satoh, S. Okumura, K. Nakagawa, Y. Ishikawa, ATP citrate lyase: activation and therapeutic implications in non-small cell lung cancer, Cancer Res 68 (20) (2008) 8547–8554.
[21] N. Koundouros, G. Poulogiannis, Reprogramming of fatty acid metabolism in cancer, Br. J. Cancer 122 (1) (2020) 4–22.
[22] A. Carracedo, L.C. Cantley, P.P. Pandolfi, Cancer metabolism: fatty acid oxidation in the limelight, Nat. Rev. Cancer 13 (4) (2013) 227–232.
[23] L.S. Pike, A.L. Smift, N.J. Croteau, D.A. Ferrick, M. Wu, Inhibition of fatty acid oxidation by etomoxir impairs NADPH production and increases reactive oxygen species resulting in ATP depletion and cell death in human glioblastoma cells, Biochim Biophys. Acta 1807 (6) (2011) 726–734.
[24] P.J. Mullen, R. Yu, J. Longo, M.C. Archer, L.Z. Penn, The interplay between cell signalling and the mevalonate pathway in cancer, Nat. Rev. Cancer 16 (11) (2016) 718–731.
[25] C.T. Hensley, A.T. Wasti, R.J. DeBerardinis, Glutamine and cancer: cell biology, physiology, and clinical opportunities, J. Clin. Invest 123 (9) (2013) 3678–3684.
[26] J.W. Erickson, R.A. Cerione, Glutaminase: a hot spot for regulation of cancer cell metabolism? Oncotarget 1 (8) (2010) 734–740.
[27] A.J. Bott, I.C. Peng, Y. Fan, B. Faubert, L. Zhao, J. Li, S. Neidler, Y. Sun, N. Jaber, D. Krokowski, W. Lu, J.-A. Pan, S. Powers, J. Rabinowitz, M. Hatzoglou, D. J. Murphy, R. Jones, S. Wu, G. Girnun, W.-X. Zong, Oncogenic myc induces expression of glutamine synthetase through promoter demethylation, Cell Metab. 22 (6) (2015) 1068–1077.

[28] P. Gao, I. Tchernyshyov, T.C. Chang, Y.S. Lee, K. Kita, T. Ochi, K.I. Zeller, A.M. De Marzo, J.E. Van Eyk, J.T. Mendell, C.V. Dang, c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism, Nature 458 (7239) (2009) 762–765.
[29] M.A. Desbats, I. Giacomini, T. Prayer-Galetti, M. Montopoli, Metabolic plasticity in chemotherapy resistance, Front. Oncol. 10 (2020), 281-281.
[30] A.C. Gonçalves, E. Richiardone, J. Jorge, B. Polónia, C.P.R. Xavier, I.C. Salaroglio, C. Riganti, M.H. Vasconcelos, C. Corbet, A.B. Sarmento-Ribeiro, Impact of cancer metabolism on therapy resistance - Clinical implications, Drug Resist. Updates (2021), 100797.
[31] L. Wang, X. Zhao, J. Fu, W. Xu, J. Yuan, The role of tumour metabolism in cisplatin resistance, Front. Mol. Biosci. 8 (603) (2021).
[32] M.M. Gottesman, O. Lavi, M.D. Hall, J.-P. Gillet, Toward a better understanding of the complexity of cancer drug resistance, Annu. Rev. Pharmacol. Toxicol. 56 (1) (2016) 85–102.
[33] Y.G. Assaraf, A. Brozovic, A.C. Gonçalves, D. Jurkovicova, A. Linē, M. Machuqueiro, S. Saponara, A.B. Sarmento-Ribeiro, C.P.R. Xavier, M. H. Vasconcelos, The multi-factorial nature of clinical multidrug resistance in cancer, Drug Resist. Updates 46 (2019), 100645.
[34] M.H. Vasconcelos, H.R. Caires, A. Ābols, C.P.R. Xavier, A. Linē, Extracellular vesicles as a novel source of biomarkers in liquid biopsies for monitoring cancer progression and drug resistance, Drug Resist Updat 47 (2019), 100647.
[35] K.O. Alfarouk, C.-M. Stock, S. Taylor, M. Walsh, A.K. Muddathir, D. Verduzco, A. H.H. Bashir, O.Y. Mohammed, G.O. Elhassan, S. Harguindey, S.J. Reshkin, M. E. Ibrahim, C. Rauch, Resistance to cancer chemotherapy: failure in drug response from ADME to P-gp, Cancer Cell Int. 15 (1) (2015) 71.
[36] I. Dagogo-Jack, A.T. Shaw, Tumour heterogeneity and resistance to cancer therapies, Nat. Rev. Clin. Oncol. 15 (2) (2018) 81–94.
[37] E. Ozyerli-Goknar, T. Bagci-Onder, Epigenetic deregulation of apoptosis in cancers, Cancers (Basel) 13 (13) (2021).
[38] R.P. Riechelmann, A. Del Giglio, Drug interactions in oncology: how common are they? Ann. Oncol. 20 (12) (2009) 1907–1912.
[39] L. Bu, H. Baba, T. Yasuda, T. Uchihara, T. Ishimoto, Functional diversity of cancer-associated fibroblasts in modulating drug resistance, Cancer Sci. 111 (10) (2020) 3468.
[40] D. Kadel, Y. Zhang, H.-R. Sun, Y. Zhao, Q.-Z. Dong, L.-x Qin, Current perspectives of cancer-associated fibroblast in therapeutic resistance: potential mechanism and future strategy, Cell Biol. Toxicol. 35 (5) (2019) 407–421.
[41] C.P.R. Xavier, I. Castro, H.R. Caires, D. Ferreira, B. Cavadas, L. Pereira, L. L. Santos, M.J. Oliveira, M.H. Vasconcelos, 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 (2021) 210–223.
[42] R.T. Lima, L.M. Martins, J.E. Guimarães, C. Sambade, M.H. Vasconcelos, 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 (5) (2004) 309–316.
[43] M. Mollaei, Z.M. Hassan, F. Khorshidi, L. Langroudi, Chemotherapeutic drugs: Cell death- and resistance-related signaling pathways. Are they really as smart as the tumor cells? Transl. Oncol. 14 (5) (2021), 101056.
[44] L.-y Li, Y.-d Guan, X.-s Chen, J.-m Yang, Y. Cheng, DNA repair pathways in cancer therapy and resistance, Front. Pharmacol. 11 (2520) (2021).
[45] H. Seca, R.T. Lima, V. Lopes-Rodrigues, J.E. Guimaraes, G.M. Almeida, M. H. Vasconcelos, Targeting miR-21 induces autophagy and chemosensitivity of leukemia cells, Curr. Drug Targets 14 (10) (2013) 1135–1143.
[46] R.T. Lima, S. Busacca, G.M. Almeida, G. Gaudino, D.A. Fennell, M.H. Vasconcelos, MicroRNA regulation of core apoptosis pathways in cancer, Eur. J. Cancer 47 (2) (2011) 163–174.
[47] H. Joyce, A. McCann, M. Clynes, A. Larkin, Influence of multidrug resistance and drug transport proteins on chemotherapy drug metabolism, Expert Opin. Drug Metab. Toxicol. 11 (5) (2015) 795–809.
[48] A. Garnier-Suillerot, C. Marbeuf-Gueye, M. Salerno, C. Loetchutinat, I. Fokt, M. Krawczyk, T. Kowalczyk, W. Priebe, Analysis of drug transport kinetics in multidrug-resistant cells: implications for drug action, Curr. Med Chem. 8 (1) (2001) 51–64.
[49] J. Lin, L. Xia, J. Liang, Y. Han, H. Wang, L. Oyang, S. Tan, Y. Tian, S. Rao, X. Chen, Y. Tang, M. Su, X. Luo, Y. Wang, H. Wang, Y. Zhou, Q. Liao, The roles of glucose metabolic reprogramming in chemo- and radio-resistance, J. Exp. Clin. Cancer Res 38 (1) (2019) 218.
[50] M.A.S. Broggi, L. Maillat, C.C. Clement, N. Bordry, P. Corthésy, A. Auger, M. Matter, R. Hamelin, L. Potin, D. Demurtas, E. Romano, A. Harari, D.E. Speiser, L. Santambrogio, M.A. Swartz, Tumor-associated factors are enriched in lymphatic exudate compared to plasma in metastatic melanoma patients, J. Exp. Med. 216 (5) (2019) 1091–1107.
[51] K. Platko, S. Haas-Neill, T. Aziz, K. Al-Nedawi, The role of circulating extracellular vesicles in breast cancer classification and molecular subtyping, Breast J. 25 (4) (2019) 691–695.
[52] M. Colombo, G. Raposo, C. Théry, Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles, Annu Rev. Cell Dev. Biol. 30 (2014) 255–289.
[53] C. Théry, K.W. Witwer, E. Aikawa, M.J. Alcaraz, J.D. Anderson, R. Andriantsitohaina, A. Antoniou, T. Arab, F. Archer, G.K. Atkin-Smith, D. C. Ayre, J.M. Bach, D. Bachurski, H. Baharvand, L. Balaj, S. Baldacchino, N. N. Bauer, A.A. Baxter, M. Bebawy, C. Beckham, A. Bedina Zavec, A. Benmoussa, A.C. Berardi, P. Bergese, E. Bielska, C. Blenkiron, S. Bobis-Wozowicz, E. Boilard, W. Boireau, A. Bongiovanni, F.E. Borràs, S. Bosch, C.M. Boulanger, X. Breakefield, A.M. Breglio, M. Brennan, D.R. Brigstock, A. Brisson, M.L. Broekman, J. F. Bromberg, P. Bryl-Górecka, S. Buch, A.H. Buck, D. Burger, S. Busatto, D. Buschmann, B. Bussolati, E.I. Buzás, J.B. Byrd, G. Camussi, D.R. Carter, S. Caruso, L.W. Chamley, Y.T. Chang, C. Chen, S. Chen, L. Cheng, A.R. Chin, A. Clayton, S.P. Clerici, A. Cocks, E. Cocucci, R.J. Coffey, A. Cordeiro-da-Silva, Y. Couch, F.A. Coumans, B. Coyle, R. Crescitelli, M.F. Criado, C. D'Souza-Schorey, S. Das, A. Datta Chaudhuri, P. de Candia, E.F. De Santana, O. De Wever, H.A. Del Portillo, T. Demaret, S. Deville, A. Devitt, B. Dhondt, D. Di Vizio, L.C. Dieterich, V. Dolo, A.P. Dominguez Rubio, M. Dominici, M.R. Dourado, T.A. Driedonks, F. V. Duarte, H.M. Duncan, R.M. Eichenberger, K. Ekström, S. El Andaloussi, C. Elie-Caille, U. Erdbrügger, J.M. Falcón-Pérez, F. Fatima, J.E. Fish, M. Flores-Bellver, A. Försönits, A. Frelet-Barrand, F. Fricke, G. Fuhrmann, S. Gabrielsson, A. Gámez-Valero, C. Gardiner, K. Gärtner, R. Gaudin, Y.S. Gho, B. Giebel, C. Gilbert, M. Gimona, I. Giusti, D.C. Goberdhan, A. Görgens, S.M. Gorski, D.W. Greening, J. C. Gross, A. Gualerzi, G.N. Gupta, D. Gustafson, A. Handberg, R.A. Haraszti, P. Harrison, H. Hegyesi, A. Hendrix, A.F. Hill, F.H. Hochberg, K.F. Hoffmann, B. Holder, H. Holthofer, B. Hosseinkhani, G. Hu, Y. Huang, V. Huber, S. Hunt, A. G. Ibrahim, T. Ikezu, J.M. Inal, M. Isin, A. Ivanova, H.K. Jackson, S. Jacobsen, S. M. Jay, M. Jayachandran, G. Jenster, L. Jiang, S.M. Johnson, J.C. Jones, A. Jong, T. Jovanovic-Talisman, S. Jung, R. Kalluri, S.I. Kano, S. Kaur, Y. Kawamura, E. T. Keller, D. Khamari, E. Khomyakova, A. Khvorova, P. Kierulf, K.P. Kim, T. Kislinger, M. Klingeborn, D.J. Klinke, 2nd, M. Kornek, M.M. Kosanović, F. Kovács Á, E.M. Krämer-Albers, S. Krasemann, M. Krause, I.V. Kurochkin, G. D. Kusuma, S. Kuypers, S. Laitinen, S.M. Langevin, L.R. Languino, J. Lannigan, C. Lässer, L.C. Laurent, G. Lavieu, E. Lázaro-Ibáñez, S. Le Lay, M.S. Lee, Y.X. F. Lee, D.S. Lemos, M. Lenassi, A. Leszczynska, I.T. Li, K. Liao, S.F. Libregts, E. Ligeti, R. Lim, S.K. Lim, A. Linē, K. Linnemannstöns, A. Llorente, C.A. Lombard, M.J. Lorenowicz, M. Lörincz Á, J. Lötvall, J. Lovett, M.C. Lowry, X. Loyer, Q. Lu, B. Lukomska, T.R. Lunavat, S.L. Maas, H. Malhi, A. Marcilla, J. Mariani, J. Mariscal, E.S. Martens-Uzunova, L. Martin-Jaular, M.C. Martinez, V.R. Martins, M. Mathieu, S. Mathivanan, M. Maugeri, L.K. McGinnis, M.J. McVey, D. G. Meckes, Jr, K.L. Meehan, I. Mertens, V.R. Minciacchi, A. Möller, M. Møller Jørgensen, A. Morales-Kastresana, J. Morhayim, F. Mullier, M. Muraca, L. Musante, V. Mussack, D.C. Muth, K.H. Myburgh, T. Najrana, M. Nawaz, I. Nazarenko, P. Nejsum, C. Neri, T. Neri, R. Nieuwland, L. Nimrichter, J.P. Nolan, E.N. Nolte-'t Hoen, N. Noren Hooten, L. O'Driscoll, T. O'Grady, A. O'Loghlen, T. Ochiya, M. Olivier, A. Ortiz, L.A. Ortiz, X. Osteikoetxea, O. Østergaard, M. Ostrowski, J. Park, D.M. Pegtel, H. Peinado, F. Perut, M.W. Pfaffl, D. G. Phinney, B.C. Pieters, R.C. Pink, D.S. Pisetsky, E. Pogge von Strandmann, I. Polakovicova, I.K. Poon, B.H. Powell, I. Prada, L. Pulliam, P. Quesenberry, A. Radeghieri, R.L. Raffai, S. Raimondo, J. Rak, M.I. Ramirez, G. Raposo, M. S. Rayyan, N. Regev-Rudzki, F.L. Ricklefs, P.D. Robbins, D.D. Roberts, S. C. Rodrigues, E. Rohde, S. Rome, K.M. Rouschop, A. Rughetti, A.E. Russell, P. Saá, S. Sahoo, E. Salas-Huenuleo, C. Sánchez, J.A. Saugstad, M.J. Saul, R. M. Schiffelers, R. Schneider, T.H. Schøyen, A. Scott, E. Shahaj, S. Sharma, O. Shatnyeva, F. Shekari, G.V. Shelke, A.K. Shetty, K. Shiba, P.R. Siljander, A. M. Silva, A. Skowronek, O.L. Snyder, 2nd, R.P. Soares, B.W. Sódar, C. Soekmadji, J. Sotillo, P.D. Stahl, W. Stoorvogel, S.L. Stott, E.F. Strasser, S. Swift, H. Tahara, M. Tewari, K. Timms, S. Tiwari, R. Tixeira, M. Tkach, W.S. Toh, R. Tomasini, A. C. Torrecilhas, J.P. Tosar, V. Toxavidis, L. Urbanelli, P. Vader, B.W. van Balkom, S.G. van der Grein, J. Van Deun, M.J. van Herwijnen, K. Van Keuren-Jensen, G. van Niel, M.E. van Royen, A.J. van Wijnen, M.H. Vasconcelos, I.J. Vechetti, Jr, T.D. Veit, L.J. Vella, É. Velot, F.J. Verweij, B. Vestad, J.L. Viñas, T. Visnovitz, K. V. Vukman, J. Wahlgren, D.C. Watson, M.H. Wauben, A. Weaver, J.P. Webber, V. Weber, A.M. Wehman, D.J. Weiss, J.A. Welsh, S. Wendt, A.M. Wheelock, Z. Wiener, L. Witte, J. Wolfram, A. Xagorari, P. Xander, J. Xu, X. Yan, M. Yáñez-Mó, H. Yin, Y. Yuana, V. Zappulli, J. Zarubova, V. Žėkas, J.Y. Zhang, Z. Zhao, L. Zheng, A.R. Zheutlin, A.M. Zickler, P. Zimmermann, A.M. Zivkovic, D. Zocco, E.K. Zuba-Surma, Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines, J. Extra Vesicles 7 (1) (2018) 1535750.
[54] R.H. Xu, H. Pelicano, Y. Zhou, J.S. Carew, L. Feng, K.N. Bhalla, M.J. Keating, P. Huang, Inhibition of glycolysis in cancer cells: a novel strategy to overcome drug resistance associated with mitochondrial respiratory defect and hypoxia, Cancer Res 65 (2) (2005) 613–621.
[55] W. Xu, S. Wang, Q. Chen, Y. Zhang, P. Ni, X. Wu, J. Zhang, F. Qiang, A. Li, O. D. Røe, S. Xu, M. Wang, R. Zhang, J. Zhou, TXNL1-XRCC1 pathway regulates cisplatin-induced cell death and contributes to resistance in human gastric cancer, Cell Death Dis. 5 (2) (2014), e1055.
[56] M.R. Ambrosio, V. D'Esposito, V. Costa, D. Liguoro, F. Collina, M. Cantile, N. Prevete, C. Passaro, G. Mosca, M. De Laurentiis, M. Di, G. Bonito, R. Botti, R. Franco, F. Beguinot, A. Ciccodicola, P. Formisano, Glucose impairs tamoxifen responsiveness modulating connective tissue growth factor in breast cancer cells, Oncotarget 8 (65) (2017) 109000–109017.
[57] K.M. Koczula, C. Ludwig, R. Hayden, L. Cronin, G. Pratt, H. Parry, D. Tennant, M. Drayson, C.M. Bunce, F.L. Khanim, U.L. Günther, Metabolic plasticity in CLL: adaptation to the hypoxic niche, Leukemia 30 (1) (2016) 65–73.
[58] M. Wartenberg, M. Richter, A. Datchev, S. Günther, N. Milosevic, M.M. Bekhite, H.R. Figulla, J.M. Aran, J. Pétriz, H. Sauer, Glycolytic pyruvate regulates P-Glycoprotein expression in multicellular tumor spheroids via modulation of the intracellular redox state, J. Cell Biochem 109 (2) (2010) 434–446.
[59] W. Wagner, W.M. Ciszewski, K.D. Kania, L- and D-lactate enhance DNA repair and modulate the resistance of cervical carcinoma cells to anticancer drugs via histone deacetylase inhibition and hydroxycarboxylic acid receptor 1 activation, Cell Commun. Signal 13 (2015) 36.

[60] K.A. Zub, M.M. Sousa, A. Sarno, A. Sharma, A. Demirovic, S. Rao, C. Young, P. A. Aas, I. Ericsson, A. Sundan, O.N. Jensen, G. Slupphaug, Modulation of cell metabolic pathways and oxidative stress signaling contribute to acquired melphalan resistance in multiple myeloma cells, PLoS One 10 (3) (2015), e0119857.
[61] P.E. Porporato, S. Dhup, R.K. Dadhich, T. Copetti, P. Sonveaux, Anticancer targets in the glycolytic metabolism of tumors: a comprehensive review, Front. Pharmacol. 2 (2011), 49-49.
[62] C.D. Bovenzi, J. Hamilton, P. Tassone, J. Johnson, D.M. Cognetti, A. Luginbuhl, W.M. Keane, T. Zhan, M. Tuluc, V. Bar-Ad, U. Martinez-Outschoorn, J.M. Curry, Prognostic indications of elevated MCT4 and CD147 across cancer types: a meta-analysis, Biomed. Res Int 2015 (2015), 242437.
[63] M. Bacci, E. Giannoni, A. Fearns, R. Ribas, Q. Gao, M.L. Taddei, G. Pintus, M. Dowsett, C.M. Isacke, L.A. Martin, P. Chiarugi, A. Morandi, miR-155 drives metabolic reprogramming of ER+ breast cancer cells following long-term estrogen deprivation and predicts clinical response to aromatase inhibitors, Cancer Res 76 (6) (2016) 1615–1626.
[64] J. Doyen, C. Trastour, F. Ettore, I. Peyrottes, N. Toussant, J. Gal, K. Ilc, D. Roux, S. K. Parks, J.M. Ferrero, J. Pouysségur, Expression of the hypoxia-inducible monocarboxylate transporter MCT4 is increased in triple negative breast cancer and correlates independently with clinical outcome, Biochem Biophys. Res Commun. 451 (1) (2014) 54–61.
[65] M. Zhou, Y. Zhao, Y. Ding, H. Liu, Z. Liu, O. Fodstad, A.I. Riker, S. Kamarajugadda, J. Lu, L.B. Owen, S.P. Ledoux, M. Tan, Warburg effect in chemosensitivity: targeting lactate dehydrogenase-A re-sensitizes taxol-resistant cancer cells to taxol, Mol. Cancer 9 (2010) 33.
[66] Y. Zhao, H. Liu, Z. Liu, Y. Ding, S.P. Ledoux, G.L. Wilson, R. Voellmy, Y. Lin, W. Lin, R. Nahta, B. Liu, O. Fodstad, J. Chen, Y. Wu, J.E. Price, M. Tan, Overcoming trastuzumab resistance in breast cancer by targeting dysregulated glucose metabolism, Cancer Res 71 (13) (2011) 4585–4597.
[67] P. Maiso, D. Huynh, M. Moschetta, A. Sacco, Y. Aljawai, Y. Mishima, J.M. Asara, A.M. Roccaro, A.C. Kimmelman, I.M. Ghobrial, Metabolic signature identifies novel targets for drug resistance in multiple myeloma, Cancer Res. 75 (10) (2015) 2071.
[68] K.P. Locher, Mechanistic diversity in ATP-binding cassette (ABC) transporters, Nat. Struct. Mol. Biol. 23 (6) (2016) 487–493.
[69] N.T. Moldogazieva, I.M. Mokhosoev, A.A. Terentiev, Metabolic heterogeneity of cancer cells: an interplay between HIF-1, GLUTs, and AMPK, Cancers 12 (4) (2020).
[70] K.J. Morten, L. Badder, H.J. Knowles, Differential regulation of HIF-mediated pathways increases mitochondrial metabolism and ATP production in hypoxic osteoclasts, J. Pathol. 229 (5) (2013) 755–764.
[71] J.F. Geschwind, C.S. Georgiades, Y.H. Ko, P.L. Pedersen, Recently elucidated energy catabolism pathways provide opportunities for novel treatments in hepatocellular carcinoma, Expert Rev. Anticancer Ther. 4 (3) (2004) 449–457.
[72] Y.H. Ko, P.L. Pedersen, J.F. Geschwind, Glucose catabolism in the rabbit VX2 tumor model for liver cancer: characterization and targeting hexokinase, Cancer Lett. 173 (1) (2001) 83–91.
[73] B. Ruprecht, E.A. Zaal, J. Zecha, W. Wu, C.R. Berkers, B. Kuster, S. Lemeer, Lapatinib resistance in breast cancer cells is accompanied by phosphorylation-mediated reprogramming of glycolysis, Cancer Res 77 (8) (2017) 1842–1853.
[74] E.J. Sullivan, M. Kurtoglu, R. Brenneman, H. Liu, T.J. Lampidis, Targeting cisplatin-resistant human tumor cells with metabolic inhibitors, Cancer Chemother. Pharmacol. 73 (2) (2014) 417–427.
[75] L. Edry Botzer, S. Maman, O. Sagi-Assif, T. Meshel, I. Nevo, I. Yron, I.P. Witz, Hexokinase 2 is a determinant of neuroblastoma metastasis, Br. J. Cancer 114 (7) (2016) 759–766.
[76] K. Fan, Z. Fan, H. Cheng, Q. Huang, C. Yang, K. Jin, G. Luo, X. Yu, C. Liu, Hexokinase 2 dimerization and interaction with voltage-dependent anion channel promoted resistance to cell apoptosis induced by gemcitabine in pancreatic cancer, Cancer, Medicine 8 (13) (2019) 5903–5915.
[77] Y. Zhu, L. Lu, C. Qiao, Y. Shan, H. Li, S. Qian, M. Hong, H. Zhao, J. Li, Z. Yang, Y. Chen, Targeting PFKFB3 sensitizes chronic myelogenous leukemia cells to tyrosine kinase inhibitor, Oncogene 37 (21) (2018) 2837–2849.
[78] H.S. Shi, D. Li, J. Zhang, Y.S. Wang, L. Yang, H.L. Zhang, X.H. Wang, B. Mu, W. Wang, Y. Ma, F.C. Guo, Y.Q. Wei, Silencing of pkm2 increases the efficacy of docetaxel in human lung cancer xenografts in mice, Cancer Sci. 101 (6) (2010) 1447–1453.
[79] J. Shu, X. Li, J. Dang, Y. Liu, S. Duan, R. Zhu, L. Yin, Y. Chen, Drug resistance reversal by interventing cancer bioenergetics with spherical helical polypeptide-potented gene silencing, Chem. Eng. J. 414 (2021), 128545.
[80] W. Guo, Y. Zhang, T. Chen, Y. Wang, J. Xue, Y. Zhang, W. Xiao, X. Mo, Y. Lu, Efficacy of RNAi targeting of pyruvate kinase M2 combined with cisplatin in a lung cancer model, J. Cancer Res Clin. Oncol. 137 (1) (2011) 65–72.
[81] P. Yu, A.-x Li, X.-s Chen, M. Tian, H.-y Wang, X.-l Wang, Y. Zhang, K.-s Wang, Y. Cheng, PKM2–c-Myc–survivin cascade regulates the cell proliferation, Migr., Tamoxifen Resist. Breast Cancer, Front. Pharmacol. 11 (1414) (2020).
[82] B.C. Yoo, J.-L. Ku, S.-H. Hong, Y.-K. Shin, S.Y. Park, H.K. Kim, J.-G. Park, Decreased pyruvate kinase M2 activity linked to cisplatin resistance in human gastric carcinoma cell lines, Int. J. Cancer 108 (4) (2004) 532–539.
[83] E. Martinez-Balibrea, C. Plasencia, A. Ginés, A. Martinez-Cardús, E. Musulén, R. Aguilera, J.L. Manzano, N. Neamati, A. Abad, A proteomic approach links decreased pyruvate kinase M2 expression to oxaliplatin resistance in patients with colorectal cancer and in human cell lines, Mol. Cancer Ther. 8 (4) (2009) 771–778.
[84] M. Bacci, N. Lorito, A. Smiriglia, A. Morandi, Fat and furious: lipid metabolism in antitumoral therapy response and resistance, Trends Cancer 7 (3) (2021) 198–213.
[85] S. Stamatakos, G.L. Beretta, E. Vergani, M. Dugo, C. Corno, E. Corna, S. Tinelli, S. Frigerio, E. Ciusani, M. Rodolfo, P. Perego, L. Gatti, Deregulated FASN expression in BRAF inhibitor-resistant melanoma cells unveils new targets for drug combinations, Cancers (Basel) 13 (9) (2021).
[86] Y. Yang, H. Liu, Z. Li, Z. Zhao, M. Yip-Schneider, Q. Fan, C.M. Schmidt, E. G. Chiorean, J. Xie, L. Cheng, J.-H. Chen, J.-T. Zhang, Role of fatty acid synthase in gemcitabine and radiation resistance of pancreatic cancers, Int J. Biochem Mol. Biol. 2 (1) (2011) 89–98.
[87] S. Tadros, S.K. Shukla, R.J. King, V. Gunda, E. Vernucci, J. Abrego, N.V. Chaika, F. Yu, A.J. Lazenby, L. Berim, J. Grem, A.R. Sasson, P.K. Singh, De Novo lipid synthesis facilitates gemcitabine resistance through endoplasmic reticulum stress in pancreatic cancer, Cancer Res 77 (20) (2017) 5503–5517.
[88] E. Papaevangelou, G.S. Almeida, C. Box, N.M. deSouza, Y.L. Chung, The effect of FASN inhibition on the growth and metabolism of a cisplatin-resistant ovarian carcinoma model, Int J. Cancer 143 (4) (2018) 992–1002.
[89] H. Liu, Y. Liu, J.T. Zhang, A new mechanism of drug resistance in breast cancer cells: fatty acid synthase overexpression-mediated palmitate overproduction, Mol. Cancer Ther. 7 (2) (2008) 263–270.
[90] E. Polonio-Alcalá, S. Palomeras, D. Torres-Oteros, J. Relat, M. Planas, L. Feliu, J. Ciurana, S. Ruiz-Martínez, T. Puig, Fatty acid synthase inhibitor g28 shows anticancer activity in EGFR tyrosine kinase inhibitor resistant lung adenocarcinoma models, Cancers (Basel) 12 (5) (2020).
[91] J. Mims, N. Bansal, M.S. Bharadwaj, X. Chen, A.J. Molina, A.W. Tsang, C. M. Furdui, Energy metabolism in a matched model of radiation resistance for head and neck squamous cell cancer, Radiat. Res 183 (3) (2015) 291–304.
[92] N. Zhan, B. Li, X. Xu, J. Xu, S. Hu, Inhibition of FASN expression enhances radiosensitivity in human non-small cell lung cancer, Oncol. Lett. 15 (4) (2018) 4578–4584.
[93] I.R. Schlaepfer, C.A. Hitz, M.A. Gijón, B.C. Bergman, R.H. Eckel, B.M. Jacobsen, Progestin modulates the lipid profile and sensitivity of breast cancer cells to docetaxel, Mol. Cell Endocrinol. 363((1–2) (2012) 111–121.
[94] J.W. Lee, J.Y. Ryu, G. Yoon, H.K. Jeon, Y.J. Cho, J.J. Choi, S.Y. Song, I.G. Do, Y. Y. Lee, T.J. Kim, C.H. Choi, B.G. Kim, D.S. Bae, Sphingosine kinase 1 as a potential therapeutic target in epithelial ovarian cancer, Int J. Cancer 137 (1) (2015) 221–229.
[95] H. Devalapally, Z. Duan, M.V. Seiden, M.M. Amiji, Modulation of drug resistance in ovarian adenocarcinoma by enhancing intracellular ceramide using tamoxifen-loaded biodegradable polymeric nanoparticles, Clin. Cancer Res 14 (10) (2008) 3193–3203.
[96] R. Kolesnick, D. Altieri, Z. Fuks, A. CERTain, role for ceramide in taxane-induced cell death, Cancer Cell 11 (6) (2007) 473–475.
[97] S. Faict, I. Oudaert, L. D'Auria, J. Dehairs, K. Maes, P. Vlummens, K. De Veirman, E. De Bruyne, K. Fostier, I. Vande Broek, R. Schots, K. Vanderkerken, J. V. Swinnen, E. Menu, The transfer of sphingomyelinase contributes to drug resistance in multiple myeloma, Cancers (Basel) 11 (12) (2019).
[98] C. Huang, Y. Tu, C.E. Freter, Fludarabine-resistance associates with ceramide metabolism and leukemia stem cell development in chronic lymphocytic leukemia, Oncotarget 9 (69) (2018) 33124–33137.
[99] B. Ogretmen, Sphingolipid metabolism in cancer signalling and therapy, Nat. Rev. Cancer 18 (1) (2018) 33–50.
[100] J. Kopecka, P. Trouillas, A. Gašparović, E. Gazzano, Y.G. Assaraf, C. Riganti, Phospholipids and cholesterol: Inducers of cancer multidrug resistance and therapeutic targets, Drug Resist Updat 49 (2020), 100670.
[101] O. Soriano, M. Alcón-Pérez, M. Vicente-Manzanares, E. Castellano, The crossroads between RAS and RHO signaling pathways in cellular transformation, motility and contraction, Genes (Basel) 12 (6) (2021).
[102] D.C. Belisario, M. Akman, M. Godel, V. Campani, M.P. Patrizio, L. Scotti, C. M. Hattinger, G. De Rosa, M. Donadelli, M. Serra, J. Kopecka, C. Riganti, ABCA1/ABCB1 ratio determines chemo- and immune-sensitivity in human osteosarcoma, Cells 9 (3) (2020).
[103] I.C. Salaroglio, D.C. Belisario, M. Akman, S. La Vecchia, M. Godel, D.P. Anobile, G. Ortone, S. Digiovanni, S. Fontana, C. Costamagna, M. Rubinstein, J. Kopecka, C. Riganti, Mitochondrial ROS drive resistance to chemotherapy and immune-killing in hypoxic non-small cell lung cancer, J. Exp. Clin. Cancer Res 41 (1) (2022) 243.
[104] T. Rivel, C. Ramseyer, S. Yesylevskyy, The asymmetry of plasma membranes and their cholesterol content influence the uptake of cisplatin, Sci. Rep. 9 (1) (2019) 5627.
[105] H.-C. Yoo, J.-M. Han, Amino acid metabolism in cancer drug resistance, Cells 11 (1) (2022).
[106] F. Baenke, B. Chaneton, M. Smith, N. Van Den Broek, K. Hogan, H. Tang, A. Viros, M. Martin, L. Galbraith, M.R. Girotti, N. Dhomen, E. Gottlieb, R. Marais, Resistance to BRAF inhibitors induces glutamine dependency in melanoma cells, Mol. Oncol. 10 (1) (2016) 73–84.
[107] J.E. Hernandez-Davies, T.Q. Tran, M.A. Reid, K.R. Rosales, X.H. Lowman, M. Pan, G. Moriceau, Y. Yang, J. Wu, R.S. Lo, M. Kong, Vemurafenib resistance reprograms melanoma cells towards glutamine dependence, J. Transl. Med 13 (2015) 210.
[108] C.D. Hudson, A. Savadelis, A.B. Nagaraj, P. Joseph, S. Avril, A. DiFeo, N. Avril, Altered glutamine metabolism in platinum resistant ovarian cancer, Oncotarget 7 (27) (2016) 41637–41649.
[109] C.P. Masamha, P. LaFontaine, Molecular targeting of glutaminase sensitizes ovarian cancer cells to chemotherapy, J. Cell Biochem 119 (7) (2018) 6136–6145.

[110] Y.H. Ko, Z. Lin, N. Flomenberg, R.G. Pestell, A. Howell, F. Sotgia, M.P. Lisanti, U. E. Martinez-Outschoorn, Glutamine fuels a vicious cycle of autophagy in the tumor stroma and oxidative mitochondrial metabolism in epithelial cancer cells: implications for preventing chemotherapy resistance, Cancer Biol. Ther. 12 (12) (2011) 1085–1097.
[111] K. Tanaka, T. Sasayama, Y. Irino, K. Takata, H. Nagashima, N. Satoh, K. Kyotani, T. Mizowaki, T. Imahori, Y. Ejima, K. Masui, B. Gini, H. Yang, K. Hosoda, R. Sasaki, P.S. Mischel, E. Kohmura, Compensatory glutamine metabolism promotes glioblastoma resistance to mTOR inhibitor treatment, The, J. Clin. Investig. 125 (4) (2015) 1591–1602.
[112] R.M. Thompson, D. Dytfeld, L. Reyes, R.M. Robinson, B. Smith, Y. Manevich, A. Jakubowiak, M. Komarnicki, A. Przybylowicz-Chalecka, T. Szczepaniak, A. K. Mitra, B.G. Van Ness, M. Luczak, N.G. Dolloff, Glutaminase inhibitor CB-839 synergizes with carfilzomib in resistant multiple myeloma cells, Oncotarget 8 (22) (2017) 35863–35876.
[113] M. Wangpaichitr, C. Wu, Y.Y. Li, D.J.M. Nguyen, H. Kandemir, S. Shah, S. Chen, L. G. Feun, J.S. Prince, M.T. Kuo, N. Savaraj, Exploiting ROS and metabolic differences to kill cisplatin resistant lung cancer, Oncotarget 8 (30) (2017) 49275–49292.
[114] R. Chen, L.A. Lai, Y. Sullivan, M. Wong, L. Wang, J. Riddell, L. Jung, V. G. Pillarisetty, T.A. Brentnall, S. Pan, Disrupting glutamine metabolic pathways to sensitize gemcitabine-resistant pancreatic cancer, Sci. Rep. 7 (1) (2017) 7950.
[115] R. Marullo, E. Werner, N. Degtyareva, B. Moore, G. Altavilla, S.S. Ramalingam, P. W. Doetsch, Cisplatin induces a mitochondrial-ROS response that contributes to cytotoxicity depending on mitochondrial redox status and bioenergetic functions, PLoS One 8 (11) (2013), e81162.
[116] L. Galluzzi, L. Senovilla, I. Vitale, J. Michels, I. Martins, O. Kepp, M. Castedo, G. Kroemer, Molecular mechanisms of cisplatin resistance, Oncogene 31 (15) (2012) 1869–1883.
[117] M. Wangpaichitr, C. Wu, M. You, J.C. Maher, V. Dinh, L.G. Feun, N. Savaraj, N', N'-dimethyl-N',N'-bis(phenylcarbonothioyl) propanedihydrazide (Elesclomol) selectively kills cisplatin resistant lung cancer cells through reactive oxygen species (ROS), Cancers 1 (1) (2009) 23–38.
[118] P. Corazao-Rozas, P. Guerreschi, M. Jendoubi, F. André, A. Jonneaux, C. Scalbert, G. Garçon, M. Malet-Martino, S. Balayssac, S. Rocchi, A. Savina, P. Formstecher, L. Mortier, J. Kluza, P. Marchetti, Mitochondrial oxidative stress is the Achille's heel of melanoma cells resistant to Braf-mutant inhibitor, Oncotarget 4 (11) (2013) 1986–1998.
[119] J. Zhou, P. Li, X. Xue, S. He, Y. Kuang, H. Zhao, S. Chen, Q. Zhi, X. Guo, Salinomycin induces apoptosis in cisplatin-resistant colorectal cancer cells by accumulation of reactive oxygen species, Toxicol. Lett. 222 (2) (2013) 139–145.
[120] R. Rashmi, X. Huang, J.M. Floberg, A.E. Elhammali, M.L. McCormick, G.J. Patti, D.R. Spitz, J.K. Schwarz, Radioresistant cervical cancers are sensitive to inhibition of glycolysis and redox metabolism, Cancer Res 78 (6) (2018) 1392–1403.
[121] I.S. Song, H.K. Kim, S.R. Lee, S.H. Jeong, N. Kim, K.S. Ko, B.D. Rhee, J. Han, Mitochondrial modulation decreases the bortezomib-resistance in multiple myeloma cells, Int J. Cancer 133 (6) (2013) 1357–1367.
[122] L. Besse, A. Besse, M. Mendez-Lopez, K. Vasickova, M. Sedlackova, P. Vanhara, M. Kraus, J. Bader, R.B. Ferreira, R.K. Castellano, B.K. Law, C. Driessen, A metabolic switch in proteasome inhibitor-resistant multiple myeloma ensures higher mitochondrial metabolism, protein folding and sphingomyelin synthesis, Haematologica 104 (9) (2019) e415–e419.
[123] M. Fiorillo, F. Sotgia, D. Sisci, A.R. Cappello, M.P. Lisanti, Mitochondrial "power" drives tamoxifen resistance: NQO1 and GCLC are new therapeutic targets in breast cancer, Oncotarget 8 (12) (2017) 20309–20327.
[124] E.A. Zaal, W. Wu, G. Jansen, S. Zweegman, J. Cloos, C.R. Berkers, Bortezomib resistance in multiple myeloma is associated with increased serine synthesis, Cancer Metab. 5 (1) (2017) 7.
[125] N. Vié, V. Copois, C. Bascoul-Mollevi, V. Denis, N. Bec, B. Robert, C. Fraslon, E. Conseiller, F. Molina, C. Larroque, P. Martineau, M. Del Rio, C. Gongora, Overexpression of phosphoserine aminotransferase PSAT1 stimulates cell growth and increases chemoresistance of colon cancer cells, Mol. Cancer 7 (2008) 14.
[126] D.C. Montrose, S. Saha, M. Foronda, E.M. McNally, J. Chen, X.K. Zhou, T. Ha, J. Krumsiek, M. Buyukozkan, A. Verma, O. Elemento, R.K. Yantiss, Q. Chen, S. S. Gross, L. Galluzzi, L.E. Dow, A.J. Dannenberg, Exogenous and endogenous sources of serine contribute to colon cancer metabolism, growth, and resistance to 5-fluorouracil, Cancer Res 81 (9) (2021) 2275–2288.
[127] B. Liu, Y. Jia, Y. Cao, S. Wu, H. Jiang, X. Sun, J. Ma, X. Yin, A. Mao, M. Shang, Overexpression of phosphoserine aminotransferase 1 (PSAT1) predicts poor prognosis and associates with tumor progression in human esophageal squamous cell carcinoma, Cell Physiol. Biochem 39 (1) (2016) 395–406.
[128] K.C. Ross, A.J. Andrews, C.D. Marion, T.J. Yen, V. Bhattacharjee, 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 (8) (2017) 1596–1609.
[129] J. Dai, J. Escara-Wilke, J.M. Keller, Y. Jung, R.S. Taichman, K.J. Pienta, E. T. Keller, Primary prostate cancer educates bone stroma through exosomal pyruvate kinase M2 to promote bone metastasis, J. Exp. Med 216 (12) (2019) 2883–2899.
[130] C. Wang, J. Xu, D. Yuan, Y. Bai, Y. Pan, J. Zhang, C. Shao, Exosomes carrying ALDOA and ALDH3A1 from irradiated lung cancer cells enhance migration and invasion of recipients by accelerating glycolysis, Mol. Cell Biochem 469((1–2) (2020) 77–87.
[131] O. Yogev, S. Henderson, M.J. Hayes, S.S. Marelli, Y. Ofir-Birin, N. Regev-Rudzki, J. Herrero, T. Enver, Herpesviruses shape tumour microenvironment through exosomal transfer of viral microRNAs, PLoS Pathog. 13 (8) (2017) e1006524-e1006524.
[132] S.L. Shu, Y. Yang, C.L. Allen, O. Maguire, H. Minderman, A. Sen, M.J. Ciesielski, K.A. Collins, P.J. Bush, P. Singh, X. Wang, M. Morgan, J. Qu, R.B. Bankert, T. L. Whiteside, Y. Wu, M.S. Ernstoff, Metabolic reprogramming of stromal fibroblasts by melanoma exosome microRNA favours a pre-metastatic microenvironment, Sci. Rep. 8 (1) (2018) 12905.
[133] M.Y. Fong, W. Zhou, L. Liu, A.Y. Alontaga, M. Chandra, J. Ashby, A. Chow, S.T. F. O'Connor, S. Li, A.R. Chin, G. Somlo, M. Palomares, Z. Li, J.R. Tremblay, A. Tsuyada, G. Sun, M.A. Reid, X. Wu, P. Swiderski, X. Ren, Y. Shi, M. Kong, W. Zhong, Y. Chen, S.E. Wang, Breast-cancer-secreted miR-122 reprograms glucose metabolism in premetastatic niche to promote metastasis, Nat. Cell Biol. 17 (2) (2015) 183–194.
[134] T. Skotland, K. Sagini, K. Sandvig, A. Llorente, An emerging focus on lipids in extracellular vesicles, Adv. Drug Deliv. Rev. 159 (2020) 308–321.
[135] J.S. Brzozowski, H. Jankowski, D.R. Bond, S.B. McCague, B.R. Munro, M. J. Predebon, C.J. Scarlett, K.A. Skelding, J. Weidenhofer, Lipidomic profiling of extracellular vesicles derived from prostate and prostate cancer cell lines, Lipids Health Dis. 17 (1) (2018) 211.
[136] I. Lazar, E. Clement, S. Dauvillier, D. Milhas, M. Ducoux-Petit, S. LeGonidec, C. Moro, V. Soldan, S. Dalle, S. Balor, M. Golzio, O. Burlet-Schiltz, P. Valet, C. Muller, L. Nieto, Adipocyte exosomes promote melanoma aggressiveness through fatty acid oxidation: a novel mechanism linking obesity and cancer, Cancer Res 76 (14) (2016) 4051–4057.
[137] E. Clement, I. Lazar, C. Attané, L. Carrié, S. Dauvillier, M. Ducoux-Petit, D. Esteve, T. Menneteau, M. Moutahir, S. Le Gonidec, S. Dalle, P. Valet, O. Burlet-Schiltz, C. Muller, L. Nieto, Adipocyte extracellular vesicles carry enzymes and fatty acids that stimulate mitochondrial metabolism and remodeling in tumor cells, Embo J. 39 (3) (2020), e102525.
[138] G. Sagar, R.P. Sah, N. Javeed, S.K. Dutta, T.C. Smyrk, J.S. Lau, N. Giorgadze, T. Tchkonia, J.L. Kirkland, S.T. Chari, D. Mukhopadhyay, Pathogenesis of pancreatic cancer exosome-induced lipolysis in adipose tissue, Gut 65 (7) (2016) 1165–1174.
[139] Q. Wu, S. Sun, Z. Li, Q. Yang, B. Li, S. Zhu, L. Wang, J. Wu, J. Yuan, C. Yang, J. Li, S. Sun, Tumour-originated exosomal miR-155 triggers cancer-associated cachexia to promote tumour progression, Mol. Cancer 17 (1) (2018) 155.
[140] W. Wang, N. Zhu, T. Yan, Y.-N. Shi, J. Chen, C.-J. Zhang, X.-J. Xie, D.-F. Liao, L. Qin, The crosstalk: exosomes and lipid metabolism, Cell Commun. Signal. 18 (1) (2020) 119.
[141] Q. Wu, J. Li, Z. Li, S. Sun, S. Zhu, L. Wang, J. Wu, J. Yuan, Y. Zhang, S. Sun, C. Wang, Exosomes from the tumour-adipocyte interplay stimulate beige/brown differentiation and reprogram metabolism in stromal adipocytes to promote tumour progression, J. Exp. Clin. Cancer Res 38 (1) (2019) 223.
[142] X. Zhang, Y. Xu, L. Ma, K. Yu, Y. Niu, X. Xu, Y. Shi, S. Guo, X. Xue, Y. Wang, S. Qiu, J. Cui, H. Wang, X. Tian, Y. Miao, F. Meng, Y. Qiao, Y. Yu, J. Wang, Essential roles of exosome and circRNA_101093 on ferroptosis desensitization in lung adenocarcinoma, Cancer Commun. (Lond.) 42 (4) (2022) 287–313.
[143] K.C. Vallabhaneni, P. Penfornis, S. Dhule, F. Guillonneau, K.V. Adams, Y.Y. Mo, R. Xu, Y. Liu, K. Watabe, M.C. Vemuri, R. Pochampally, Extracellular vesicles from bone marrow mesenchymal stem/stromal cells transport tumor regulatory microRNA, proteins, and metabolites, Oncotarget 6 (7) (2015) 4953–4967.
[144] J.S. Sung, C.W. Kang, S. Kang, Y. Jang, Y.C. Chae, B.G. Kim, N.H. Cho, ITGB4-mediated metabolic reprogramming of cancer-associated fibroblasts, Oncogene 39 (3) (2020) 664–676.
[145] W. Yan, X. Wu, W. Zhou, M.Y. Fong, M. Cao, J. Liu, X. Liu, C.H. Chen, O. Fadare, D.P. Pizzo, J. Wu, L. Liu, X. Liu, A.R. Chin, X. Ren, Y. Chen, J.W. Locasale, S. E. Wang, Cancer-cell-secreted exosomal miR-105 promotes tumour growth through the MYC-dependent metabolic reprogramming of stromal cells, Nat. Cell Biol. 20 (5) (2018) 597–609.
[146] A. Rai, D.W. Greening, M. Chen, R. Xu, H. Ji, R.J. Simpson, Exosomes derived from human primary and metastatic colorectal cancer cells contribute to functional heterogeneity of activated fibroblasts by reprogramming their proteome, Proteomics 19 (8) (2019), e1800148.
[147] X. Wu, Z. Zhou, S. Xu, C. Liao, X. Chen, B. Li, J. Peng, D. Li, L. Yang, Extracellular vesicle packaged LMP1-activated fibroblasts promote tumor progression via autophagy and stroma-tumor metabolism coupling, Cancer Lett. 478 (2020) 93–106.
[148] C. Zhang, X.-Y. Wang, P. Zhang, T.-C. He, J.-H. Han, R. Zhang, J. Lin, J. Fan, L. Lu, W.-W. Zhu, H.-L. Jia, J.-B. Zhang, J.-H. Chen, Cancer-derived exosomal HSPC111 promotes colorectal cancer liver metastasis by reprogramming lipid metabolism in cancer-associated fibroblasts, Cell Death Dis. 13 (1) (2022) 57.
[149] M. Yáñez-Mó, P.R. Siljander, Z. Andreu, A.B. Zavec, F.E. Borràs, E.I. Buzas, K. Buzas, E. Casal, F. Cappello, J. Carvalho, E. Colás, A. Cordeiro-da Silva, S. Fais, J.M. Falcon-Perez, I.M. Ghobrial, B. Giebel, M. Gimona, M. Graner, I. Gursel, M. Gursel, N.H. Heegaard, A. Hendrix, P. Kierulf, K. Kokubun, M. Kosanovic, V. Kralj-Iglic, E.M. Krämer-Albers, S. Laitinen, C. Lässer, T. Lener, E. Ligeti, A. Linē, G. Lipps, A. Llorente, J. Lötvall, M. Manček-Keber, A. Marcilla, M. Mittelbrunn, I. Nazarenko, E.N. Nolte-'t Hoen, T.A. Nyman, L. O'Driscoll, M. Olivan, C. Oliveira, É. Pállinger, H.A. Del Portillo, J. Reventós, M. Rigau, E. Rohde, M. Sammar, F. Sánchez-Madrid, N. Santarém, K. Schallmoser, M. S. Ostenfeld, W. Stoorvogel, R. Stukelj, S.G. Van der Grein, M.H. Vasconcelos, M. H. Wauben, O. De Wever, , Biological properties of extracellular vesicles and their physiological functions, J. Extra Vesicles 4 (2015) 27066.
[150] M. Bebawy, V. Combes, E. Lee, R. Jaiswal, J. Gong, A. Bonhoure, G.E.R. Grau, Membrane microparticles mediate transfer of P-glycoprotein to drug sensitive cancer cells, Leukemia 23 (9) (2009) 1643–1649.

[151] C. Corcoran, S. Rani, K. O'Brien, A. O'Neill, M. Prencipe, R. Sheikh, G. Webb, R. McDermott, W. Watson, J. Crown, L. O'Driscoll, Docetaxel-resistance in prostate cancer: evaluating associated phenotypic changes and potential for resistance transfer via exosomes, PLoS One 7 (12) (2012), e50999.
[152] F.F. Zhang, Y.F. Zhu, Q.N. Zhao, D.T. Yang, Y.P. Dong, L. Jiang, W.X. Xing, X. Y. Li, H. Xing, M. Shi, Y. Chen, I.C. Bruce, J. Jin, X. Ma, Microvesicles mediate transfer of P-glycoprotein to paclitaxel-sensitive A2780 human ovarian cancer cells, conferring paclitaxel-resistance, Eur. J. Pharm. 738 (2014) 83–90.
[153] J. Pasquier, L. Galas, C. Boulangé-Lecomte, D. Rioult, F. Bultelle, P. Magal, G. Webb, F. Le, Foll, Different modalities of intercellular membrane exchanges mediate cell-to-cell p-glycoprotein transfers in MCF-7 breast cancer cells, J. Biol. Chem. 287 (10) (2012) 7374–7387.
[154] C.P.R. Xavier, H.R. Caires, M.A.G. Barbosa, R. Bergantim, J.E. Guimarães, M. H. Vasconcelos, The role of extracellular vesicles in the hallmarks of cancer and drug resistance, Cells 9 (5) (2020).
[155] C.P.R. Xavier, D.C. Belisario, R. Rebelo, Y.G. Assaraf, E. Giovannetti, J. Kopecka, M.H. Vasconcelos, The role of extracellular vesicles in the transfer of drug resistance competences to cancer cells, Drug Resist. Updates 62 (2022), 100833.
[156] D. Sousa, R.T. Lima, M.H. Vasconcelos, Intercellular transfer of cancer drug resistance traits by extracellular vesicles, Trends Mol. Med 21 (10) (2015) 595–608.
[157] V. Lopes-Rodrigues, A. Di Luca, J. Mleczko, P. Meleady, M. Henry, M. Pesic, D. Cabrera, S. van Liempd, R.T. Lima, R. O'Connor, J.M. Falcon-Perez, M. H. Vasconcelos, Identification of the metabolic alterations associated with the multidrug resistant phenotype in cancer and their intercellular transfer mediated by extracellular vesicles, Sci. Rep. 7 (1) (2017) 44541.
[158] H. Wang, L. Wang, H. Pan, Y. Wang, M. Shi, H. Yu, C. Wang, X. Pan, Z. Chen, Exosomes derived from macrophages enhance aerobic glycolysis and chemoresistance in lung cancer by stabilizing c-myc via the inhibition of NEDD4L, Front. Cell Dev. Biol. 8 (2021).
[159] L. Zhuang, B. Zhang, X. Liu, L. Lin, L. Wang, Z. Hong, J. Chen, Exosomal miR-21-5p derived from cisplatin-resistant SKOV3 ovarian cancer cells promotes glycolysis and inhibits chemosensitivity of its progenitor SKOV3 cells by targeting PDHA1, Cell Biol. Int 45 (10) (2021) 2140–2149.
[160] F. Chen, J. Chen, L. Yang, J. Liu, X. Zhang, Y. Zhang, Q. Tu, D. Yin, D. Lin, P.-P. Wong, D. Huang, Y. Xing, J. Zhao, M. Li, Q. Liu, F. Su, S. Su, E. Song, Extracellular vesicle-packaged HIF-1α-stabilizing lncRNA from tumour-associated macrophages regulates aerobic glycolysis of breast cancer cells, Nat. Cell Biol. 21 (4) (2019) 498–510.
[161] X. Wang, H. Zhang, H. Yang, M. Bai, T. Ning, T. Deng, R. Liu, Q. Fan, K. Zhu, J. Li, Y. Zhan, G. Ying, Y. Ba, Exosome-delivered circRNA promotes glycolysis to induce chemoresistance through the miR-122-PKM2 axis in colorectal cancer, Mol. Oncol. 14 (3) (2020) 539–555.
[162] Z. Zeng, Y. Zhao, Q. Chen, S. Zhu, Y. Niu, Z. Ye, P. Hu, D. Chen, P. Xu, J. Chen, C. Hu, Y. Hu, F. Xu, J. Tang, F. Wang, S. Han, M. Huang, C. Wang, G. Zhao, Hypoxic exosomal HIF-1α-stabilizing circZNF91 promotes chemoresistance of normoxic pancreatic cancer cells via enhancing glycolysis, Oncogene 40 (36) (2021) 5505–5517.
[163] W.Q. Tan, L. Yuan, X.Y. Wu, C.G. He, S.C. Zhu, M. Ye, Exosome-delivered circular RNA DLGAP4 induces chemoresistance via miR-143-HK2 axis in neuroblastoma, Cancer Biomark. 34 (3) (2022) 375–384.
[164] J. Cui, G. Li, J. Yin, L. Li, Y. Tan, H. Wei, B. Liu, L. Deng, J. Tang, Y. Chen, L. Yi, GSTP1 and cancer: Expression, methylation, polymorphisms and signaling (Review), Int J. Oncol. 56 (4) (2020) 867–878.
[165] S.-j Yang, D.-d Wang, J. Li, H.-z Xu, H.-y Shen, X. Chen, S.-y Zhou, S.-l Zhong, J.-h Zhao, J.-h Tang, Predictive role of GSTP1-containing exosomes in chemotherapy-resistant breast cancer, Gene 623 (2017) 5–14.
[166] M. Alharbi, A. Lai, S. Sharma, P. Kalita-de Croft, N. Godbole, A. Campos, D. Guanzon, A. Salas-Burgos, F. Carrion, F.A. Zuñiga, L. Perrin, Y. He, T. Pejovic, C. Winters, T. Morgan, J.D. Hooper, G.E. Rice, C. Salomon, Extracellular vesicle transmission of chemoresistance to ovarian cancer cells is associated with hypoxia-induced expression of glycolytic pathway proteins, and prediction of epithelial ovarian cancer disease recurrence, Cancers 13 (14) (2021) 3388.
[167] D. Wang, C. Zhao, F. Xu, A. Zhang, M. Jin, K. Zhang, L. Liu, Q. Hua, J. Zhao, J. Liu, H. Yang, G. Huang, Cisplatin-resistant NSCLC cells induced by hypoxia transmit resistance to sensitive cells through exosomal PKM2, Theranostics 11 (6) (2021) 2860–2875.
[168] Q. Zhang, T. Deng, H. Zhang, D. Zuo, Q. Zhu, M. Bai, R. Liu, T. Ning, L. Zhang, Z. Yu, H. Zhang, Y. Ba, Adipocyte-derived exosomal MTTP suppresses ferroptosis and promotes chemoresistance in colorectal cancer, Adv. Sci. 9 (28) (2022) 2203357.
[169] B. Wang, X. Wang, D. Hou, Q. Huang, W. Zhan, C. Chen, J. Liu, R. You, J. Xie, P. Chen, H. Huang, Exosomes derived from acute myeloid leukemia cells promote chemoresistance by enhancing glycolysis-mediated vascular remodeling, J. Cell. Physiol. 234 (7) (2019) 10602–10614.
[170] F. Li, L. Zhan, Q. Dong, Q. Wang, Y. Wang, X. Li, Y. Zhang, J. Zhang, Tumor-derived exosome-educated hepatic stellate cells regulate lactate metabolism of hypoxic colorectal tumor cells via the IL-6/STAT3 pathway to confer drug resistance, Onco Targets Ther. 13 (2020) 7851–7864.

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