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Cancer metabolism in space and time: Beyond the Warburg effect

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ABSTRACT

Altered metabolism in cancer cells is pivotal for tumor growth, most notably by providing energy, reducing equivalents and building blocks while several metabolites exert a signaling function promoting tumor growth and progression. A cancer tissue cannot be simply reduced to a bulk of proliferating cells. Tumors are indeed complex and dynamic structures where single cells can heterogeneously perform various biological activities with different metabolic requirements. Because tumors are composed of different types of cells with metabolic activities affected by different spatial and temporal contexts, it is important to address metabolism taking into account cellular and biological heterogeneity. In this review, we describe this heterogeneity also in metabolic fluxes, thus showing the relative contribution of different metabolic activities to tumor progression according to the cellular context. This article is part of a Special Issue entitled Respiratory complex I, edited by Giuseppe Gasparre, Rodrigue Rossignol and Pierre Sonveaux.

Abbreviations: ACL, ATP citrate lyase; AMPK, adenosine monophosphate kinase; ARG1, L-arginine-metabolizing enzyme arginase 1; BCAA, branched-chain amino acid; Bcl2, B-cell lymphoma 2; CAF, cancer-associated fibroblast; CIC, cancer-initiating cell; COX2, cytochrome oxidase; CSC, cancer stem cell; CREB, cyclic adenosine monophosphate response element binding protein; DEC1, differentially expressed in chondrocytes 1; EMT, epithelial-to-mesenchymal transition; FAK, focal adhesion kinase; FAS, fatty acid synthase; FBP, fructose 1,6-bisphosphate; FDG-PET, [^{18}F]-fluorodeoxyglucose-positron emission tomography; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HIF-1, hypoxia-activated factor-1; HK2, hexokinase 2; HMGB1, high-mobility group box 1; HUVEC, human umbilical vein endothelial cell; IFN-γ, interferon gamma; LDH, lactate dehydrogenase; MEF, murine embryonic fibroblast; MET, mesenchymal to epithelial transition; MRI, magnetic resonance imaging; mTORC1, mammalian target of rapamycin complex 1; NSCLC, non-small cell lung cancer; OXPHOS, oxidative phosphorylation; PDAC, pancreatic ductal adenocarcinoma; PHD, prolylhydroxylase; pHe, extracellular pH; pHi, intracellular pH; PK, pyruvate kinase; PPP, pentose phosphate pathway; REDD1, regulated in development and DNA damage response 1; RhoA, Ras homolog gene family, member A; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SCO2, synthesis of cytochrome oxidase 2; SGK-1, serum and glucocorticoid-regulated kinase-1 Sirt1, sirtuin 1; TAM, tumor-associated macrophage; TIGAR, TP53-induced glycolysis and apoptosis regulator; TSC2, tuberous sclerosis 2; VDAC, voltage-dependent anion channel; VEGF, vascular endothelial growth factor; ZEB, Zinc finger E-box-binding homeobox

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1. Introduction

The notion that cancer cells harbor a different metabolic profile with respect to somatic cells dates back to the seminal observation by Otto Warburg almost 100 years ago on glucose metabolism [1]. While glucose consumption in normal cells is refrained by energy-rich metabolites produced in the presence of oxygen, a phenomenon known as the Pasteur Effect, Warburg reported that cancer cells behave differently. Indeed, by comparing cancerous and normal tissues, he found that cancer cells are able to maintain a high rate of glycolysis, thus converting glucose to lactate at high speed, even in the presence of oxygen, a phenomenon known as 'aerobic glycolysis' that has also been termed the 'Warburg effect' [2,3]. This observation is at the basis of [^{18}F]-fluorodeoxyglucose-positron emission tomography (FDG-PET) scans of tumors, which allows to detect a tumor tissue because of its generally high avidity for the glucose analogue FDG. Another metabolite that has been identified as being important for tumor growth is glutamine, which is pivotal for biomass production, most notably as a nitrogen donor [4]. Nevertheless, it is overly reductive to assume that cancer metabolism can be summarized as an upregulation of glucose and glutamine metabolism for energy production. (See Figs. 1–3.)

As will be detailed hereafter, our understanding of cancer cell metabolism drastically advanced in the recent years. Despite the key roles of aerobic glycolysis and glutamine metabolism in fostering tumor growth, several other metabolic pathways have been identified and characterized in cancer. Consequently, it is no longer tenable to claim that alterations of cancer metabolism can be simply summarized as accelerated glycolysis and glutaminolysis. Several factors contribute to such complexity: (i) the perfusion of a tumor is not optimal, thus the delivery of nutrients is often insufficient for cancer cells to rely on few metabolic fuels; (ii) in addition to cancer cells, different cellular populations contribute to the tumor tissue, defining the tumor stroma; (iii) cancer cells present a variety of mutational backgrounds making them heterogeneous; (iv) different activities are performed by cancer cells at different times, ranging from proliferation, to dormancy and invasion. It is thus reductive and even incorrect to picture cancer metabolism unidimensionally as a metabolically homogenous entity. On the contrary, one must study tumor metabolism as being heterogeneous, both in space and in time.

From the spatial standpoint, different tumor areas present various degrees of perfusion, immune infiltration and clonal evolution. This overall complexity results in the development of different metabolic adaptations, such as metabolic symbiosis [5,6], related to a cooperation between cancer cells with different metabolic needs and adaptation to limited perfusion and acidosis [7,8]. This metabolic heterogeneity is also mirrored by the biological heterogeneity of tumors, where cells will have diverse metabolic requirements according to the specific biological activity occurring in that particular area, *e.g.* whether it is at the invasive front or close to the necrotic core, or interacting with specific stromal population. Metabolic heterogeneity can also be interpreted in time, as cancer cells adapt their metabolic activities according to specific requirements bound to ongoing processes. A paradigmatic example of temporal influences is metastasis formation, during which cancer cells undergo sequential metabolic reprogramming according to the specific steps that are involved in the metastatic process, ranging from decreased mitochondrial respiration following early cell detachment [9] to higher mitochondrial oxygen consumption to promote migration and invasion [10,11].

In this review we will address this complexity by explaining how single metabolic alterations might differentially affect the various activities of a tumor.

2. Metabolic contribution to cell proliferation

Normal cells proliferate to sustain their population, and this process is limited to a defined number of replication cycles. Comparatively, cancer cells are able to replicate indefinitely, as they circumvent the check-points controlling replication (hence the term neoplasia: new formation) [12]. A complex network of regulation is altered

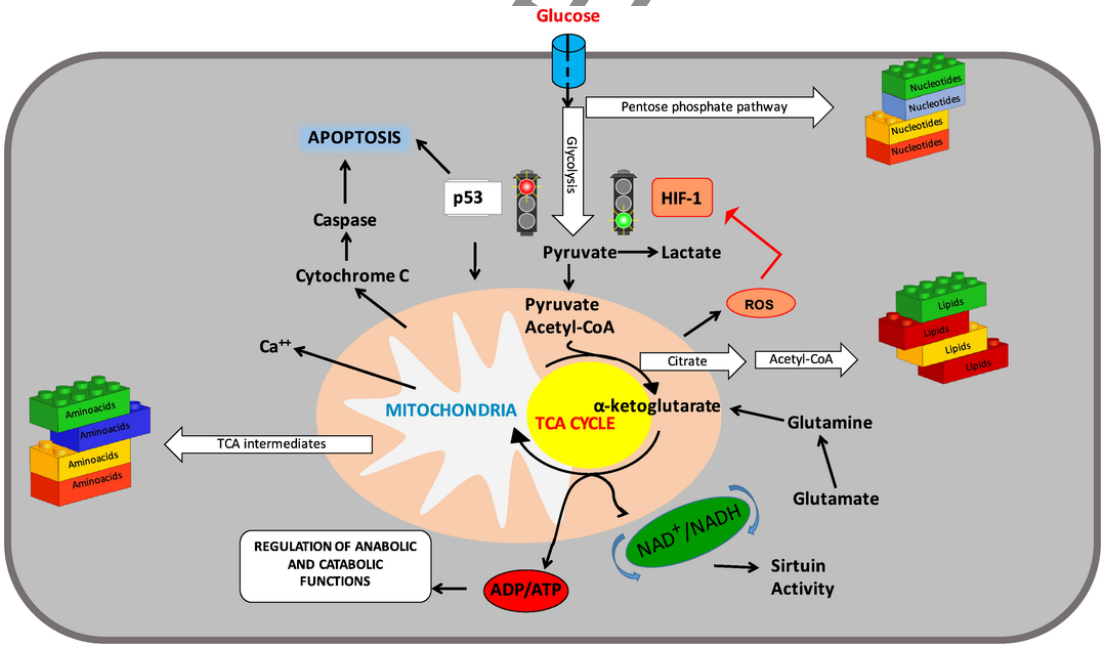

Fig. 1. Simplified version of metabolic pathways leading to the production of metabolic intermediates required for cellular growth. P53 and HIF-1 act as pivotal regulators leading to regulation of glycolysis (positive and negative respectively). Mitochondria stand at the cross-road between energy metabolism and signaling regulation acting both as a cellular "factory" and signalling organelle by regulating the availability of various factors, *e.g.* ROS, Ca^{++}, cytochrome C, ATP and NAD^{+}.

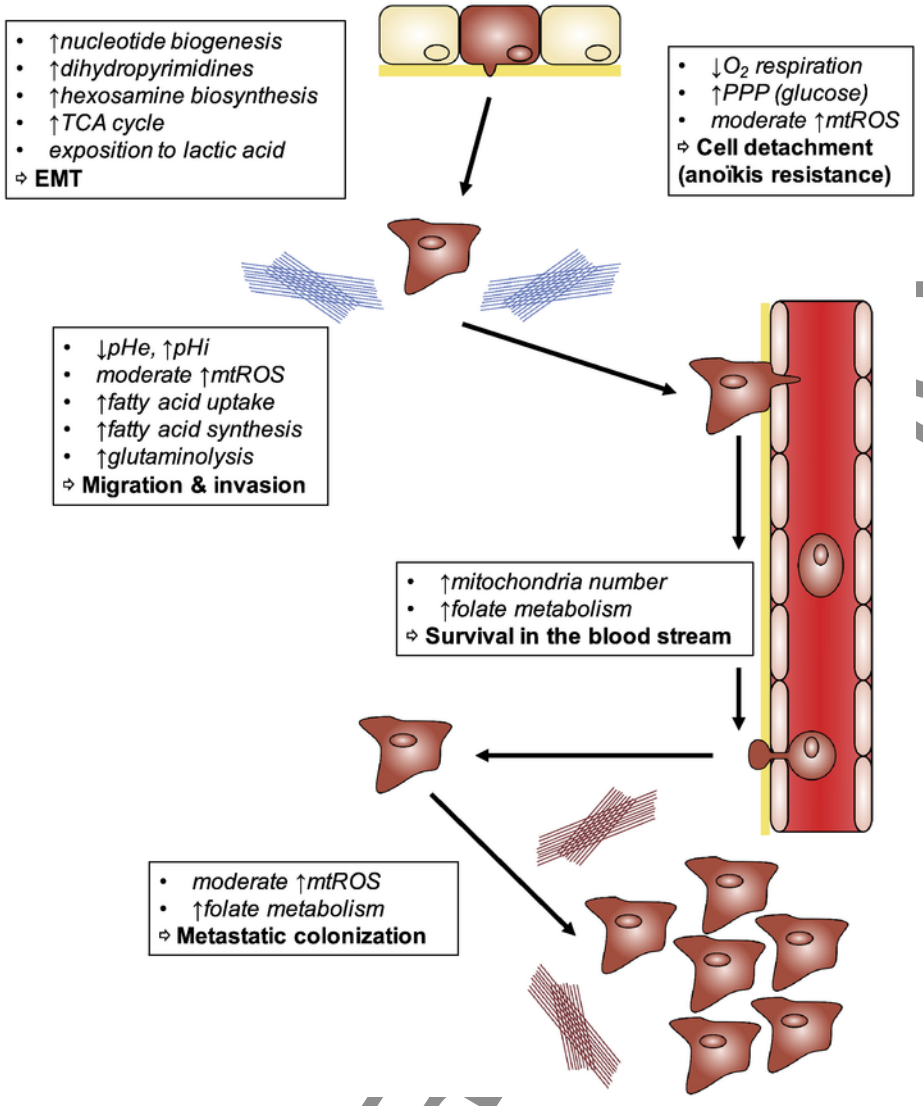

Fig. 2. Metabolism in transit. Cancer cells undergo specific and multiple metabolic alterations according to the specific spatio-temporal step they are located, from initial EMT (epithelial-to-mesenchymal transition) to final successful metastatic colonization. The different metabolic alterations identified at different steps support the notion that the invading cancer cell needs the acquisition of different properties at different steps. The upturned arrow indicates an increase of the metabolic pathway indicated, while for pHi means intracellular alkaline pH. The downturned arrow indicates the opposite, *i.e.* the positive effect on metastasis of the downregulation of the indicated pathway or, for pHe, the acidification of extracellular pH.

in order to allow cancer cells to proliferate at a high rate even in harsh conditions (*i.e.*, nutrient and oxygen limitation, immune attack). In order to develop this particular set of skills, cancer cells need to alter specific metabolic pathways [13].

In order to proliferate, a cancer cell must generate a biomass sufficient to sustain both daughter cells produced during division. Proliferating cells therefore need to gather high levels of lipids, nucleotides and amino acids. Cells can produce this biomass by using precursors and products of the TCA (tricarboxylic acid) cycle. This leads to a situation where more ATP is used and cataplerosis provides a constant outflow of intermediates [14,15]. Indeed, cataplerosis in proliferating cells is observable with the synthesis of lipids that are mainly derived from glucose [13,16]. A constant supply of lipids is indeed necessary for membrane production [13]. In hematopoietic cells, glucose conversion to lipids is regulated by cytokines and the PI3K/AKT signaling pathway. In these cells, IL-3-mediated activation of PI3K/AKT signaling is considered to be necessary and sufficient for the conversion of glucose to lipids [17]. Moreover, citrate originating from mitochondria is an important precursor of lipogenesis in the cytosol.

Accordingly, ACL and FAS are necessary for cell proliferation and are induced both in cancer cells and in proliferating hematopoietic cells [15]. While ACL cleaves citrate to produce acetyl-CoA and oxaloacetate, FAS generates palmitate from acetyl-CoA and malonyl-CoA [18,19]. ACL is a homotetrameric enzyme located in the cytoplasm. It is ATP-dependent and activated by AKT [20]. Several studies have suggested that inhibition of ACL [17,21] and fatty acid synthesis [22,23] can limit tumorigenesis. More particularly, stable knock down of ACL in various cancerous cells was shown to significantly reduce glucose-dependent lipid synthesis, caused an increase in the mitochondrial membrane potential and reduced cell proliferation, ultimately limiting tumor growth *in vivo* [21]. Of note, the production of cholesterol from citrate is also important for cell proliferation. It is proportional to the rate of citrate efflux from mitochondria

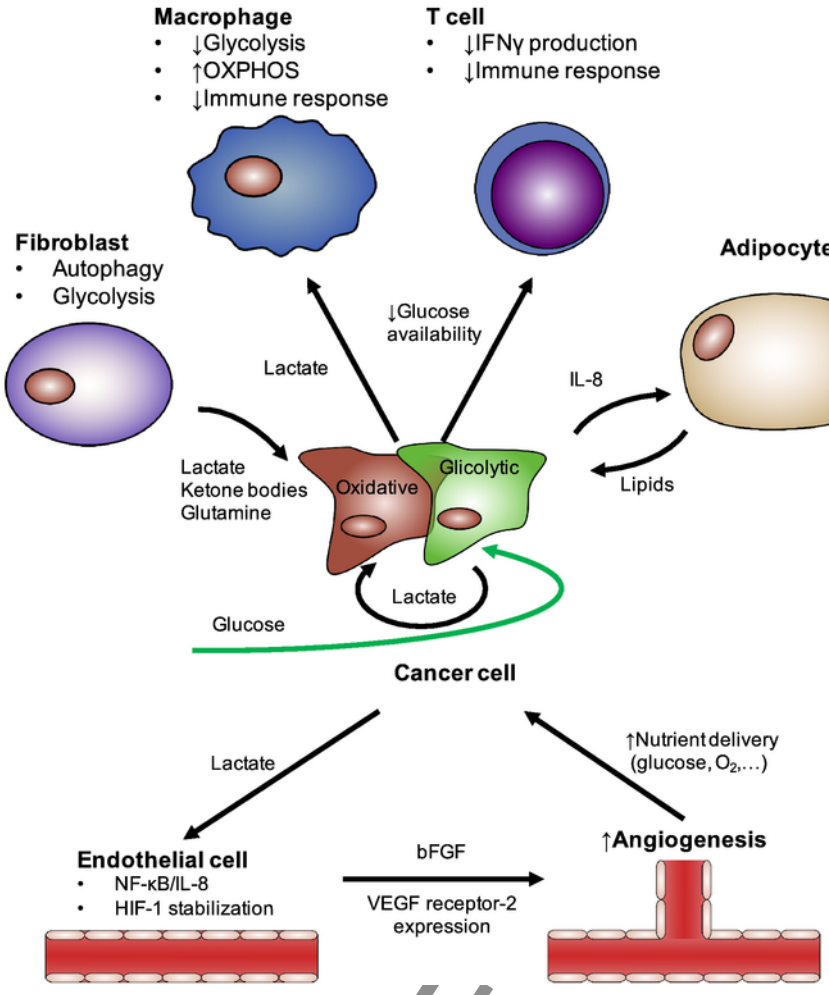

Fig. 3. Cellular and metabolic heterogeneity of tumor. Cancer cells establish different interactions with different stromal cells or within different cancer cells subpopulations, these interactions are driven by certain metabolites (*e.g.* lactate), nutrient availability (especially glucose and oxygen) or growth factors and cytokines such as IL-8. The effects of these relationships are diverse: from the biological hijacking (reprogramming immune cells) to the metabolic symbiosis (between oxidative and glycolytic cancer cells), up to the metabolic parasitism (promoting lipolysis and autophagy). During the metabolic symbiosis glycolytic cancer cells (in green) or other cell types fuels oxidative cancer cells (in red) with lactate and other metabolites, thus sparing glucose from the bloodstream (green arrow) for the glycolytic (and hypoxic) compartment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and inversely proportional to citrate-stimulated respiration [24,25]. Hepatoma cells and other malignant tumor types are characterized by a defective negative feedback loop in cholesterogenesis [15].

Anaplerosis encompasses processes that allow the biosynthesis of fatty acids, glucose and non-essential fatty acids from intermediates of TCA cycle. The replenishment of anions removed from the TCA cycle is necessary to keep the cycle active. The main enzyme that contributes to anaplerosis is pyruvate carboxylase [14], which uses pyruvate to generate oxaloacetate. Conversely, cataplerosis encompasses reactions that remove 4- and 5-carbon compounds from mitochondria. These compounds come from the catabolism of amino acids and they cannot be fully oxidized by the TCA cycle [14].

Cancer cells that use the TCA cycle for cataplerosis resupply lost intermediates *via* anaplerosis, which is crucial for growth [26]. As such, anaplerosis is a better indicator of cell growth than a high glycolytic flux that is not obligatorily coupled to biomass production [15]. Amino acids, in particular glutamine, may also be metabolized for anaplerosis. Glutamine is metabolized in many different pathways to generate energy and biomass in proliferating cells [27,28]. Accordingly, glutamine metabolism can replace glucose oxidation when cells perform aerobic glycolysis [29]. Because glutaminolysis overlaps with a part of the TCA cycle, it is generally accepted that proliferating cells use glutamine as a source of energy [15].

Mammalian cells use signaling pathways for the regulation of nutrient uptake and the regulation of cell growth and proliferation [30]. In normal conditions, cells produce energy via oxidative phosphorylation (OXPHOS) and glycolysis. As detailed in paragraph 4, when cells face nutrient limitation, a situation commonly encountered in cancer, they turn to a self-eating state called autophagy, through which they are able to produce enough energy and biomass to sustain proliferation [15].

AKT is one of the most important signaling molecules controlling cell metabolism as it stimulates glucose uptake and glucose metabolism in cancer cells [31]. It is therefore not surprising that AKT is often constitutively active in malignant cells, even if its stimulation of glucose metabolism is not obligatorily associated to increased cell survival and proliferation [32]. As reviewed in reference [15], the PI3K/AKT/mTOR pathway is considered to be responsible in normal and cancer cells for the enhancement of many metabolic activities leading to the biosynthesis of macromolecules. In particular, AKT is able to induce the Warburg Effect in nontransformed and cancer cells by increasing glycolytic lactate production [32–34]. PI3K and AKT

also stimulate lipogenic gene expression and lipid synthesis, whereas protein translation is regulated by mTOR [17,35,36].

In addition to AKT, transcription factor hypoxia-activated factor-1 (HIF-1) promotes glycolysis, but not biosynthesis at the cellular level. Oxygen-dependent enzymes of the prolylhydroxylase (PHD) family control the transcription factor HIF-1 [37], resulting in HIF-1 activation under hypoxia and, downstream, increased transcription and expression of glycolytic enzymes and transporters, including glucose transporters GLUT1 and GLUT3 and lactate transporter monocarboxylate transporter 4 (MCT4) [38,39].

Through its transcriptional effects and a cascade of events, HIF-1 indeed limits the amount of glycolytic carbon that enters into the TCA cycle and increases the production of lactate from pyruvate [40,41]. Although necessary for metabolic adaptation to hypoxia, HIF-1 activation limits the production of TCA cycle intermediate production that is necessary for biosynthesis, hence having a limiting effect on cell proliferation [15].

Thus, thanks to HIF-1 and other transcription factors that cooperate with HIF-1 (such as c-Myc) [42], cancer cells can sustainably rely on a glycolytic metabolism in order to survive and proliferate under hypoxia. Nevertheless, hypoxia stimulates tumor growth advantage also by decreasing the activity of TET (oxygen-dependent ten-eleven translocation enzymes) demethylases, leading to reduced transcription of oncosuppressor genes [43,44]. Indeed, severe hypoxia (0.5% O_2) decreased the activity of TET enzymes in several mouse and human cell lines [44]. Loss of hypoxia-induced TET activity in turn led to the hypermethylation of genes at the promoter level [44]. Further investigation is required to determine the exact contribution of this newly discovered epigenetic adaptation mechanism of tumor hypoxia in glycolysis, angiogenesis and metastasis.

Acceleration of the glycolytic flux serves the purposes of energy production, biosynthesis and the production of reducing equivalents necessary for cell division. Two glycolytic enzymes have been broadly associated with proliferation: hexokinase 2 (HK2) and pyruvate kinase M2 (PKM2). While HK2 catalyzes a fast conversion of glucose to glucose-6-phosphate, thus trapping glucose inside cells [45], the mode of action of PKM2 is more complex. The *PK* gene encodes 2 splicing variants, PKM1 and PKM2. While PKM1 is constitutively active, PKM2 is tunable, being allosterically activated by factors such as serine [46] and fructose 1,6-bisphosphate (FBP) [47] and repressed by tyrosine phosphorylation [48], alanine [49], and oxidation [50]. Thus, active PKM2 promotes glycolytic ATP production and inactive PKM2 diverts glycolytic intermediates to branched pathways, for example to the PPP for nucleotide synthesis and the production of NADPH for reactive oxygen species (ROS) detoxification [50].

In the 1950s, methodic analyses were performed to identify the sources and fate of the biomass of *Escherichia coli* [51–53]. It is only recently that another team addressed this issue in mammalian cells. In their work, Hosios et al. [16] quantified the fraction of cell mass derived from various nutrients. They concluded that although glucose and glutamine had the highest and second highest consumption rates during rapid cell proliferation, respectively, these nutrients did not contribute to the carbons used for biomass production. The authors rather found that amino acids are the main source of carbon in cells, although their consumption rate is much lower. When studying non-small cell lung cancer lines H1299 and A549 (rapidly proliferating human cells characterized by a high rate of aerobic glycolysis), glucose was consumed at about half the rate of lactate excretion. When labelling glucose with carbon-14, the authors found that only around 10% of the cell carbon was labelled, although carbon amounted to about 50% of the cellular mass. Interestingly, a quarter of glucose carbon was used for ribose production and was traced to DNA and RNA. Another 10% of the biomass was attributable to glutamine carbon, and by far its most common fate was incorporation into proteins. Following similar experiments with multiple cancer cell lines from various tissue origins, the authors confirmed that these are standard results when looking at glucose and glutamine, and concluded that most of the biomass comes from other sources. Indeed, when analyzing various human cancer cell lines (from lung, breast, brain tumors) and murine embryonic fibroblast (MEF) cells, they showed that amino acids are the main contributors to the biomass, producing approximatively between 25% and 40% of the carbon content. When studying non-proliferating cells, results were more heterogeneous, depending on the cell type. Further experiments showed that more glucose-derived carbon was incorporated into cell mass when cells were grown in lipid-depleted medium. Interestingly, glutamine-derived carbon incorporation into the biomass was not affected under the same growing conditions, but the incorporation of glutamine carbon into the non-polar material approximately doubled. Finally, the authors stated that, if the assumption that cellular lipids are derived only from glucose, glutamine and extracellular lipids is true, then up to 70% of lipid carbon came from the extracellular environment, 20% to 30% came from glucose and about 5% from glutamine [16]. Glycine consumption and catabolism was reported by others to be important for fast cell proliferation [54]. With respect to nucleotides, glucose contributed to 60%–80%, glutamine to 10%–20% and serine to approximately 15% of nucleotide carbon content [16]. Of note, the consumption of one molecule of glutamine can further provide 2 ni trogen atoms that contribute to biomass generation [54]. Several amino acids have been identified as critically involved in the regulation of cellular proliferation. Glutamine is an important donor of electrons in the anaplerotic synthesis of aspartate [55,56]. Through a series of biochemical events, glutamine indeed leads to the production of α-ketoglutarate (AKG), from which aspartate can be produced *via* both reductive and oxidative pathways. Thus, inhibition of cellular respiration, associated to reduced levels of electron acceptors can result in aspartate deficiency [57]. Conversely, supplementing respiration-deficient cancer cells with supra-physiological levels of aspartate can resume exponential cellular growth, as shown in the case of cytochrome B-mutated 143B CytB human osteosarcoma cells [57]. These results support the idea that maintaining aspartate synthesis is a major task of cellular respiration in proliferating cells [58]. Others have shown that several cancer cells are highly dependent on the uptake of exogenous serine [59,60], which suggested the essential role of serine in proliferation. For instance, cancer cells lacking p53 are not capable to cope with serine deprivation, rapidly suffering from oxidative stress [60]. Several studies have also focused on the role of L-arginine availability on cell proliferation [61–63]. The murine embryonic fibroblast cell line, NIH-3T3, and primary human dermal fibroblast show increased proliferation when treated with L-arginine. GPRC6A, a receptor for basic amino-acids like L-arginine, L-lysine and L-ornithine, activates downstream cellular pathways ERK1/2, AKT, PKA, and cAMP response element binding protein (CREB) [64]. When GPRC6A, ERK1/2, Akt and CREB where inhibited, L-arginine induced fibroblast proliferation was blocked by disrupting GPRC6A, ERK1/2 and PI3K/Akt pathways [64]. These recent analyses provide a better understanding of the relative contribution of different nutrients and metabolic pathways to biomass production and cell proliferation.

3. Metabolic cooperation in cancer

Cancers are highly heterogeneous on a cellular as well as on a metabolic level, encompassing populations of host and cancer cells exposed to different microenvironmental conditions. From the cellular standpoint, different cell types (*e.g.* endothelial cells, fibroblasts, adipocytes and immune cells) constituting the tumor stroma contribute to tumor growth and survival. From a metabolic standpoint, different degrees of perfusion further contribute to increase metabolic complexity. While some cancer cells are close to blood vessels allowing them to operate OXPHOS, other cells reside in areas characterized by low oxygen and low nutrient bioavailability. When glucose is present, hypoxic cancer cells can survive and proliferate by switching from an oxidative to a more glycolytic metabolism coupled to lactate fermentation [65]. Removing allosteric brakes indeed allows an acceleration of the glycolytic flux, providing enough ATP for short term cell survival. If hypoxia persists, oxygen sensing systems trigger transcription programs that further improve the glycolytic rate [37], as described in the previous paragraph.

Glucose is an essential nutrient for glycolytic cancer cells and can become a limiting resource. Upon glucose starvation, cancer cells rely on their high metabolic plasticity to exploit other resources originating from their microenvironment, such as glutamine, lipids, various amino acids and even nearby host and cancer cells that can be engulfed to generate metabolic intermediates and precursors in the process of cellular cannibalism [66–68]. Upon persistent nutrient starvation, cancer cells can further survive on autophagy, a process by which cells recycle dispensable components (such as proteins and organelles) for short to medium term survival under starvation [69]. If nutrient and oxygen delivery remain low, microenvironmental forage and autophagy, however, further decrease the available resources. Ultimately, cancer cells die from necrosis.

More sustainable modes for nutrient supply and use consist for starving cancer cells to cooperate with distant cancer cells or, alternatively, to exploit the metabolic capabilities of host cells. Metabolic cooperation between cancer cells relies on metabolic exchanges that create win-win relationships, which can result in metabolic symbiosis. Accordingly, in the context of cancer hypoxia, glycolytic cancer cells were shown to cooperate with oxidative cancer cells by swapping lactate for glucose [5]. A high glycolytic flux is associated with the release of lactate, which, on average, amounts to 10–40 mM in clinical tumors [70]. Lactate diffuses along its concentration gradient from glycolytic tumor areas towards blood vessels that clear lactate. In the vicinity of perfused blood vessels, oxidative cancer cells were found to rely on lactate preferentially to glucose as a main fuel for OXPHOS [71]. Consequently, this metabolic preference was proposed to result in glucose sparing near blood vessels, thus improving glucose delivery to distant hypoxic/glycolytic tumor areas. In the symbiosis, higher glucose availability is a metabolic reward for glycolytic cancer cells that consume glucose and produce lactate [72]. For oxidative cancer cells, using lactate preferentially to glucose provides a subtler metabolic advantage. The oxidative pathway of lactate comprises lactate uptake in a process primarily facilitated by MCT1, a monocarboxylate transporter with a high affinity for lactate [72], the conversion of lactate and NAD^+ to lactate, NADH and H^+ by lactate dehydrogenase B (LDHB), and the mitochondrial use of pyruvate [5] and NADH (imported into mitochondria through the malate-aspartate shuttle) [73]. Importantly, other authors have reported that LDHB can also reside in the mitochondria of some cancer cell lines, where they would generate pyruvate and NADH from lactate to directly fuel the TCA cycle and the electron transport chain, respectively [74,75]. The mitochondrial localization of LDHB would be particularly important for glycolytic cancer cells that were recently shown to use lactate derived from glycolysis as a mitochondrial resource to support lipid biosynthesis [75]. The oxidative pathway of lactate is more concise and, comparatively to glycolysis, does not necessitate ATP investment. But what could be the primary advantage for oxidative cancer cells to use lactate is that protons derived from the LDHB reaction in the cytosol fuel lysosomes, owing to a direct interaction between LDHB and V-ATPase at the surface of these vesicles [76]. Hence, the oxidative metabolism of lactate promotes autophagy, which for oxidative cancer cells on fast-forward metabolic mode represents an antioxidant defense system that actively recycles damaged/oxidized proteins and organelles. Of note, lactate also promotes autophagy in glycolytic cancer cells, where endogenously produced lactate can be re-oxidized to pyruvate and NAD^+ reduced to NADH and H^+, thus providing protons to lysosomes [76]. This pathway would optimize protein and organelle recycling for bioenergetic purposes, and ensure pH homeostasis of the cytosol.

A more pernicious metabolic relationship supports sustainable lactate delivery to oxidative cancer cells. It involves the cooption of the metabolic activities of stromal cells by oxidative cancer cells in a process that can be viewed as metabolic enslavement or commensalism. Respiration is indeed associated with the production of ROS, among which H_2O_2, which has a relatively long half-life, can permeate membranes and can reach nearby fibroblasts where it oxidizes proteins including those involved in cellular respiration [77]. When exposed to paracrine H_2O_2, fibroblasts undergo oxidative damage and switch from an oxidative to a more glycolytic metabolism, thus providing lactate and ketone bodies to oxidative cancer cells that use these fuels to aliment their own metabolism. Commensalism further includes mobilizing lipids from adipocytes and amino acids from host cells [78]. Indeed, recent work supports the hypothesis that cancer-associated fibroblasts (CAFs) undergo a catabolic shift to supply tumor cells with ketone bodies and glutamine [79]. For instance, Ko et al. [80] showed that autophagy increased in fibroblasts grown in the presence of MCF7 breast cancer cells. Glutamine secreted by autophagic fibroblasts in turn fueled the mitochondrial activity of MCF7 cancer cells [79,80]. Another study showed that prostate cancer cells can redirect the metabolism of adjacent fibroblasts towards a glycolytic phenotype. The subsequent release of lactate by fibroblasts in turn promoted prostate tumor growth [81].

CAFs can also reprogram cancer cells. Recent evidence points at the glycolytic enzyme PKM2 in cancer cells as a master regulator of CAF-induced metabolic reprogramming. Giannoni et al. [79,82] indeed observed that, after exposure to conditioned CAF medium, PKM2 in PC3 prostate cancer cells was oxidized by ROS as a consequence of a hyperactive mitochondrial metabolism and was phosphorylated by Src kinase. Oxidation and phosphorylation of the active tetrameric PKM2 complex led to its conversion to the less active dimeric form, and the PKM2 dimer translocated to the nucleus where it associated with HIF-1 and the transcriptional repressor differentially expressed in chondrocytes 1 (DEC1). The resulting PKM2/HIF-1/DEC1 complex then promoted EMT and the expression of the inward lactate transporter MCT1 (monocarboxylate transporter 1). The consecutive increase in lactate uptake allowed fueling OXPHOS and anabolic pathways in cancer cells [79]. Exploitation of byproducts released by CAFs, such as lactate, illustrates the metabolic adaptation of cancer cells to a low-glucose environment.

Lactate exchanges have been substantiated in different types of cancers [72,83], indicating that they constitute a general metabolic adaptation to harsh microenvironmental conditions. The oxidative use of lactate is not unique to cancer cells and can be found for exam-

ple in the brain, where astrocytes fuel neurons with lactate [72], and in the muscle, where slow-twitching fibers use oxidatively the lactate produced by fast-twitching fibers [84,85]. What is unique to cancers is that hypoxic cancer cells have little metabolic options and primarily rely on glucose for survival, growth and proliferation. The remarkable dependency for survival of hypoxic/glycolytic cancer cells on the metabolic preferences of normoxic/oxidative ones motivated the development of strategies aimed to interfere with the exchange of lactate. Therapeutic interventions could be aimed at inhibiting MCT4 in hypoxic cancer cell compartments [86], inhibiting MCT1 [5,87–89] and lactate uptake [90,91] in oxygenated/oxidative cancer cells, inhibiting LDHB [76,92] or, possibly, inhibiting the mitochondrial pyruvate carrier in oxidative cancer cells [93]. In our opinion, future therapeutic developments should aim at targeting the oxidative pathway of lactate in cancer cells that reside close to drug-delivering blood vessels. Indeed, this strategy has been shown to indirectly eradicate hypoxic cancer cells [71], which are otherwise difficult to treat with chemotherapy (poor diffusion of chemotherapeutic drugs) and radiotherapy (poor oxygenation).

Although lactate *per se* fuels anabolic pathways in cancer cells, lactate released by cancer cells also drives the behavior of surrounding cells, most notably endothelial cells. In this context, Végran et al. found that lactate produced by glycolytic tumors stimulates the autocrine NF-κB-IL-8 pathway in human umbilical vein endothelial cells (HUVEC) in a MCT1-dependent manner [94]. In addition, evidence showed that exogenous lactate activates HIF-1 in normoxic endothelial cells [95]. After its uptake by MCT1, lactate is indeed oxidized into pyruvate by LDHB, and, when produced in the cytosol, pyruvate outcompetes α-ketoglutarate (the required co-substrate) from PHD, promoting HIF-1α stabilization. Consequently, HIF-1 activation triggers the production of pro-angiogenic basic fibroblast growth factor [95]. Moreover, lactate treatment significantly increased the expression of vascular endothelial growth factor (VEGF) receptor-2, a HIF-1-target gene product and a major transducer of VEGF-mediated angiogenesis in endothelial cells.

Notably, other tumor stroma-derived metabolic fuels have been recently detected. For example, stroma-associated pancreatic stellate cells (myofibroblast-like cells) produce non-essential amino acids, in particular alanine that support pancreatic tumor metabolism [96]. In another example, adipocytes, which are abundant in the tumor microenvironment of renal, breast, prostate and ovarian cancers and have been for long considered as passive bystanders to cancer development [97–99], usually display fewer lipid droplets compared to normal adipocytes, suggesting that they supply fatty acids to nearby cancer cells [78]. Nieman et al. [99] showed that human omental adipocytes promote the invasion, migration and metastasis of SKOV3ip1 human ovarian cancer cells toward the omentum. The increase in cancer aggressiveness was mediated by adipokines, such as IL-8. Additional adipocyte-ovarian cancer cell co-culture experiments evidenced that adipocytes can directly transfer lipids to cancer cells and, thereby, sustain their proliferation [99]. This study evidenced that tumor lipid metabolism was not only set by the (epi)genetic characteristics of the cancer cells, but also by the lipid availability in the tumor microenvironment.

Tumor escape from the immune system is an important hallmark of cancer [100]. Many examples indicate that the tumor microenvironment drives metabolic changes in immune cells that alter the immune response. Details on the complete metabolic adaptations of several immune cell types are provided in references [101,102]. Recent evidence shows that immune cells reprogram their metabolism upon activation. For instance, naïve T cells rely on fatty acid oxidation and mitochondrial respiration for energy production. When activated, T cells upregulate glycolysis to sustain interferon gamma (IFN-γ) production [101,103]. Another study showed that glucose levels significantly decrease when T cells were co-cultured with lymphoma cells [103]. The resulting glucose deprivation limited the ability of T cells to secrete effector cytokines [103]. Immune cells also shift their metabolism during cancer progression. During the early inflammatory phase of cancer, tumor-associated macrophages (TAMs) are mainly glycolytic. This metabolic phenotype promotes tumorigenesis through cancer-related inflammation, which increases genetic instability. In developed tumors, it has been suggested that IL-4 produced by infiltrated Th2 cells and lactate secreted by cancer cells inhibit glycolysis and upregulate OXPHOS in immune cells [101]. This metabolic shift supports immunosuppression and tumor growth [101]. In addition, lactate taken up by TAMs activates the transcription of VEGF and L-arginine-metabolizing enzyme arginase 1 (ARG1) genes through HIF-1α stabilization [102,104,105]. Overexpression of VEGF and ARG1 by TAMs sustains tumor growth and tissue remodeling [104], as well as immune escape [106]. A recent study also showed that hypoxic TAMs regulated tumor blood vessel formation through the mTORC1 inhibitor REDD1 (regulated in development and DNA damage response 1) overexpression. REDD1 upregulation inhibited mTOR, thereby blocking glycolysis and preventing excessive angiogenesis. Genetic deletion of REDD1 in TAMs restored glycolysis and led to tumor vessel normalization, which prevents metastasis formation [107].

4. Metabolic regulation of cancer cell death

Alteration in the control of cell death contributes to several human diseases, notably cancer [12,108]. Therefore, many studies have focused on devising ways to overcome cell death resistance of cancer cells. It is well-known that cell death can occur by different mechanisms, further highlighting the importance of this process in tissue homeostasis. The most common and well-defined form of programmed cell death is apoptosis, resulting in the organized destruction and complete removal of the apoptotic cell. It is specifically triggered following defined (intrinsic or extrinsic) signals by the cell itself, often resulting from damage, stress or consisting a barrier against tumorigenesis (as reviewed in reference [109]). In addition to apoptosis, various other biological processes can lead to cell destruction. Anoikis is related to apoptosis as it is a caspase-dependent cell death mechanism triggered by the detachment of cells from the extracellular matrix [9,110,111]. Necrosis, as opposed to the highly regulated apoptosis, is an accidental death occurring spontaneously following external stresses that block normal physiological processes. The unorganized nature of this form of death leads to the release of cellular debris in the surrounding tissue [112]. Senescence is a process in which cells enter a form of cell-cycle arrest and permanently lose their ability to divide. Senescent cells cannot be stimulated to proliferate by know physiological stimuli [113]. Finally, while it is not only referred to as a type of cell death but also as a protective process, autophagy is still related to cellular viability.

Although many links are still indirect and further studies are required to understand the underlying molecular mechanisms, there is a clear connection between metabolism and cell death mediated by various signal transduction pathways. In cancer cells, p53 coordinates a common central pathway at the cross-road between cell death and metabolism [114]. p53 is the most important pro-apoptotic protein and is mutated/inactivated in approximately 50% of tumors [115]. While p53 has a central role in tumor suppression, it is also involved in the modulation of cancer metabolism. Two well-known transcriptional targets of p53 regulating metabolism are TP53-induced glycol-

ysis and apoptosis regulator (TIGAR) [116] and synthesis of cytochrome oxidase 2 (SCO2), a cytochrome oxidase 2 (COX2) assembly protein [117]. While TIGAR decreases the glycolytic flux by dephosphorylating fructose-2,6-bisphosphate, SCO2 promotes electron transport chain assembly and OXPHOS. p53 is thus able to repress glycolysis and to promote OXPHOS and fatty acid oxidation [114].

Abnormal tumor perfusion and, consequently, nutrient deprivation impact on cell death. For instance, one common microenvironmental alteration in tumors is hypoxia, which can act as a signal for p53 stabilization and cell death induction [118]. Also, the metabolic status of the cell acts as a signal for p53 induction. When cellular ATP levels decline, the resulting decrease in the ATP/ADP ratio activates adenosine monophosphate kinase (AMPK), and AMPK phosphorylates p53 on serine 15, thus initiating AMPK-dependent cell-cycle arrest [119,120]. AMPK activation acts in most cases as a tumor suppressor by inducing a cell cycle arrest and by inhibiting the synthesis of most cellular macromolecules. It inhibits mTOR complex 1 (mTORC1) by phosphorylating its upstream regulator tuberous sclerosis complex 2 (TSC2), which inhibits cell growth [121]. ATP levels and AMPK thus provide an important connection between p53-mediated regulation of energy metabolism and programmed cell death [121]. Of note, adenosine signaling can further induce apoptosis by stimulating adenosine receptor A2B, which activates a caspase- and PUMA-dependent apoptotic response involving a downregulation of anti-apoptotic B-cell lymphoma 2 (Bcl-2) protein [114].

Mitochondria constitute an important cross-road between metabolism and cell death. In specific circumstances where cells rely on mitochondrial respiration to cope with glucose deprivation, targeting OXPHOS has been reported to induce cell death [122]. Besides energy metabolism, mitochondria play an essential role in cell signaling and cell death modulation through apoptosis (most notably by regulating the release of cytochrome C through VDAC [voltage-dependent anion channel] and the mitochondrial permeability transition pore) and some form of necrosis [123]. Mitochondria control the intrinsic apoptosis pathway through mitochondrial outer membrane permeabilization, which is tightly regulated by the Bcl-2 family of proteins [113]. The release of mitochondrial Ca^{2+} is critically involved in the initiation and effectuation of apoptotic cell death. In this context, AKT activation confers resistance to apoptosis by stimulating Bcl-2 protein expression [124] and the binding of HK2 to VDAC on the mitochondrial surface [125].

Bcl-2-associated agonist of cell death (BAD), a BH3-only family member that controls apoptosis by facilitating mitochondrial outer membrane permeabilization [126], is also a clear regulator of mitochondrial metabolism [127]. In $BAD^{-/-}$ hepatocytes, glycolysis decreases while fatty acid oxidation (FAO) and gluconeogenesis increase [126]. The loss of BAD is also associated to altered mitochondrial metabolism, as lack of BAD leads to reduced mitochondrial respiration in response to glucose [127]. BAD activity is regulated by phosphorylation of its Bcl-2 homology (BH)-3 domains that suppresses gluconeogenesis and activates anti-apoptotic Bcl-2 family members [126,128]. Therefore, BAD is at the cross-road between metabolism and cell death control.

To highlight the importance of metabolism in influencing cell death processes in cancer, it is worth focusing on the metabolic alterations that occur following chemotherapy. Altered glucose metabolism has been described as a cause of chemoresistance in multiple tumor types, but the precise mechanisms are still unclear [129,130]. It was initially envisioned that aerobic glycolysis could be responsible for cell death resistance [131]. However, very recent studies provide evidence that cancer cells take advantage of enhancing their respiratory function to become more aggressive [132]. In particular, a high oxidative metabolism has been identified to confer chemoresistance to certain chemotherapeutic agents. For example, in ovarian cancer, one of the most lethal cancers worldwide, cisplatin-resistant cells displayed increased OXPHOS and ROS levels compared to sensitive cells, and this phenotype was reversed upon pharmacological inhibition of mitochondrial OXPHOS or ROS scavenging [133]. The opposite phenomenon, chemoresistance by a low oxidative metabolism, has been identified as well [134,135]. Despite that these two types of metabolic chemoresistance may appear to be opposite, they both act through a decreased capability of mitochondria to generate ROS, either by upregulating antioxidant defenses in a high OXPHOS context [136] or by decreasing ROS generation at the electron transport chain when OXPHOS is low. These observations indicate that cancer cells can achieve chemoresistance by different metabolic means.

An interesting phenomenon occurring upon chemotherapy is referred to as 'therapy-induced senescence' (TIS) [137]. Senescence is potentially harmful because of its peculiar secretory profile known as the senescence-associated secretory phenotype (SASP), which has been identified to drive tumor inflammation and progression [138]. Senescent cancer cells have a hypermetabolic phenotype characterized by accelerated glycolysis and mitochondrial oxygen consumption [139]. This metabolic reprogramming is required to cope with SASP as it is a highly energy-demanding process. Therefore, targeting metabolism can be an associated anticancer treatment against TIS cancer cells.

Another form of tumor resistance related to metabolic alterations is resistance to high-mobility group box 1 (HMGB1), secreted by macrophages and NK cells [140]. HMGB1 induces a distinct form of necrotic cell death in cancer cells through reducing mitochondrial oxygen consumption. Mechanistically, HMGB1 allosterically inhibits tetrameric pyruvate kinase isoform M2, which blocks glucose-dependent aerobic respiration, subsequently causing an acute metabolic shift that restricts the energy supply of the cell to glycolysis. Resistance occurs when cancer cells increase (anaerobic) glycolysis and glutaminolysis. Therefore, enhanced glucose fermentation and increased glutaminolysis can render cancer cells resistant to HMGB1 [141].

As detailed in the next chapter, when cancer cells acquire the ability to spread to distant parts of the body, they must also acquire resistance to anoikis. It is indeed well-known that cancer cells must rectify metabolic defects (*e.g.* ATP generation) in addition to blocking anoikis in order to survive to detachment from the extracellular matrix [9]. Both stimulation of ATP production and anoikis inhibition are regulated by a similar signaling pathway operating downstream of oncogenic Ras by activation of AKT and serum and glucocorticoid-regulated kinase-1 (SGK-1) [142].

Different from classical types of cell death, autophagy is considered to have dual functions in cancer, as it is both a tumor suppressor and a protector of cancer cell survival [143]. Autophagy is indirectly modulated by metabolic enzymes. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is involved in multiple cellular processes based mainly on its subcellular localization [144]. During glucose deprivation, GAPDH is phosphorylated by AMPK and is translocated to the cell nucleus where it interacts with NAD^{+}-dependent deacetylase sirtuin 1 (Sirt1). Both AMPK-dependent phosphorylation and the nuclear translocation of GAPDH mediate rapid Sirt1 activation, leading to the transcriptional induction of the autophagy program [145]. Upon nutrient starvation, cancer cells can survive on autophagy. [67]. However, if nutrient and oxygen delivery are persistently low, autophagy ultimately leads to necrotic cell death.

5. Metabolic contribution to cancer metastasis

Tumor cells undergo considerable metabolic reprogramming to survive and proliferate within the hostile environment of solid tumors, often characterized by limited oxygen and nutrient supply. Another important parameter defining tumor malignancy is the ability of tumor cells to invade and metastasize, and we here summarize our current knowledge of the contribution of metabolism to the metastatic process.

A typical metabolic alteration well established to promote metastasis is acidosis in the primary tumor [146]. In many patients, an inverted pH gradient across the plasma membrane of cancer cells has been observed compared to corresponding healthy tissues. As opposed to normal tissue, tumors are indeed characterized by a more acidic extracellular pH (pHe) and a slightly alkaline intracellular pH (pHi) [147–149]. This results from the abnormal metabolic activity of cancer cells, including increased glycolytic flux and lactic acid release [150]; carbon dioxide production by the TCA cycle and the pentose phosphate pathway (PPP) [151–154]; overexpression or upregulated activity of carbonic anhydrases [155,156] and proton transporters [156]; and decreased proton clearance in the tumor environment [157]. Proton extrusion and extracellular acidification make adherent junctions lose [158], stimulate migration and cytoskeleton reorganization [159–163], and promote the expression [164,165], release [166,167] and activity [167,168] of proteases that degrade the extracellular matrix. Hence, acidic priming was shown to be sufficient to increase lung colonization following sarcoma and melanoma tumor cell injection in the tail vein of mice [163,167,169,170].

Besides acidity, high levels of lactate are correlated with metastases in several cancer types [171–175]. Lactate is normally exported through MCT 1 to 4 in combination with protons [176]. Whether lactate is an indirect indicator of tumor acidity or exerts itself a pro-metastatic activity remains to be fully elucidated; yet, tumor lactate mapping revealed a lack of correlation with pHe mapping [177], suggesting that pHe alone fails to explain why high levels of lactate are related to poor outcome. As lactate itself directly promotes HIF-signaling [178,179], angiogenesis and tumor progression [180,181], future studies should be aimed to investigate the direct role of lactate in tumor metastasis.

Interestingly, cell detachment from the extracellular matrix and neighboring cells is *per se* able to induce early metabolic changes, including diversion of glucose from glycolysis and the TCA cycle to the PPP [9], and decreases the oxygen consumption rate [111]. The PPP is an anabolic pathway that produces NADPH, a cofactor necessary for glutathione recycling and ROS detoxification. Diverting glucose from glycolysis to the PPP could therefore help the cells to resist to detachment-induced oxidative stress [9]. As a main contributor to extracellular acidification and lactate production and because of its connection with the PPP, an increased glycolytic flux has been associated with cancer metastasis [146]. However, oxidative mitochondrial metabolism is currently emerging as another major regulator of tumor metastasis. Recent works on breast cancer and melanoma models have revealed that at least some metastatic cancer cells have a high oxidative metabolism and that mitochondrial metabolism increases along with the progressive acquisition of metastatic traits [11,132]. Moreover, mitochondrial transfer from stromal to cancer cells has been shown to increase the ability to metastasize [182]. Among mitochondrial metabolism regulators, peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) is a master promoter of mitochondria biogenesis and impacts a majority of metabolic pathways. It has recently been shown as a positive or negative metastasis regulator in different tumor models. For instance, PGC-1α/estrogen-related receptor α (ERRα) axis is critical for breast cancer cells by increasing glutamine-derived carbon flux into lipogenesis notably under hypoxia, thereby sustaining their proliferation [183], but also by promoting VEGF secretion and angiogenesis [184–186], thereby paving a plausible road for cancer cell dissemination. Breast circulating cancer cells and particularly those with a brain tropism rely on PGC-1α-enhanced mitochondrial activity during metastatic spread [132,187]. Conversely, PGC-1α-expressing melanoma cells have a low metastatic potential independently on its influence on mitochondrial metabolism [188] while PGC-1α suppresses metastatic spread of prostate cancer cells through the enhancement of mitochondrial catabolic pathways, counteracting the acquisition of malignant traits by highly glycolytic prostate carcinomas. This dual role of PGC-1α should be deciphered in light of tissue-specificity, of complex, heterogeneous and dynamic regulation of metabolic phenotypes in cancer cells according to their microenvironment, and of metabolic and non-metabolic targets of this protein.

That oxidative metabolism promotes metastasis can in part be explained by the fact that mitochondria are one of the major sites of ROS production when electrons leak from the electron transport chain [189]. If high levels of mitochondrial ROS promote apoptosis and low levels ensure cellular homeostasis [190], intermediate sublethal levels were shown to activate pro-metastatic signaling pathways (including Src and Pyk2) [11] and to increase cell tolerance to stress [10,191,192]. Both a partial inhibition and an overload of the electron transport chain result in electron leak and were shown to promote tumor metastasis in a mtROS-dependent way [11,193]. Conversely, oxidative stress inhibited distant metastasis in a melanoma model, as circulating metastatic cells, compared to cancer cells of the primary tumor, were characterized by decreased stores of reduced glutathione and an upregulation of NADPH-generating and a downregulation of NADPH-consuming enzymes of the folate pathway [194]. These observations raise the importance of ROS levels and compartmentalization on their effect on cell signaling. Indeed, both mitochondria-targeted superoxide scavenger mitoTEMPO [11] and methotrexate [194] interfering with folate metabolism can decrease the occurrence of metastasis in melanoma models, whereas the general antioxidant *N*-acetyl-cysteine does not [194]. In these models, *N*-acetyl-cysteine rather promoted metastasis [194].

Glutamine metabolism can promote not only cell transformation and tumor growth, but also cell migration and invasion [195]. Accordingly, inhibition of glutaminase, the enzyme converting glutamine into glutamate, was sufficient to inhibit cancer cell invasion in a model of breast cancer [195]. Whether the contribution of glutaminase to cancer cell migration is linked to an effect on pH regulation (the reaction generates NH_4^+), glutathione synthesis (glutamate is a precursor of glutathione), mitochondrial respiration or other pathways still requires investigation.

There is currently a growing interest for the role of lipid metabolism in tumor growth and progression. *In vitro*, inhibition of ACL and FAS can decrease cancer cell migration [196], whereas fatty acid exposure can promote migration and invasion [197]. *In vivo*, FAS silencing or inhibition with Orlistat was reported to decrease tumor regrowth and metastatic burden following withdrawal of Sorafenib or Sunitinib, relapses and metastases being highly dependent on lipid synthesis following antiangiogenic therapies [7]. In colorectal tumor models, silencing FAS decreased liver metastasis [196].

From these observations, one can conclude there is no unique metabolic phenotype leading to successful metastases. A recent study analyzed the metabolic gene expression signature in 20 different tumor types to correlate it with the clinical outcome [198]. The results

showed that the metabolic signature of cancers has a tissue specific component, which is reminiscent of the tissue of origin, and a tissue independent component. Considering the tissue independent component, mitochondrial genes downregulation is associated with the worst prognosis, epithelial to mesenchymal transition (EMT) and metastasis.

Distinct metabolic phenotypes can promote different steps of the complex metastatic process, according to the sites of the primary tumor and of the metastases. Primary cancer cells often display extensive metabolic heterogeneity and engage distinct metabolic patterns depending on their site of metastasis: in breast cancer, aerobic glycolysis was the dominant metabolic phenotype specifically identified in liver metastasis, compared to bone and lung metastases that were more dependent on OXPHOS [199]. In an independent study [187], metastatic breast cancer cells with a selective tropism for the brain displayed increased glycolysis coupled to TCA cycle and increased mitochondrial respiration, PPP flux and fatty acid β-oxidation compared to parental circulating cancer cells. These evidences suggest that there might be a high degree of organ selectivity in the selection of metabolic traits enabling successful metastatic dissemination [200].

Premetastatic epithelial cells undergo an EMT that confers a mesenchymal morphology and is associated with cell detachment. Physiologically, EMT occurs during embryonic development and leads to the acquisition of an elongated, spine-like morphology together with changes of the membrane protein expression pattern (including downregulation of E-cadherin and upregulation of vimentin and N-cadherin), cell detachment, resistance to anoikis and acquisition of migratory and invasive traits [201]. It results from the activation of a complex and coordinated transcriptional program implicating TWIST-1 and -2, Snail, Slug, ZINC finger E-box-binding homeobox (ZEB)-1 and -2 transcription factors but also repression of microRNAs among miR-200. In cancer, it is currently thought that EMT is a critical event to produce a metastatic form of epithelial cancer. Mesenchymal cells show a metabolic signature characterized by the diversion of glucose from glycolysis to the TCA cycle for ATP and glutamate production [202,203], and to the hexosamine biosynthetic pathway for the posttranslational modification of glycoproteins and Snail-1 [204–206]. Interestingly, emerging evidence reported the role of oncometabolites succinate, fumarate and D-2-hydroxyglutarate derived from TCA cycle as modulators of epigenetic dysregulation driving the EMT process. Succinate and fumarate accumulations respectively result from loss of function of succinate dehydrogenase (mainly subunit B) observed *i.e.* in paragangliomas, pheochromocytomas, renal cell carcinoma and gastrointestinal tumors [207–209]; and fumarate hydratase in leiomyomata and renal cell carcinoma [210].

Conversely, D-2-hydroxyglutarate build up is mostly due to isocitrate dehydrogenase abnormal activity resulting from mutations reported *i.e.* in acute myeloid leukemia and glioblastoma [211,212], although significant levels of this oncometabolite were also detected in colon carcinoma cell lines independently of any mutation [213]. These metabolites are able to inhibit α-ketoglutarate-dependent dioxygenases among which the aforementioned HIF-1α negative regulator PHD2 [214–216], but also TET family of 5-methylcytosine hydroxylases and Jumonji family of histone demethylases [217–219], as previously discussed in paragraph 2. Inhibition of the last two results in DNA and histone hypermethylation which, in turn, represses miR-200 expression [220,221] and/or induces EMT-related transcription factors [220], leading to repression of epithelial markers, expression of mesenchymal markers, and acquisition of migratory and invasive traits [213,220,222,223].

Mesenchymal cells further upregulate dihydropyrimidine dehydrogenase, leading to pyrimidine degradation and an intracellular accumulation of dihydropyrimidines. Dihydropyrimidine dehydrogenase activity promotes EMT, and dihydropyrimidines likely act as key signaling molecules [224]. Several other metabolites were also shown to induce EMT. For instance, lactic acid was identified to be an activator of TGF-β2 pathway in a glioma cell line [225]. Moreover, cancer cells undergoing EMT accumulate fatty acids that are taken up *via* CD36, in turn stimulating Wnt and TGF-β pathways [197]. Embryonic stem cell exposure to L-proline is sufficient to trigger EMT through modification of the methylation status of histones H3K9 and H3K36, but the relevance of these results to cancer is unknown [226].

As EMT and metastatic cascade are highly energy-consuming, the balance between ATP consumption and production could be critical for the motile and invasive capacities of cancer cells. In this context, AMPK is a major energetic biosensor and its activation maintains cell energy homeostasis under conditions of ATP depletion via inhibition of anabolic pathways and stimulation of catabolic pathways [227]. However, besides the clear role of AMPK in cell survival, it remains quite controversial whether and how AMPK affects EMT. Recent attention on the biguanide-based anticancer therapies has highlighted the involvement of AMPK in peculiar behaviours of cancer cells like the capacity to undergo EMT program and to metastasize. As metformin showed potent anticancer effects by depleting ATP production through its mitochondrial inhibitory capacity [228], consequent AMPK activation was found to be effective in mediating metabolic crisis and cytotoxic effect not only on proliferating cells but also on migrating cells, through repression of EMT pathways [229]. Other studies have shown that AMPK contributes to cell migration [230,231]. Nevertheless, most of these indications about AMPK and EMT are derived from *in vitro* investigations, further studies will be required to define the contribution of AMPK, which is probably context-dependent.

As for the metastatic process as a whole, the complex relationships between EMT and metabolism depend on the tumor type, including the heterogeneity of the cancer cell population and the surrounding microenvironment. In this context, not all cancer cells undergo EMT to successfully metastasize. Unlike many *in vitro* studies, *in vivo* models of breast carcinoma and pancreatic ductal adenocarcinoma (PDAC) suggest that EMT is dispensable for efficient metastasis development [232,233]. Nevertheless, EMT affected in both model chemosensitivity in a tissue-dependent manner. Indeed, in breast cancer the mesenchymal-like cancer cells proliferated less, which made them more resistant to conventional chemotherapy [232], while in PDAC mesenchymal-like cancer cells upregulated nucleosides transporters, which made them more sensitive to gemcitabine. Interestingly, if EMT promotes the initial steps of the metastatic process, the reversed process, the mesenchymal to epithelial transition (MET) seems important in the later steps of metastasis development [234]. If several metabolic changes are associated with or promote EMT, the question of their reversibility for MET is still open.

6. Metabolic characteristics of cancer stem cells

Over the last few years, a growing body of evidence has been obtained suggesting that cancer-initiating cells/cancer stem cells (CICs/CSCs) differ in their metabolism from that of the bulk tumor mass [235,236], although there is so far no consensus on this [201]. Cancer cell stemness can arise from EMT [203], but not necessarily so [204].

Because of their high tumorigenic potential, CICs/CSCs are most likely implicated in the formation of metastases.

A number of evidences has revealed that glycolysis is associated with stemness in cancer. For example, a subset of putative ovarian cancer stem cells ($CD44^+$ $MyD88^+$) has been found to display a glycolytic metabolic profile over OXPHOS for their ATP generation [205], and a subset of breast cancer cells able to grow as spheres increasingly rely on aerobic glycolysis and PPP flux compared to the same cells grown in adherent conditions [206]. Also, modulation of specific glycolytic enzymes (*i.e.*, decreased expression and activity of pyruvate dehydrogenase or increased expression or activity of lactate dehydrogenase A [LDHA]) plays a critical role in promoting the proglycolytic phenotype of CICs in breast tumors [237] and CSCs in lung tumors [238].

Conversely, an increasing number of studies suggest the opposite, *i.e.* that CICs and CSCs have a high oxidative metabolism. In ovarian, glioma and breast cancer models, CICs/CSCs are much more dependent on OXPHOS in terms of increased mitochondrial ROS production, increased mitochondrial membrane potential, higher number of mitochondria and lower lactate production than their differentiated progeny [235,239,240]. In ovarian tumors, dependence of CSCs ($CD44^+$ $CD117^+$) on OXPHOS does not exclude increased glucose consumption nor a higher expression of glucose transporters and glycolytic enzymes. However, ovarian CSCs were found to be resistant to glucose deprivation but sensitive to OXHOS inhibition, probably because of an upregulation of several enzymes of fatty acid β-oxidation and mitochondrial pyruvate oxidative metabolism [239]. In gliomas, CICs consume less glucose while producing more lactate [235], probably because lactate can be produced from oxidative substrates in addition to glucose. As in ovarian cancer, breast tumor CSCs consume more glucose and release less lactate than their progeny. These examples illustrate (I) the metabolic specificities of these tumorigenic subpopulations according to the cancer type, (II) the fact that increased glucose consumption and increased oxidative metabolism are not necessary mutually exclusive, and (III) the fact that glucose consumption and lactate production are not necessarily coupled. In pancreatic ductal adenocarcinoma (PDAC), KRAS ablation-resistant tumor cells, which are responsible of tumor relapses, were shown to depend less on glycolysis and more on OXPHOS together with displaying stem cell traits [238] [241]. Notably, a resistant subpopulation of PDAC CSC clones showed increased resistance to mitochondrial targeting with metformin thanks to an intermediate glycolytic/respiratory phenotype [241], highlighting the challenge of CSC metabolic plasticity for targeting CSCs pharmacologically.

The contribution of other metabolic pathways in the gain of stem-like properties was also investigated in several studies. Fatty acid β-oxidation was found to be upregulated in ovarian cancer CSCs [239], as well as the mevalonate pathway in mammosphere-forming breast tumor cells [242]. Mevalonate production was shown to be critical for the geranylgeranylation and proper membrane localization of RhoA (Ras homolog gene family, member A), a regulator of self-renewal and pluripotency of stem cells [242]. In skin squamous cell papilloma and carcinoma, SOX2 was identified as a key transcription factor re-expressed in CSCs and controlling stemness [243]. Interestingly, SOX2 directly upregulates the transcription of several genes related to glutamine and lipid metabolism, but their relevance for the stem-like properties of tumor cells remains unknown [243]. Another protein involved in energy metabolism regulation and EMT is the cAMP-activated kinase PKA (protein kinase A), which regulates diverse metabolic pathways, ranging from glycolysis to lipid oxidation [244,245]. Previously it has been shown to be activated by intermittent hypoxia [246], while it has been recently shown that its activation inhibits the mesenchymal phenotype by inducing transition to epithelial state and inhibiting CICs [247].

Although the previously stated studies have helped decipher some of the metabolic pathways and features underlying the CICs/CSCs phenotype, further studies are certainly required. In our opinion, future breakthroughs could come from the understanding of whether CSCs have a high metabolic adaptability, and whether, and to which extent their functional plasticity (and asymmetric cell division) is being affected by their metabolism and metabolic adaptability compared to non-CSCs. Resolving these issues would help to verify whether a metabolic inhibitor could be used to selectively target and ablate the CSC fraction within a given tumor. To this end, it is likely that metabolic plasticity will have to be taken into account.

Overall the reported studies highlight the importance of the metabolic plasticity of cancer cells, providing a rationale for using a combination of metabolic inhibitors against specific cancer populations (CSCs, in particular) and chemotherapeutic drugs to improve the clinical efficacy of anticancer treatment [248].

7. Metabolic differences between *in vitro* and *in vivo* models of cancer

The cross-talk between stromal and cancer cells influences the metabolic phenotype of the tumor. *In vivo*, cancer cells are growing close to surrounding stromal cells and may reprogram their metabolism at their advantage. Under the action of inflammatory cytokines, stromal cells and adipocytes release metabolic fuels for cancer cells [249–251]. In this chapter, we will provide additional examples showing that the 3D architecture, the tumor environment and the tissue of origin are other major drivers of tumor metabolism.

Numerous *in vitro* studies have evidenced that tumor metabolism is altered compared to normal tissues. However, reaching conclusions about tumor metabolism is often hampered by differences between tissue culture (2D growth of cancer cells on plastic dishes) and *in vivo* conditions [252]. Cancer cells mostly rely on glucose and glutamine for survival and growth *in vitro*. However, strong evidence shows that the metabolic landscape is more complex *in vivo* [252–254]. It is now clear that cancer metabolism is heterogeneous, with different metabolic phenotypes according to (*i*) the cell type, (*ii*) the cellular location and (*iii*) the biological activity performed at a precise time. *In vitro*, it is rather difficult to appreciate this complexity, because of the lack of heterogeneity, both metabolic [5] and cellular [251], but also because of the lack of environmental clues [8], as well as cellular polarization [255]. The requirement of growing cells *in vitro* with concentration of glucose far exceeding the physiological levels also leads to specific metabolic adaptations [256–258]. While the current cell culture conditions are mostly aimed at allowing cellular proliferation at a doubling rate generally higher than 24 h, it is now necessary to develop more accurate cell culture conditions to mimic nutrient conditions recapitulating the tumor milieu [256]. For instance, Onodera et al. [255] used a physiologically relevant 3D cell culture model to show that overexpression of GLUT3 in nonmalignant human breast cells activates oncogenic signaling pathways, such as EGFR (Epidermal growth factor receptor), β1 integrin, MEK and AKT. Conversely, inhibition of glucose uptake using 2-deoxy-D-glucose led to the suppression of these signaling pathways in malignant cells. Of note, authors did not observe phenotypic reversion in conventional 2D cell cultures after treatment with the same glycolytic inhibitor. This study highlights the importance of the 3D structure for studying glucose metabolism in specific tissues [255].

FDG-PET and hyperpolarized ^{13}C magnetic resonance spectroscopy studies confirmed that most tumors are avid of glucose and

release large amounts of lactate *in vivo* [259–261]. Although studies on cell cultures showed that mitochondrial respiration is limited in several cancer cell lines [262–264], *in vivo* data showed that mitochondrial oxygen consumption is not impaired in tumors and that oxidative glucose metabolism is required for tumor growth [265]. The discrepancy between *in vitro* and *in vivo* observations pleads for the use of spontaneously arising tumor models, which integrate driver mutations, the tumor microenvironment and the surrounding 3D tissue architecture [253,266,267]. In a recent study [253], authors characterized glutamine metabolism in genetically engineered mouse models of lung cancer. They showed that tumor cells mostly rely on glutamine consumption for proliferation *in vitro*, whereas glutamine carbon contribution to the TCA cycle is minimal in mouse lung tumors. In addition, these authors did not find any difference in glutamine consumption between tumor tissues and adjacent normal tissues. Furthermore, glutaminase deletion did not affect tumor growth. Comparatively, tumor-derived cell lines grown in cell cultures were addicted to glutamine and highly sensitive to glutaminase inhibitor CB-839. Importantly, the metabolic phenotype was reverted when cancer cells were injected back into syngeneic mice, rendering cancer cells insensitive to glutaminase inhibitors [253]. In another study [254], *in vivo* imaging highlighted the link between the tumor microenvironment and the heterogeneity of tumor metabolism in non-small cell lung cancer (NSCLC). The authors investigated glucose metabolism and the tumor environment in NSCLC from nine untreated patients. For this purpose, they used a pre-operative imaging workflow based on FDG-PET and multiparametric magnetic resonance imaging (MRI) for characterizing several parameters, such as glucose uptake, anatomy, cellularity and perfusion of tumors. On the day of surgery, patients received an infusion of ^{13}C-glucose. After surgery, tumor samples were collected for histological, genetic and metabolic analysis. Interestingly, glucose oxidation was increased in tumor tissues compared to adjacent normal tissues, and pyruvate dehydrogenase was found to drive glucose carbon flux into the TCA cycle. A significant increase in pyruvate carboxylase activity was also observed. Other experiments suggested that lung tumors use lactate as a nutrient source for pyruvate synthesis. These findings challenge the common idea that a high FDG uptake indicates a Warburg phenotype and suppressed glucose oxidation in NSCLC [252,254]. In addition, dynamic contrast-enhanced MRI revealed that perfusion inversely correlates with glucose consumption, indicating the preferential use of non-glucose nutrients (*e.g.* lactate) in highly perfused tumor areas.

These above-referenced studies suggest that the tumor environment is at least as important as the genetics of a tumor for predicting its metabolic profile [252–254]. Another recent study also points at the tissue of origin as a major driver of the metabolic behavior of a tumor [268]. Mayers et al. [268] indeed used a mouse model with *Kras* activation and *Trp53* deletion in the pancreas or in the lungs to generate spontaneous PDAC and NSCLC, respectively. Although both tumor models shared the same initiating mutations, authors observed major differences in branched-chain amino acid (BCAA) metabolism: NSCLC, but not PDAC, had high BCAA uptake and contained high levels of BCAA-derived proteins [268,269]. Further experiments demonstrated that NSCLC rely on BCAA as a main nitrogen source [268,269]. Genetic deletion of *Bcat1* and *Bcat2*, which encode the two isoforms of BCAA transaminase, significantly impaired NSCLC tumor formation but did not affect PDAC tumor growth.

8. Discussion

Many challenges are upcoming in the field of cancer metabolism, represented by several currently ongoing clinical trials [270]. Despite today's vibrant research on cancer metabolism and the high potential of this field for cancer therapy, the next years will be crucial for understanding the current contribution of research on tumor metabolism to the development of novel treatments. While antimetabolic drugs have been historically one of the first approved chemotherapy [271], and that several drugs have further shown an activity on metabolic pathways [272], specific therapies are still missing to target cancer metabolism *per se*. Indeed, while there is a consensus on the fact that cancer metabolism differs from that of normal cells, it is not yet firmly established how to target this difference effectively [273]. Given the genetic and metabolic heterogeneity of cancers, proper patient stratification will be required according to the metabolic status of their tumors in order to design robust clinical trials and to ultimately tailor treatments targeting metabolism [273,274], even though it is emerging that different cancers converge their metabolism alongside tumor progression [198]. Nevertheless, a systematic understanding of how activated oncogenes specifically influence metabolism, especially in relationship to the tissue of origin [267], will be essential for the success of future clinical trials.

Much attention has been given to the role of metabolism in generating energy and building blocks. However, one must take into account that many of the metabolites generated by such reactions exert other biological activities (*e.g.* the influence of AKG, succinate and fumarate on AKG-dependent dioxygenases) [214,275,276]. Moreover, certain metabolites can act as signaling factors. As such, the accumulation of fumarate has been shown to directly promote oncogenic posttranslational modifications known as protein succination [277]. Epigenetic regulation dictated by metabolite availability and in relation to the peculiar metabolic alterations of cancer cells is also an emerging field of research for the understanding of the role of metabolism far beyond the domain of energy generation [220].

Most recent findings in human tumors challenge many of the current notions of cancer metabolism, supporting the need for more refined culture conditions to recapitulate the *in vivo* conditions of variable nutrient availability, which have been shown valuable in screening for drug targets [256]. Ultimately, the study of cancer metabolism beyond the Warburg effect will help to grasp its plasticity and heterogeneity, thus potentially opening novel therapeutic avenues.

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