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REVIEW

Metabolic changes associated with tumor metastasis, part 2: Mitochondria, lipid and amino acid metabolism

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Abstract Metabolic alterations are a hallmark of cancer controlling tumor progression and metastasis. Among the various metabolic phenotypes encountered in tumors, this review focuses on the contributions of mitochondria, lipid and amino acid metabolism to the metastatic process. Tumor cells require functional mitochondria to grow, proliferate and metastasize, but shifts in mitochondrial activities confer pro-metastatic traits encompassing increased production of mitochondrial reactive oxygen species (mtROS), enhanced resistance to apoptosis and the increased or de novo production of metabolic intermediates of the TCA cycle behaving as oncometabolites, including succinate, fumarate, and D-2-hydroxyglutarate that control energy production, biosynthesis and the redox state. Lipid metabolism and the metabolism of amino acids, such as glutamine, glutamate and proline are also currently emerging as focal control points of cancer metastasis.

Keywords Tumor metastasis · Oxidative phosphorylation (OXPHOS) · Electron transport chain (ETC) · Reactive oxygen species (ROS) · Tricarboxylic acid cycle (TCA cycle) · Lipogenesis · Glutaminolysis · Proline metabolism

Abbreviations

αKG	α-Ketoglutarate
Aco	Aconitase
ACLY	ATP-citrate lyase
CoA	Coenzyme A
CS	Citrate synthase
D-2HG	D-2-Hydroxyglutarate
EMT	Epithelial-to-mesenchymal transition
ETC	Electron transport chain
eSC	Embryonic stem cell
FASN	Fatty acid synthase
FH	Fumarate hydratase
GDH	Glutamate dehydrogenase
GLS	Glutaminase
HGFR	Hepatocyte growth factor receptor
HIF-1	Hypoxia-inducible factor-1
IDH	Isocitrate dehydrogenase
KEAP1	Kelch-like ECH-associated protein 1
KRAS	Kirsten Rat Sarcoma
MCL-1	Myeloid cell leukemia-1
mtROS	Mitochondrial reactive oxygen species
mTORC1	Mammalian target of rapamycin complex 1
NF-κB	Nuclear factor-κB
NRF2	Nuclear factor-like 2
OXPHOS	Oxidative phosphorylation
PGC-1	Peroxisome proliferator-activated receptor γ coactivator-1

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PHD	Prolylhydroxylase
PI3K	Phosphoinositide 3-kinase
PKB/Akt	Protein kinase B
ROS	Reactive oxygen species
SDH	Succinate dehydrogenase
SOD	Superoxide dismutase
SRC2	Steroid receptor coactivator 2
SREBP	Sterol regulatory element-binding protein
STAT3	Signal transducer and activator of transcription 3
TCA (cycle)	Tricarboxylic acid (cycle)
TET (enzyme)	Ten-eleven translocation (enzyme)

Introduction

While intensive research aims to characterize primary tumor biology for the sake of new therapeutic and diagnostic tools, less attention has been paid until recently to the biology of metastases. Metastasis, however, is estimated to be responsible for ~90 % of cancer-associated deaths [1], representing a yearly toll of ~8,200,000 patients worldwide (Globoscan 2012).[1] Growing evidence points to a metabolic control of tumor progression affecting many phenotypic traits of malignancy, including metastasis. While the specific contributions of tumor pH, glycolysis and the pentose phosphate pathway to the metastatic process are addressed in a companion paper, this review focuses on mitochondrial, lipid and amino acid metabolism.

Defects of mitochondrial function have long been suspected to contribute to the development and progression of cancer. Almost a century ago, Otto Warburg [2] initiated research on mitochondrial alterations in cancer and proposed a mechanism to explain the differences in energy metabolism between normal and cancer cells. He suggested that mitochondrial alterations could provide unique therapeutic targets in various cancer types [3]. The concept promoted by Warburg that mitochondrial damage is the cause of cancer is no longer tenable as a general concept [4]. However, specific cancer-associated mutations have been reported in nuclear-encoded mitochondrial enzymes of the tricarboxylic acid (TCA) cycle, including fumarate hydratase (FH) [5], succinate dehydrogenase (SDH) [5] and isocitrate dehydrogenase (IDH) [6]. SDH deficiency has been linked to hereditary paraganglioma and pheochromocytoma, and FH inactivation promotes leiomyoma, leiomyosarcoma and renal cell carcinoma [7, 8]. Besides these mutations, several other cancer-related mitochondrial alterations have been identified, and mitochondria are now emerging as key players in tumor transformation and progression. This is not surprising since mitochondria are not passive bystanders involved in bioenergetics. They rather act as metabolic and signaling hubs, interconnecting metabolism and cell signaling.

From a metabolic standpoint, one of the main activities of mitochondria is to perform the TCA cycle where the acetyl group of acetyl-coenzyme A (acetyl-CoA), mostly derived from pyruvate, is progressively oxidized to CO_2 to provide reducing equivalents for oxidative phosphorylation (OXPHOS) (Fig. 1). In addition to pyruvate, the TCA cycle can be fueled by products of anaplerotic reactions (from Greek ἀνά [up] and πληρόω [fill in]), among which α-ketoglutarate (αKG) from glutaminolysis is a major substrate [9]. OXPHOS occurs at the mitochondrial electron transport chain (ETC) and represents a highly efficient pathway for ATP generation. Importantly, the TCA cycle also generates intermediates connecting the cycle to other metabolic pathways by means of the so-called cataplerotic reactions (from Greek κατα [down] and πληρόω [deplete]) that drain the TCA cycle from its metabolites. These reactions provide substrates for biosynthesis, thus supporting normal cellular functions, cell growth and proliferation [10].

Besides metabolism sensu stricto, mitochondria are also critical regulators of compartmentalized cellular signaling. One typical example is the modulation of apoptosis, which mitochondria achieve by regulating the release of cytochrome *c* and calcium. Mitochondria further host several signaling pathways involved in tumor transformation and growth. For example, the mitochondrial fraction of signal transducer and activator of transcription 3 (STAT3) promotes OXPHOS and pancreatic cancer initiation [11, 12], ERK activation promotes tumor cell resistance to apoptosis by inhibiting the opening of the permeability transition pore [13], and c-Src regulates OXPHOS by phosphorylating several ETC subunits [14]. These signaling pathways are directly related to mitochondrial metabolism. It is therefore not surprising that mitochondria exert critical roles not only in tumorigenesis but also in cancer metastasis, which is the topic of this review.

Oxidative phosphorylation and mitochondrial reactive oxygen species

Mitochondria are involved in OXPHOS, which couples redox reactions of the ETC to ATP synthesis (Fig. 1). During this process, electrons derived from NADH and $FADH_2$ are transferred to molecular oxygen through sequential redox reactions that generate a proton gradient across the inner mitochondrial membrane. Four macromolecular protein complexes located at the inner mitochondrial membrane are required for driving the

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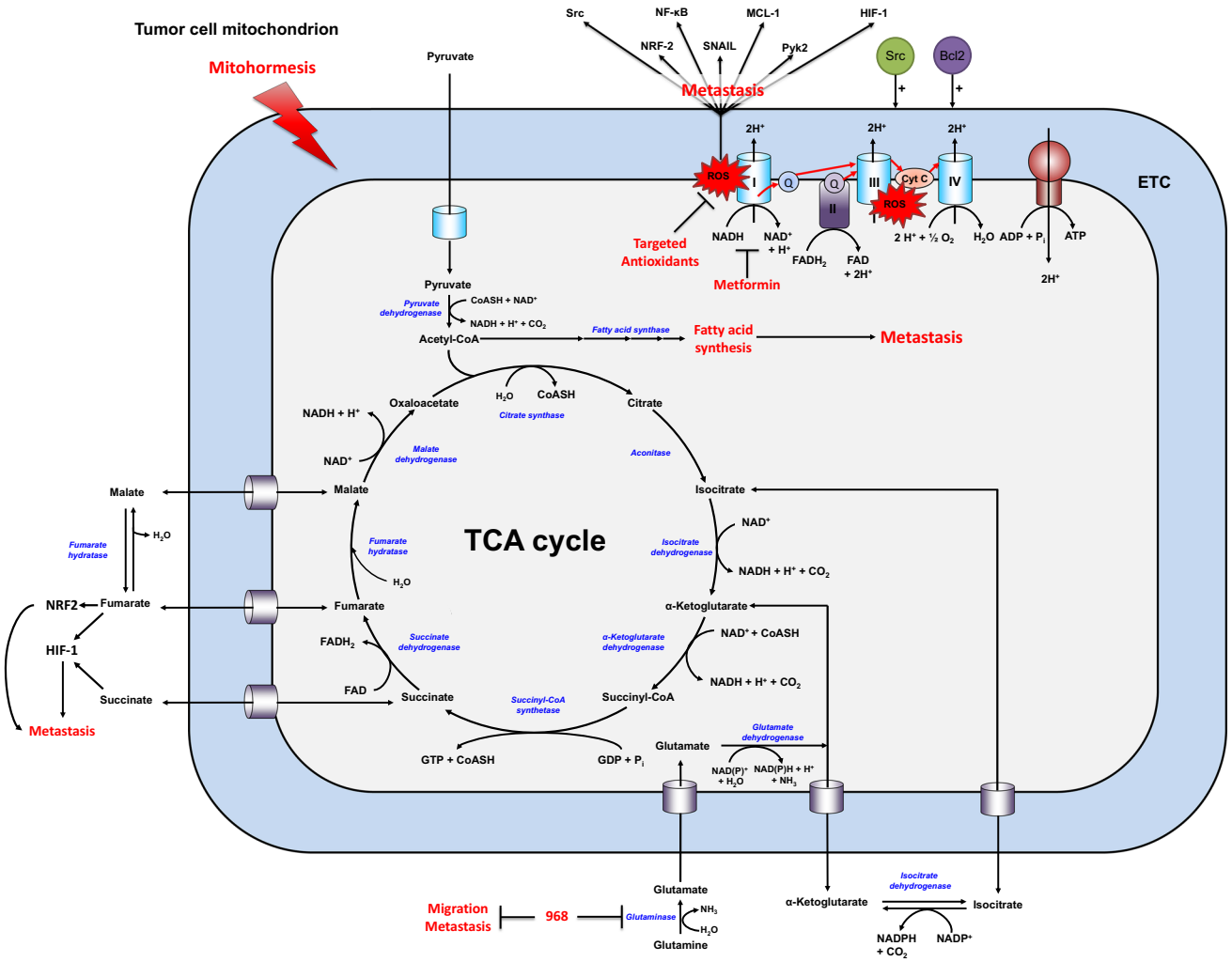

Fig. 1 Simplified scheme highlighting the contribution of mitochondria, lipid and amino acid metabolism to tumor metastasis. The scheme depicts a mitochondrion where enzymes are represented in *italicized blue font* and their substrates in *bold black*. Upon entering into the mitochondria, pyruvate is broken down during the catabolic part of the tricarboxylic acid (TCA) cycle. This produces reducing agents that fuel the electron transport chain (ETC) to generate the proton motive force needed for the production of ATP and, as a byproduct, mitochondrial reactive oxygen species (mtROS). Increased mtROS levels have been proposed to increase resistance to stress (mitohormesis). Furthermore, several anaplerotic reactions replenish the TCA cycle. Many of these reactions promote tumor metastasis, as indicated in *red*. Other abbreviations: *HIF-1* hypoxia-inducible factor-1, *MCL-1* myeloid cell leukemia-1, *NF-kB* nuclear factor-kB, *NRF2* nuclear factor-like 2

generation of the gradient, which triggers the activity of the ATP-synthase complex at the inner mitochondrial membrane. Thus, protons transferred from the intermembrane space to the mitochondrial matrix through ATP-synthase along their concentration gradient provide the energy for ATP generation in mitochondria.

While O_2 is fully reduced to water to foster ATP synthesis in mitochondria, a small proportion is converted into superoxide [15, 16] (Fig. 1). Superoxide is a radical anion and a highly reactive oxygen species (ROS) acting as a strong oxidant. In normal circumstances, superoxide is detoxified by superoxide dismutases (SODs) that rapidly convert it to H_2O_2. SODs are excellent catalysts that are rate-limited primarily by the speed of diffusion of the substrate in solution [17]. When superoxide is produced at a supraphysiological rate and ROS rise to a critical level, they can oxidize cytochrome *c* and impair its binding to the inner mitochondrial membrane [18]. Cytochrome *c* is normally bound to the phospholipid cardiolipin at the inner mitochondrial membrane where it transfers electrons from complex III to IV of the ETC. Following oxidation, this interaction is repressed and cytochrome*c* is released from mitochondria, thus triggering apoptosis [19]. However, mitochondrial ROS (mtROS) are not only triggering

apoptosis. At non-lethal levels, they are essential for cellular adaptation to stress [20] and to hypoxia through activation of transcription factor hypoxia-inducible factor-1 (HIF-1) [21], as well as for the induction of autophagy [22] and mitochondrial biogenesis by activation of the transcriptional coactivator peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1) [23].

The initial observation by Warburg that some tumor cells perform glycolysis at a high rate even in presence of oxygen prompted him to formulate the hypothesis according to which mitochondria are not functional in tumors [3]. Except for some specific cases, this hypothesis has not been confirmed [24]. Still, the perception of the role of mitochondria in tumor cells has often been reduced to the provision of biosynthetic intermediates for cellular proliferation [25]. But mitochondria are also emerging as essential mediators of tumorigenesis. In fact, complete abolition of ETC activity was shown to prevent tumorigenesis in a Kirsten Rat Sarcoma (KRAS)-driven mouse model of lung cancer [26], in murine breast cancer and melanoma models [27], and it inhibited the in vivo growth of human breast cancer cells [28]. In models of pancreatic cancer, mitochondrial targeting of STAT3 stimulated ETC activity and tumor transformation [11, 12], further emphasizing the critical role of mitochondria in cancer. Along the same lines, cancer cells responsible for tumor relapse following oncogene ablation specifically rely on OXPHOS for survival [29]. Consistently, the antidiabetic drug metformin, a dual AMPK activator and ETC Complex I inhibitor [30], acts synergistically with chemotherapy to eradicate resistant tumor cells and promote cancer remission [31]. This observation has been recently linked to the activity of metformin as an inhibitor of ETC Complex I [30, 32].

With regard to the specific contribution of OXPHOS to tumor metastasis, several groups challenged the view that ETC is dispensable for tumor migration and metastasis [27, 33–37]. Disseminating cancer cells actually display increased levels of mitochondrial respiration, at least in breast and melanoma models [35]. This is driven by the upregulation of PGC-1α, a master gene regulating mitochondrial biogenesis and metabolism, making PGC-1α expression a marker of poor prognosis in invasive ductal breast carcinoma [35]. Another piece of evidence arguing for an important contribution of mitochondria to tumor metastasis derives from the work of Tan et al. [27] who demonstrated that active mitochondria are required for tumor growth in vivo and that upon experimentally induced loss of mitochondrial DNA (ρ0 cells), cancer cells are capable of restoring mitochondrial respiration by "stealing" mitochondria from host cells. Interestingly, this work further showed that tumor cells display an increased mitochondrial activity (elevated O_2 consumption and increased presence of cristae) along with the progressive acquisition of metastatic traits, with circulating tumor cells characterized by an intermediate metabolic phenotype compared to primary and secondary tumors (see Figure 1 in companion paper). One of the advantages conferred by an elevation of OXPHOS activity could be a stronger resistance to apoptosis through the induction of a pro-oxidant state [38]. Altered mitochondrial metabolism has also been proposed to promote metastasis by inducing stress tolerance during nutrient deprivation [39].

In strong contrast to studies advocating for a contribution of OXPHOS to cancer metastasis, a number of independent authors reported that interfering with mitochondrial activity can promote metastasis. In particular, overexpression of oncogenes such as BAX inhibitor-1 [40, 41] or loss of metastasis suppressor genes such as KISS1 [42] induces metastasis together with a switch from an oxidative to a glycolytic metabolism. Mitochondrial DNA (mtDNA) mutations can also promote metastatic dissemination from prostate to bones and the invasive growth of melanoma cells in vivo [43, 44]. Accordingly, specific mtDNA mutations are a marker of poor prognosis in breast cancer and melanoma patients [45, 46]. As a final example, mitochondrial stress resulting from mtDNA depletion or treatment with ionophores that uncouple ETC activity from ATP generation promoted an invasive behavior in human lung cancer cells and C2C12 myoblasts [47, 48].

It has been reported that either increased or reduced OXPHOS activity promotes metastatic dissemination. A potential explanation of this conundrum is that two opposite metabolic phenotypes might contribute to metastasis by regulating different pathways. Indeed, on one hand, increased mitochondrial metabolism has been shown to promote resistance to apoptosis [35, 38, 49–51], whereas, on the other hand, mitochondrial dysfunction can favor a pro-metastatic behavior either by promoting glycolytic compensation [52] or by impacting the NAD^+/NADH redox ratio that regulates sirtuin activity, thereby directly promoting tumor metastasis [53]. We recently proposed a parallel but not mutually exclusive interpretation. In different tumor cell models, we indeed observed that either an increased or a dysfunctional mitochondrial activity are equally capable of promoting an invasive tumor phenotype [33]. We found that metabolic states of tumor cells corresponding to increased TCA cycle activity or experimentally induced ETC bottlenecking were associated with increased mtROS generation, and mtROS were a common mediator of metastasis for these two different metabolic phenotypes: targeting mtROS with mitochondria-targeted antioxidants mitoTEMPO or mitoQ inhibited metastatic dissemination in a mouse melanoma B16F10 model and abolished spontaneous metastatic dissemination in a model of MDA-MB-231 human breast cancer in mice

[33]. Despite the fact that mtROS can promote apoptosis, depending on their production level, they also behave as second messengers for retrograde mitochondrial signaling to the nucleus [54] (Fig. 1). Because mtROS are short-lived and compartmentalized in mitochondria [20], they can indeed spatially and temporally coordinate a localized signaling cascade by oxidizing specific amino acid residues [55]. One recent example comes from studies in *C. elegans* where mtROS promoted cellular adaptation to stress by stimulating, e.g., the p38-nuclear factor-like 2 (NRF2) redox-sensitive pathway [56]. This in turn primed the antioxidant machinery, resulting in increased lifespan of the nematodes, a phenomenon that has been defined as mitohormesis [56, 57]. In tumor cells, we found that mtROS can cause metastasis by activating the proto-oncogene Src and the focal adhesion kinase Pyk2, collectively resulting in resistance to anoikis and increased migration, invasion, metastasis take and spontaneous metastasis [33, 58]. Consequently, targeting mtROS generation by complete inhibition of Complex I activity or using specific mitochondria-targeted antioxidants was sufficient to abolish metastasis formation in vivo. The fact that mtROS are relevant for metastasis has been broadly demonstrated, from the initial reports indicating that metastatic cells accumulate more ROS than untransformed cells [59] to the seminal work of Ishikawa et al. [60] demonstrating that specific ROS-inducing mtDNA mutations are sufficient to promote metastasis. In the latter study, increased levels of mtROS activated the anti-apoptotic protein myeloid cell leukemia-1 (MCL-1), a member of the Bcl-2 family promoting tumor cell aggressiveness. To date, several specific mtDNA mutations have been reported to trigger tumor progression through the promotion of ROS production [61–63]. From a molecular standpoint, several downstream targets of mtROS have been identified, including FAK [64], PYK2 [58], SNAIL [65], p38 and NRF-2 [56, 66], nuclear factor-κB (NF-κB) activation mediated by c-Src oxidation [67] and HIF-1 stabilization through mtROS-mediated prolylhydroxylase (PHD) inactivation [21]. These mediators, in turn promote increased cell resistance to stress [68, 69]. Due to the particular nature of ROS, it is important to consider mtROS in a spatial context. Consequently, there are important caveats to consider when targeting mtROS with general antioxidants that can alter the total cellular ROS pool in tumor and host cells and interfere with therapy, explaining the disappointing results of several clinical trials having treated cancer patients with general antioxidants [58, 70].

Although, glycolytic compensation following mtDNA mutation certainly contributes to the pro-metastatic phenotype [42], it is not sufficient by itself [71]. In oncocytoma, for example, total loss of Complex I activity was reported to correlate with the emergence of tumors that rarely progress [72]. Oncocytomas normally occur in endocrine and exocrine tissues (e.g., thyroid, parathyroid, kidneys, salivary and pituitary glands), and are characterized by mitochondrial hyperplasia seen as a compensatory mechanism caused by complete inactivation of Complex I activity [72–75]. Further evidence is required to define the overall levels of mtROS in these tumors and their glycolytic rate. Overall, metabolic analyses of oncocytomas point at the necessity to maintain residual ETC activity for tumor invasiveness.

TCA cycle

The TCA cycle comprises eight consecutive reaction steps, starting from the condensation of acetyl-CoA with a molecule of oxaloacetate by citrate synthase (CS) to form citrate (Fig. 1). Interestingly, CS expression was found to be increased in pancreatic ductal adenocarcinoma [76] and in metastatic versus benign ovarian carcinoma [77]. Evidence is controversial for its role in metastasis, as it has been shown that CS downregulation either decreases (as seen after transient siRNA knock-down) [77] or increases (following stable shRNA expression) [78] invasion. One possible explanation for these opposite observations might be an adaptive phenotype following long-term knock-down of CS.

The product of the CS reaction, citrate, is then converted to isocitrate by aconitase (Aco). This reaction requires the conversion of citrate into the enzyme-bound intermediate *cis*-aconitate. Aco reactivation is particularly relevant for tumorigenesis in prostate cancer, where Aco is normally inactivated by the high concentration of zinc ions present in prostate cells [79]. In vitro, Aco activation has also been associated with the metastatic behavior of PC-3 M human prostate cancer cells [80].

Isocitrate is converted to αKG by IDHs, with the concomitant generation of NADH by IDH3 localized in mitochondria and NADPH by IDH1 and IDH2 that traffic between the cytoplasm and mitochondria. αKG is not only a metabolic intermediate of the TCA cycle but also an important co-substrate of several enzymes, especially the vast family of oxygenases that performs functions ranging from collagen synthesis to histone demethylation [81]. It is therefore not surprising that αKG controls complex biologic functions, with, for example, high levels of αKG promoting the maintenance of the pluripotency of embryonic stem cells (eSCs) by regulating whole genome methylation [82]. One of the classes of oxygenases requiring αKG as a co-substrate is PHDs, i.e., prolylhydroxylases that behave as oxygen sensors. PHD2 in particular tags HIF-1 subunit α for proteasome-mediated degradation under normoxia [83], and low levels of αKG

would therefore theoretically promote normoxic HIF-1 activation and tumor progression. αKG also mediates the activation of mammalian target of rapamycin complex 1 (mTORC1) in synergy with leucine [84]. It increases the lifespan of *C. elegans* by promoting a moderate mitochondrial inhibition through binding to ATP-synthase [85]. Biological activities of αKG are thus numerous. Yet, blocking the anaplerotic reactions supplementing αKG (such as glutaminolysis and alanine transamination) inhibits cell transformation and tumor invasion [26, 86], while supplementation with cell-permeable αKG is sufficient to rescue the clonogenic potential of tumor cells [86]. High intracellular levels of αKG are likely pro-metastastic, but because αKG also promotes transformation, specific research is still required to discriminate between its impact on tumor transformation and metastasis. Beyond the fact that it catalyzes αKG production, the IDH reaction is of particular interest because heterozygous mutations of *IDH1* and *IDH2* are quite common in gliomas [87]. These mutations can result in a neomorphic enzymatic activity that allows heterodimeric IDH complexes to catalyze the conversion of αKG into the oncometabolite D-2-hydroxyglutarate (D-2HG) [6]. Mutations of *IDH1* and *IDH2* genes have been found in colon cancer [88], acute myeloid leukemia [89] and enchondroma [90]. Despite the fact that D-2HG promotes tumorigenesis by altering DNA-methylation genome-wide (primarily by antagonizing αKG-dependent dioxygenases) [91], limited evidence links the *IDH1* and *IDH2* mutations to an increased metastatic potential [92].

In the TCA cycle, αKG is then sequentially converted to succinyl-CoA (with the generation of NADH), succinate (with the concurrent generation of GTP) and fumarate (by SDH) (Fig. 1). FH then converts fumarate into malate, which is used to generate oxaloacetate by malate dehydrogenase. This final reaction produces one additional molecule of NADH from NAD^+. SDH is a macromolecular complex composed of four different subunits located on the internal face of the inner mitochondrial membrane. A major characteristic of this enzymatic complex is that it is shared between the TCA cycle and the ETC where it composes Complex II. Indeed, following succinate oxidation, SDH covalently binds a molecule of FAD that is reduced to $FADH_2$, which is followed by the transfer of two electrons from $FADH_2$ to ubiquinone (also known as coenzyme Q [CoQ]), yielding ubiquinol [$CoQH_2$] in the ETC. Mutations of *SDH5*, the protein responsible for covalently attaching FAD to SDH, are causally linked to tumorigenesis [7, 8, 93–96] as they lead to accumulation of succinate, which has been identified as an oncometabolite promoting transformation [97]. On the other hand, fumarate accumulation linked to FH deficiency promotes the formation of hereditary uterine fibroids, skin leiomyomas, papillary renal cell cancers, sarcomas, pheochromocytomas and paragangliomas [98–100]. Mechanistically, succinate and fumarate are competitive inhibitors of αKG-dependent dioxygenases (i.e., enzymes that catalyze the incorporation of the two atoms of oxygen of O_2 into a substrate). They promote HIF-1 stabilization by inhibiting PHDs [97] and induce a whole genome epigenetic dysregulation by inhibiting both histone demethylases and the ten-eleven translocation (TET) family of 5-methlycytosine hydroxylases [5, 101, 102]. Both metabolites thus share a common way of inducing transformation [103]. In addition, fumarate accumulation results in a spontaneous reaction leading to posttranslational modification of cysteines in proteins known as 'succination' (i.e., a chemical modification of proteins formed by a Michael addition reaction between fumarate and thiol groups) [104]. Succination notably impairs the function of Kelch-like ECH-associated protein 1 (KEAP1), thus relieving transcription factor NRF2 from KEAP1-mediated inhibition and promoting an antioxidant response [105, 106]. In contrast, succination can also affect glutathione, promoting oxidative stress [107]. Despite the vast influence of succinate and fumarate on epigenetic regulation and signaling pathways, only a limited amount of evidence links these oncometabolites to metastatic progression. While the experimental re-expression of FH in a FH-deficient renal cell carcinoma line impaired tumor cell migration and invasion in vitro [108], treatment with dimethylfumarate, a cell-permeable form of fumarate, strongly reduced invasion and metastasis formation in melanoma [109–111]. To date, only the loss of SDH5 has been clearly shown to drive the acquisition of a mesenchymal and prometastatic phenotype in lung cancer cells, further correlating with reduced levels of SDH5 in a small group of metastatic versus non-metastatic lung patients [112]. However, no evidence links this effect to the enzymatic activity of SDH. Rather, SDH5 was found to form a complex with glycogen synthase kinase (GSK-3β, a mediator of β-catenin degradation) and protein phosphatase A (PP2A): when present, SDH5 activates GSK-3β and prevents the epithelial-to-mesenchymal transition (EMT). When SDH5 is lost, β-catenin accumulates, translocates to the cell nucleus and promotes EMT [112].

The TCA cycle is amphibolic: it not only mediates catabolic reactions aimed at energy production but also produces precursors for cell growth. Cancer cells are capable of reducing αKG to isocitrate, which has been termed reductive or reverse TCA cycle [113], ultimately increasing citrate and acetyl-CoA levels to promote lipogenesis. Glutamine directly fuels this pathway, especially when oxygen is limiting or when mitochondria are dysfunctional [114, 115]. The trigger for such "anti-clockwise" TCA cycle has been suggested to be an increased αKG/citrate ratio [116]. Although this phenotype has been strongly

linked to tumor growth [114, 115, 117–119], little is known about the specific contribution of reductive carboxylation to tumor metastasis. It has nevertheless been reported that steroid receptor coactivator 2 (SRC2) promotes lipogenesis by stimulating glutamine utilization and reductive carboxylation in prostate cancer, and SRC2 is particularly enriched in metastatic lesions in patients with prostate cancer [120, 121]. In animal models, SRC2 depletion strongly reduced tumor cell viability, tumor growth and spontaneous metastasis. Although, these data suggest that the metabolic phenotype characterized by a pronounced reductive carboxylation might promote the emergence of aggressive tumor cell clones prone to metastasis, further experiments are required to test this possibility.

Lipid metabolism

Lipid accumulation is so common in tumors that it can by itself be considered as a hallmark of cancer [122]. The transcription factors, sterol regulatory element-binding proteins -1 and -2 (SREBP-1/-2) are the main transcriptional regulators of the lipogenic program, inducing cholesterol and fatty acid biosynthesis [123, 124]. SREBPs are downstream targets of the phosphoinositide 3-kinase (PI3K)–protein kinase B (PKB/Akt)–mTORC1 signaling pathway. Their inhibition represses tumor growth by depleting lipid rafts at the plasma membrane, thereby impairing Akt activation [125]. Conversely, upregulation of SREBP expression renders tumor cells more resistant to apoptosis and makes them more aggressive, especially in conditions where nutrient and oxygen availability are limited [126]. As a matter of fact, the SREBP signature is a marker of poor prognosis in glioblastoma [126]. Notably, the mucin 1 oncoprotein (which is overexpressed in breast cancer and is important for metastatic progression [127, 128]) and SRC2 (which is overexpressed in prostate metastatic lesions [120], see above) are upstream regulators of SREBPs and, thus, of lipid metabolism. Despite, further studies are required to establish a cause–consequence relationship, regulation of lipid metabolism and cancer metastasis may thus be intertwined.

Acetyl-CoA is at the crossroad between the TCA cycle and lipid synthesis, with its production being critical for both metabolic pathways. Essential gatekeepers regulating de novo lipid synthesis are ATP-citrate lyase (ACLY) that converts citrate to oxaloacetate and acetyl-CoA, and fatty acid synthase (FASN), a macromolecular complex that catalyzes the condensation of carbon skeletons into fatty acids. With a few exceptions, e.g., in liver and mammary glands, FASN expression is low in normal tissues, but it increases during transformation [129]. In the prostate, FASN demonstrated pro-oncogenic properties, as forced overexpression was sufficient to induce resistance to apoptosis and the transformation of normal prostate cells in mice [130]. Similarly, ACLY is required for tumor growth and its inhibition is a promising strategy for tumor therapy [131, 132].

Lipid synthesis is essential for the production of membranes necessary for cell proliferation. In addition to promoting cell proliferation, data indicate that lipid synthesis further contributes to tumor progression and metastasis, with a strong increase in FASN and ACLY expression in breast cancer [132, 133], retinoblastoma [134], lung cancer [132] and colon cancer [135]. Inhibition of FASN and ACLY was found to impair the metastatic progression of colon cancer cells by reducing CD44- and hepatocyte growth factor receptor (HGFR)-mediated signaling, resulting in reduced tumor cell migration and clonogenicity on soft agar [136]. Because lipid synthesis endows tumor cells with an increased resistance to apoptosis [126], tumor cells can be expected to rewire their energy metabolism towards increased lipid synthesis to overcome therapy, an adaptation that further confers a more aggressive phenotype. In contrast, blockade of lipid synthesis can inhibit metastatic dissemination following anti-angiogenic therapy [137]. This observation holds great promise for future combination therapies since one of the major drawbacks reducing the efficacy of anti-angiogenic therapy is the induction of metastases [138]. One of the major future challenges will be the identification of the molecular mechanisms linking lipid synthesis to the acquisition of invasive traits.

Besides the role of lipid synthesis in promoting invasion and metastasis, it is becoming clear that fatty acid oxidation by itself can also promote metastasis. Indeed, simple depletion of exogenous lipids is sufficient to impair breast cancer cell migration in vitro, even in the presence of alternative oxidative fuels glucose and glutamine [139]. Similarly, in the non-small cell lung cancer cell line A549, the addition of transforming growth factor β promotes tumor invasiveness by increasing mitochondrial lipid oxidation [140]. In this model, forced lipid oxidation alone was sufficient to induce EMT. In agreement, cancer-associated adipocytes are emerging as key regulators of metastatic formation in both breast and ovarian cancers where they fuel metastases by providing tumor cells with energy substrates [141, 142].

Amino acid metabolism

Amino acid metabolism is a central part of cellular metabolic homeostasis. Among all natural amino acids, glutamine is one of the most characterized for its role in tumor formation and metastasis [9]. This non-essential amino acid is also one of the most abundant amino acids

present in bodily fluids and one of the most heavily depleted amino acid in tumor tissue, indicating the high avidity of tumors for glutamine [143]. Glutaminolysis has been proposed to be as important as glucose metabolism in tumors [144] and is primarily induced by the Myc oncogene [145]. The first step of glutamine metabolism is mediated by glutaminases GLS1 and GLS2 that catalyze the conversion of glutamine to glutamate and ammonia (NH_3). Glutamate can further be deaminated to αKG by glutamate dehydrogenase (GDH), with the concurrent production of one molecule of NADH by GDH1 or NADPH by GDH2. αKG can then be used in oxidative TCA cycling, reductive TCA cycling or as a co-factor for biochemical reactions, as detailed above. Alternatively, glutamate can also be transaminated by the glutamic-pyruvic transaminase or by glutamic-oxaloacetic transaminases (GOT1 or GOT2). GOT2 generates aspartate in the mitochondria, which may then generate oxaloacetate in the cytosol after a second transamination reaction catalyzed by GOT1. Oxaloacetate is channeled to malate dehydrogenase, resulting in the production of pyruvate and NADPH. This alternative pathway of glutamate has emerged as a critical regulator of the redox balance in pancreatic ductal adenocarcinoma [146]. Because glutamate can further be used for glutathione synthesis, glutamine metabolism is important not only for energy production but also for redox regulation in cancer. Hence, GLS inhibition impairs tumor cell migration and invasion [86] and promotes apoptosis in cells undergoing EMT as a consequence of decreased resistance to oxidative stress [147].

Interestingly, GDH1, the enzyme controlling NAD^+-dependent glutamate deamination, has been reported to be overexpressed in metastases of gallbladder [148] and murine hepatocarcinoma [149]. GDH1 is important for redox homeostasis as it controls αKG production and the subsequent generation of fumarate, which activates the antioxidant enzyme glutathione peroxidase 1 [150]. Thus, GDH1 has been shown to promote tumor progression by increasing tumor cell resistance to oxidative stress. Its specific contribution to the metastatic process remains to be determined.

A more complex story of amino acids and their role in cancer metastasis is that of proline. On one hand, proline oxidase, which catalyzes proline degradation, has been identified as a mitochondrial tumor suppressor due to its pro-apoptotic properties coupled to increased ROS generation [151]. Interestingly, the Myc oncogene inhibits proline degradation [145], by participating in the accumulation of proline in growing tumors [143, 152]. Proline further accumulates in tumors following degradation of the extracellular matrix [153] and elevated proline synthesis in glutamine catabolism [145]. On the other hand, proline degradation can turn into an important source of energy during nutrient deprivation, either by stimulating ATP production or by inducing ROS-mediated autophagy [154]. This pro-oxidant activity of proline has been proposed to promote mitohormesis [56], i.e., adaptation to stress driven by mitochondria (see also above). It most probably explains the observation that increased proline metabolism correlates with invasiveness and resistance to oxidative stress in esophageal squamous cell cancer [155]. Along the same lines, Comes et al. [156] recently reported that proline supplementation on its own was sufficient to trigger a genome-wide methylation remodeling and the acquisition of an EMT-like phenotype by eSC, promoting eSC metastasis in vivo.

Finally, amino acid metabolism could also promote metastasis via a tumor cell-extrinsic action. For example, the seminal work of Uyttenhove et al. [157] revealed that cancer cells can escape immune defenses by stimulating the degradation of tryptophan, an amino acid essential for T-cell replication. Indoleamine 2,3-dioxygenase is the main enzyme involved in tryptophan degradation and constitutes a marker of tumor aggressiveness in ovarian [158], thyroid [159], breast [160] and skin [161] cancers. In another example, enhanced serine biosynthesis has been associated with the induction of osteoclastogenesis and increased formation of bone metastases in breast cancer [162], although the molecular rationale behind this observation still remains to be elucidated.

Concluding remarks

In eukaryotic cells, mitochondria evolved as gatekeepers not only of energy producing metabolism (cataplerosis) but also of biosynthetic metabolism (anaplerosis) and apoptosis. While a vast amount of experimental data point at the key role of mitochondria in promoting tumor cell growth and proliferation in primary tumors, a rather limited number of studies directly addressed their contribution to the metastatic process. The emerging picture is that while mitochondrial metabolism is hijacked by tumor cells to promote cell growth, proliferation, redox homeostasis and survival, mitochondria could also act as bioenergetic sensors conferring migratory, invasive and metastatic phenotypes to cancer cells exposed to harsh microenvironmental conditions. Together with de novo produced D-2-hydroxyglutarate following specific IDH mutations, mtROS and TCA cycle intermediates increasingly produced in (pre)metastatic tumor cells, as well as glutamate originating from glutaminolysis, could be viewed as molecules involved in retrograde signaling from mitochondria to the cell, suggesting that in certain circumstances, mitochondria could drive cancer metastasis.

The origins of the changes affecting mitochondrial metabolism in premetastatic cells, in metastatic progenitor cells and tumor cells populating the metastatic lesion and whether they can/must be reversed at specific steps of the metastatic process remain to be determined. They could be dependent or independent from mutations affecting genomic or mitochondrial DNA. The observation that a metabolic switch from OXPHOS to glycolysis can also promote the metastatic phenotype (see companion paper) argues for the existence of temporally well-defined metabolic adaptations along the metastatic route. Alternatively, different metabolic phenotypes could independently promote tumor metastasis, with the caveat that cause–effect relationships must still be established in most instances. In our opinion, resolving these uncertainties is a task of fundamental importance not only to improve the understanding of the metabolism of metastatic progenitor cells, but also to establish a strong rationale for the development of antimetastatic treatment strategies.

A further degree of complexity of the metastatic process arises from interactions between cellular populations with different metabolic phenotypes inside a given tumor, resulting, e.g., in metabolic symbiosis [163] and commensalism [164]. For example, cancer-associated fibroblasts can fuel the oxidative metabolism of prostate cancer cells [165], which drives EMT and metastatic progression [166]. In this context, there are strong indications that oxidative lipid metabolism, lipogenesis and amino acid metabolism play critical roles that largely remain to be explored from molecular and clinical standpoints. In particular, despite the identification of specific metabolic reactions that promote metastasis, it will be pivotal to understand the molecular determinants driving the metastatic switch. It goes without saying that a better delineation of specific changes affecting mitochondria, lipid and amino acid metabolism could ultimately translate into new, original therapeutic strategies directed against cancer metastasis.

Conclusively, targeting tumor metastasis for therapy now requires distinguishing metabolic changes that can drive tumor metastasis from those that merely result from the acquisition of the metastatic phenotype, and determining whether sequential metabolic changes in a given metastatic progenitor cell along its metastatic route and/or independent metabolic changes in several different metastatic progenitor cell populations account for the metastatic process.

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