Cancer metabolism: looking forward

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Abstract | Tumour initiation and progression requires the metabolic reprogramming of cancer cells. Cancer cells autonomously alter their flux through various metabolic pathways in order to meet the increased bioenergetic and biosynthetic demand as well as mitigate oxidative stress required for cancer cell proliferation and survival. Cancer driver mutations coupled with environmental nutrient availability control flux through these metabolic pathways. Metabolites, when aberrantly accumulated, can also promote tumorigenesis. The development and application of new technologies over the last few decades has not only revealed the heterogeneity and plasticity of tumours but also allowed us to uncover new metabolic pathways involved in supporting tumour growth. The tumour microenvironment (TME), which can be depleted of certain nutrients, forces cancer cells to adapt by inducing nutrient scavenging mechanisms to sustain cancer cell proliferation. There is growing appreciation that the metabolism of cell types other than cancer cells within the TME, including endothelial cells, fibroblasts and immune cells, can modulate tumour progression. Because metastases are a major cause of death of patients with cancer, efforts are underway to understand how metabolism is harnessed by metastatic cells. Additionally, there is a new interest in exploiting cancer genetic analysis for patient stratification and/or dietary interventions in combination with therapies that target metabolism. In this Perspective, we highlight these main themes that are currently under investigation in the context of in vivo tumour metabolism, specifically emphasizing questions that remain unanswered.

Cancer metabolism has its roots in the observations made by Otto Warburg, the winner of the 1931 Nobel Prize in Medicine or Physiology for his discovery of the mitochondrial respiratory chain complex IV[1]. Warburg observed that when compared with normal tissues, cancer tissue slices in vitro used copious amounts of glucose to generate lactate, even in the presence of oxygen, a phenomenon termed aerobic glycolysis or the Warburg effect. Warburg surmised that cancer cells cause an "injury to respiration" that was a prerequisite for the transformation of a differentiated cell into a proliferative cancer cell[2]. However, the majority of cancer cells respire to promote flux through the tricarboxylic acid (TCA) cycle for tumour growth[3–8]. There are tumours that do not respire but still use the TCA cycle to provide necessary metabolites for growth[9]. Nevertheless, the Warburg effect is a true phenomenon that can be observed in vitro and in vivo both in mouse models of cancer and in human patients with cancer[10,11]. The resurgence of cancer metabolism in the past 25 years coincides with discoveries that help explain why cancer cells exhibit the Warburg effect[12]. In the 1990s, it was recognized that the glycolytic enzyme lactate dehydrogenase A (LDHA) is a transcriptional target of the oncogene MYC and is necessary for increased glycolysis and tumorigenic potential of cancer cells; thus, providing a molecular basis for the Warburg effect[13]. Moreover, AKT, mTOR and hypoxia-inducible factors (HIFs), which are often deregulated in cancer and required for tumour survival and growth, were also discovered in the 1990s (REFS[14–16]). These pathways individually increase glycolysis through transcriptional upregulation and phosphorylation of glucose transporters and glycolytic enzymes.

At the beginning of this century, much of the research effort was focused on determining why the Warburg effect is advantageous for tumour growth. One proposed explanation is that through increased glycolysis, glycolytic intermediates can funnel into anabolic side pathways to support de novo synthesis of nucleotides, lipids and amino acids needed to support cell proliferation[12,17,18]. However, in the past decade, the TCA cycle has also re-emerged as a key anabolic hub supporting tumour growth in both mouse models of cancer and patients with cancer[4,6,18]. A key finding was that genetic engineering of the electron transport chain (ETC) in cancer cells, leaving ETC-linked TCA cycle function intact but disrupting ETC-linked generation of ATP via oxidative phosphorylation, still allowed for tumour growth in vivo[6]. This indicates that ATP derived from glycolysis can support primary tumour growth. Moreover, pyruvate carboxylase (PC), which generates the TCA cycle metabolite oxaloacetate from pyruvate, has been shown to be necessary for primary and metastatic tumour growth[19–21]. Also, aspartate, which can be produced from oxaloacetate, and its derivative asparagine can both be limiting for tumour growth[4,22–24]. Thus, today it is appreciated that both glycolysis and the TCA cycle support tumour growth through metabolite biosynthesis[3,18]. A consequence of oxidative metabolism is the generation of reactive oxygen species (ROS) that can support tumorigenesis but which need to be tightly regulated at levels that do not incur cell death, that is, redox balance[25]. Strong evidence for the importance of ROS in cancer comes from human cancer genetics analysis and studies showing that loss-of-function mutations in KEAP1 result in activation of the master antioxidant transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) in the context of other cancer-promoting mutations[26]. A key set of observations that significantly impacted the field is the recognition that metabolites, beyond their biosynthetic role, can act as signalling molecules to promote tumour growth by controlling gene expression (that is, oncometabolites)[27]. In the past few years, the field has expanded from investigating central carbon pathways of glycolysis and the TCA cycle to a multitude

of branch metabolic pathways that are necessary for tumour growth, progression and metastasis. Today, the field is largely driven by findings in vivo rather than in vitro, due to the growing appreciation of the role of other cell types in the tumour microenvironment (TME), and the metabolic constraints imposed by different levels of nutrients and oxygen in vivo compared with in vitro conditions[28]. Recent data indicate that organismal metabolism can also modulate tumour growth[29,30]. The paucity of successful clinical data regarding metabolic therapies for patients with cancer continues to invigorate foundational science efforts. In this Perspective, we highlight recent key developments in the field, including signalling and metabolic pathways that support tumour growth; the molecular basis of how oncometabolites promote tumorigenesis; how cancer cells maintain redox balance during cancer progression; metabolic constraints imposed by the host organism and TME; and new approaches to targeting metabolism for cancer therapy. This article is not intended to provide detailed information about all of these important arenas of cancer metabolism, as this is covered in many recent excellent reviews[16,25,28,29,31–33], but, rather, provides a perspective that paints broad brushstrokes of themes driving the field. Importantly, we highlight key in vivo questions that remain unanswered in cancer metabolism (BOX 1).

Anabolism and tumour growth

The generation of two daughter cells requires macromolecules that support cellular proliferation (for example, nucleotides and lipids). Cancer cells use intracellular anabolic pathways to generate de novo macromolecules and can acquire them from the circulation. Two key questions are: (a) what are the macromolecules for which synthesis is rate-limiting in tumour growth; and (b) which intracellular pathways must be invoked to sustain tumour growth in vivo? These processes will likely be dependent on which macromolecules can be acquired from the TME. A hint comes from two recent studies using in vivo functional genomic CRISPR-based screens in pancreatic and lung cancers driven by oncogenic KRAS and loss of p53, where the top essential genes were related to haem and nucleotide synthesis[34,35]. Indeed, haem synthesis is necessary for mitochondrial ETC function as shown in endothelial cells[36]. Other genes observed to be essential in cells with oncogenic KRAS and loss of p53, consistent with observations from multiple previous studies[6,37,38], were encoding enzymes in glycolysis, one-carbon metabolism, and mitochondrial ETC and TCA cycle pathways that are known to be necessary for haem and nucleotide synthesis (FIG. 1). Under these specific conditions, lipids are likely acquired from the microenvironment, where in other contexts cancer cells may require de novo lipid synthesis[39]. It is therefore tempting to speculate that the necessity of these metabolic pathways in cancer cells is to sustain de novo nucleotides and haem synthesis, but this hypothesis requires experimental validation in different tumour models as lipid availability in certain TMEs is also likely to be limiting. A recent provocative study demonstrated that immortalized cells, which normally require oncogene activation to become tumorigenic, could generate tumours in vivo only if mice were supplemented with nucleosides and antioxidants[40]. It would be ironic if nucleotide synthesis, increased activity of which was identified as a target for cancer therapy early on in the history of cancer research[41], would again be one of the central themes of modern cancer metabolism research. So, has it all been a rediscovery? We would argue no. If one focuses on recent developments in research on nucleotide synthesis, it is apparent that there have been reports on numerous examples of previously unappreciated pathways that sustain nucleotide synthesis in cancer cells. For example, nucleotide synthesis requires nitrogen, which cells dispose of through urea. However, many cancer cells exhibit dysregulation in the expression of urea cycle enzymes, frequently with DNA methylation-induced downregulation of argininosuccinate synthase (ASS1) expression, which uses aspartate and citrulline as substrates[42] (FIG. 1b). The decrease in ASS1 expression in some cancers increases aspartate availability to sustain pyrimidine synthesis[42]. Additionally, non-small cell lung cancer (NSCLC) cells harbouring oncogenic KRAS and loss of tumour suppressor LKB1 upregulate expression of the urea cycle enzyme carbamoyl phosphate synthetase 1 (CPS1)[43] (FIG. 1c). CPS1 produces carbamoyl phosphate in the mitochondria from ammonia and bicarbonate to provide nitrogen for pyrimidine synthesis[43]. It is important to note that beyond canonical mechanisms, enzymes known for regulating metabolism can also have 'moonlighting functions'. One salient example of this phenomenon is how the loss of the gluconeogenic

Box 1 | **Key questions to decipher the in vivo metabolism of cancer cells**

1. How can imaging, magnetic resonance and mass spectrometry techniques be used to detect the metabolic heterogeneity of cancer cells and normal cells within the tumour microenvironment (TME) in both mouse models of cancer and patients with cancer?
2. Compared with cancer cells, how are the metabolism and nutrient sensing signalling pathways of non-malignant cells in the TME as well as normal differentiated cells wired in vivo during development, in physiology or in distinct pathologies?
3. Why does the accumulation of succinate, fumarate or D/L-2-hydroxyglutarate (D/L-2HG) exert its tumorigenic effects in only certain tissues and how do these oncometabolites alter gene expression at a specific locus?
4. How do some metabolic enzymes drive tumour progression through catalytically independent mechanisms?
5. Which reactive oxygen species (ROS) — that is, superoxide (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (^-OH) and lipid hydroperoxide (LOOH) — promote or suppress tumour initiation and progression? What are the relevant ROS targets for tumour initiation and progression?
6. What are the in vivo metabolic vulnerabilities imposed by the tissue of origin, driver mutations and the TME?
7. Are there distinct metabolites, which are not involved in anabolic pathways, that promote the metastatic invasive cellular phenotype as well as metastatic dormancy? How does the metabolism of cancer cells change to support cell survival when passing through the circulatory and lymphatic systems, ultimately leading to cancer cell colonization at a distal site?
8. How does the host organismal metabolism control tumour initiation and progression? What carbon fuels do different cancer cells utilize in vivo?
9. How can targeting metabolic pathways be best coupled with cancer genetics, diet and/or standard of care therapy such as immunotherapy? Why do effective current therapies targeting metabolism, for example 5-fluorouracil (5-FU), work in some patients and not others?
10. Does ageing increase the cancer risk through intracellular and/or organismal metabolic changes?

enzymes fructose-1,6-bisphosphatase 1 (FBP1) in renal and liver cancer[44,45], and FBP2 in soft tissue sarcoma[46], can promote tumorigenesis through both the catalytically dependent increase in glycolytic flux and the catalytically independent control of gene expression (FIG. 2a). The generation of knock-in alleles that discern between catalytic versus non-catalytic functions of FBP1/2 will be crucial to resolve which function is dominant in cancer.

Our understanding of how anabolic pathways support tumour growth has also come from patients with cancer. Injection and tracing of isotope-labelled glucose revealed that human lung tumours in patients and lung tumours in mouse models as well as human breast tumours display both enhanced flux through glycolysis and glucose oxidation by the TCA cycle compared with normal adjacent lung tissue[18,21,47]. Subsequent metabolic flux studies uncovered that multiple nutrients, including lactate and glutamine, funnel carbon into the TCA cycle in different human cancers, as well as in mouse models of cancer[48,49]. Moreover, mouse models of cancer have revealed that different oncogenic drivers within the same tissue of origin can induce distinct metabolism, whereas the same oncogenic driver in distinct tissues of origin elicits divergent metabolism[50,51]. Thus, metabolic profiles of tumours are dependent on the genotype and tissue of origin. It is important to note that isotope tracing studies do not indicate causality but, rather, these techniques are discovery tools to generate hypotheses. There have been spirited debates that arose from conducting similar isotope studies with different conclusions regarding the importance of glucose versus lactate as the dominant carbon fuel for the TCA cycle[49,52,53]. However, in the absence of genetic or pharmacologic perturbations, it is difficult to know whether a particular pathway is a dominant driver of tumour metabolism, and ultimately whether it impacts tumour growth in vivo. A recent study highlights this concept, where a combination of isotopic tracing and pharmacologic inhibition of serine hydroxymethyltranserases (SHMT1 and SHMT2) was used to show that SHMT inhibition synergized with methotrexate to diminish the T cell acute lymphoblastic leukaemia burden in mice[54]. Collectively, the study of cancer metabolism in vivo has led to a resurgence of using quantitative methods to examine cell metabolism in vivo during physiology and pathology[55,56], leading researchers to decipher how anabolic pathways in healthy tissues are distinct from tumours.

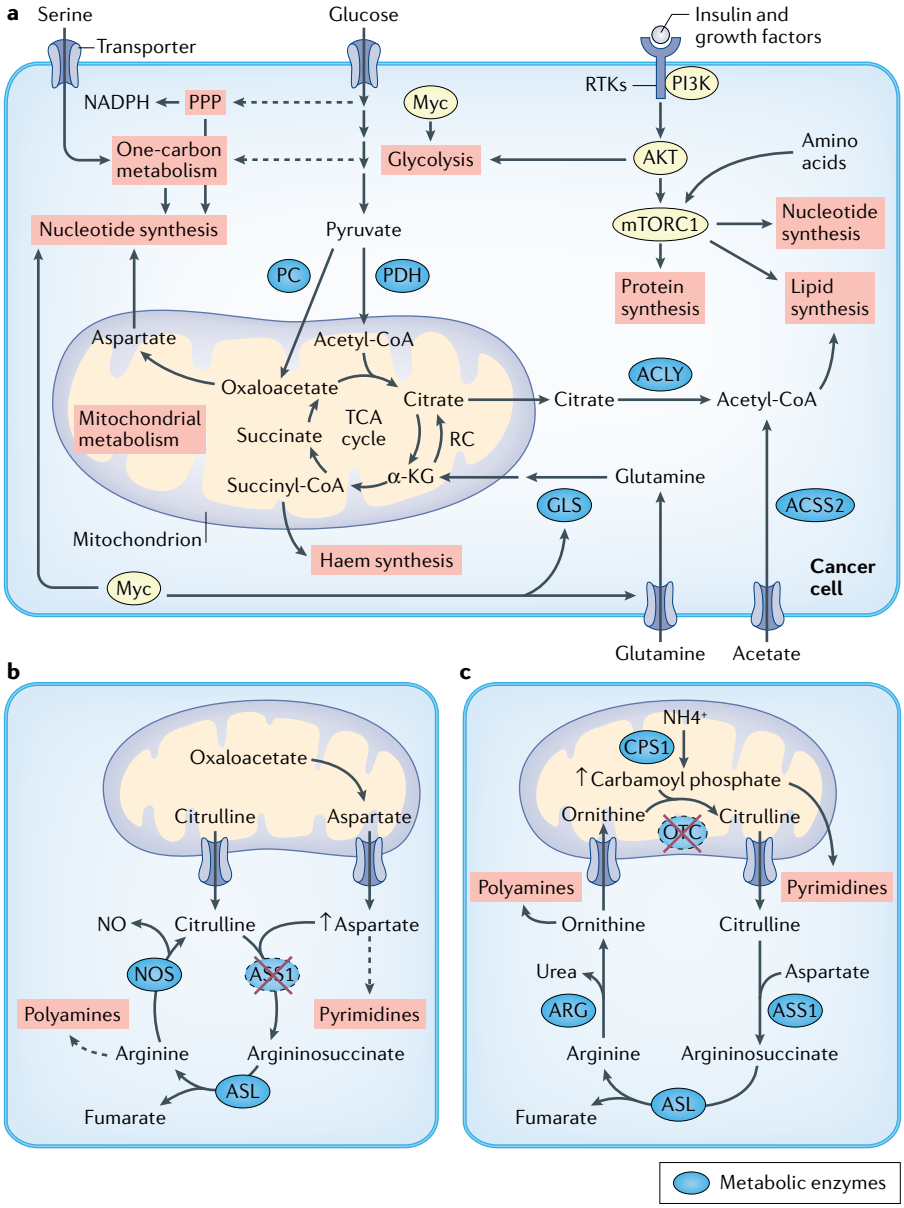

Fig. 1 | **Metabolic and signalling pathways supporting tumour biomass production. a** | MYC and PI3K–AKT–mTORC1 pathways are often deregulated in cancer cells and increase flux through glycolysis, the tricarboxylic acid (TCA) cycle and one-carbon metabolism to support production of nucleotides and haem synthesis in vivo needed for tumour progression. **b** | Certain cancers downregulate argininosuccinate synthase (ASS1) expression to increase aspartate levels for pyrimidine synthesis. **c** | LKB1-null non-small cell lung cancer (NSCLC) tumours express carbamoyl phosphate synthetase 1 (CPS1) concomitant with decreased ornithine transcarbamylase (OTC) expression, to produce carbamoyl phosphate in the mitochondria from ammonia and bicarbonate for pyrimidine synthesis. α-KG, α-ketoglutarate; ARG, arginase; PC, pyruvate carboxylase; PPP, pentose phosphate pathway.

Co-opted signalling pathways

One aspect of anabolism that is not covered in classic biochemistry textbooks is the fact that cancer cells co-opt signalling pathways and transcriptional networks (for example, PI3K–AKT–mTORC1 and MYC) to increase metabolic flux through intermediary metabolism to sustain proliferation[16,57] (FIG. 1a). Tumour suppressors such as p53 can also regulate cellular metabolism[58]. A provocative genetic study suggested that the dominant tumour-suppressive function of p53 in a mouse model of lymphoma is not linked to canonical p53-dependent tumour-suppressive functions — for example, cell cycle arrest, apoptosis or senescence — but, rather, control of

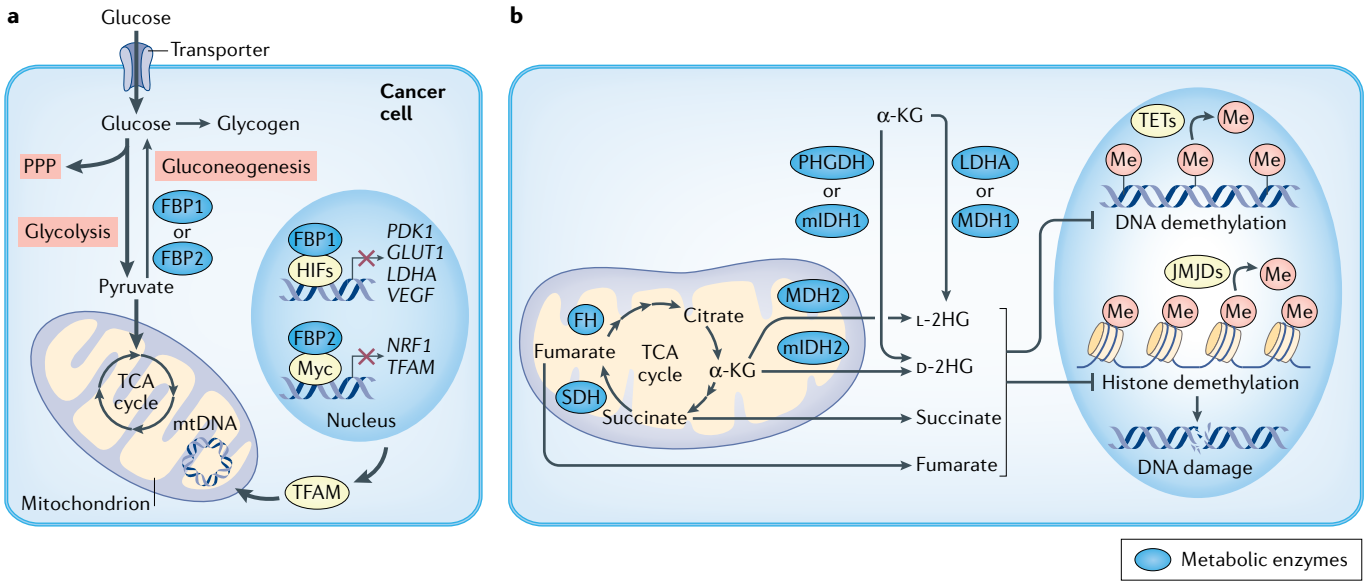

Fig. 2 | **Signalling and non-canonical mechanisms in cancer metabolism. a** | Gluconeogenic enzymes fructose-1,6-bisphosphatase 1 (FBP1) and FBP2 function as tumour suppressors in liver, soft tissue sarcoma and kidney cancers, in part, through a non-canonical function in the nucleus. **b** | Mutations in the genes encoding succinate dehydrogenase (SDH), fumarate hydratase (FH) and isocitrate dehydrogenase 1 or 2 (IDH1 or IDH2) are linked to certain cancers because of the resulting accumulation of the oncometabolites succinate, fumarate and D(*R*)-2-hydroxyglutarate (D(*R*)-2HG). The wild-type enzyme phosphoglycerate dehydrogenase (PHGDH) can also generate D(*R*)-2HG. Wild-type enzymes MDH2 and lactate dehydrogenase A (LDHA) under conditions of high NADH/NAD$^+$ such as hypoxia or electron transport chain (ETC) dysfunction can produce L(*S*)-2HG. These oncometabolites can inhibit enzymes that control histone and DNA demethylation to exert their pro-tumorigenic effects. Oncometabolites can also suppress DNA repair through hypermethylation of histones. α-KG, α-ketoglutarate; HIF, hypoxia-inducible factor; PPP, pentose phosphate pathway; TCA, tricarboxylic acid; TET, Ten–eleven translocation.

metabolism and antioxidant functions[59]. It is likely that distinct p53 tumour-suppressive functions are context-dependent.

The mTORC1 pathway has emerged as a central node for nutrient sensing and a coordinator for increased anabolic flux through pathways such as lipid and nucleotide synthesis in proliferating cells[16,60]. Recently, physiological growth signals or oncogenic activation of RAS or RAF stimulates the ERK signalling pathway to promote de novo purine synthesis for tumour growth[61]. A critical area currently being explored is the metabolic vulnerabilities that cancer cells incur upon hyperactivation of MYC and mTORC1, as this might provide unique therapeutic interventions in diminishing cancer cell proliferation and survival compared with non-malignant cells[62,63]. The ability of cancer cells to prevent anabolism when nutrients are limiting is, in part, controlled by AMPK, activation of which decreases anabolic pathways and induces a catabolic programme including autophagy to promote survival[64]. LKB1, expression of which is lost in various cancers including NSCLC, is one of the upstream kinases that activates AMPK when the AMP to ATP ratio is elevated. Loss-of-function mutations in *STK11*, which encodes LKB1, promote cancer, and thus it was assumed that loss of AMPK activity would similarly promote tumour growth. However, a recent rigorous genetic study in an oncogenic KRAS-driven mouse model of lung cancer clearly demonstrated that the loss of AMPK activity decreases tumour growth[65]. How these signalling pathways that are sensitive to nutrient inputs and control metabolic pathways are distinct between normal and cancer tissues in vivo remains an open question. For example, mTORC1 is inhibited by ETC inhibition in cancer cells[66] but, surprisingly, is hyperactivated in vivo in certain tissues that harbour mutations in genes encoding ETC proteins[67]. Moreover, there might be organ-specificity of how signalling pathways are controlled based on the distinct environmental nutrient availability of tissues. Thus, examining both signalling and metabolic pathways in vivo in normal and cancer cells will yield new insights into regulation of metabolism in vivo.

Metabolites as signalling molecules

The abundance of the metabolites succinate, fumarate and 2-hydroxyglutarate (2HG) was observed to increase to millimolar concentrations in specific tumours due to loss-of-function mutations in the genes encoding succinate dehydrogenase (SDH) subunits and fumarate hydratase (FH) as well as neomorphic mutations in the genes encoding isocitrate dehydrogenase 1 or 2 (IDH1 or IDH2). These metabolites were termed 'oncometabolites' as they are causal agents in driving these distinct cancers[68] (FIG. 2b). The accumulation of any of these three oncometabolites has proven to contribute to the development of malignancies, but only in certain tissues. Despite the ubiquitous expression of the TCA cycle enzymes SDH and FH, germline heterozygous mutations in the genes encoding SDH and FH progress to loss of heterozygosity only in certain tissues, resulting in cancer. For example, *SDH* loss-of-function mutations are commonly found in hereditary paraganglioma, pheochromocytoma and gastrointestinal stromal tumours, whereas inactivating mutations in *FH* cause hereditary leiomyomatosis and renal cell carcinoma[69,70]. A mystery is why some cells, upon losing the second allele, become transformed whereas others do not. It is important to note that cancer cells harbouring *SDH* and/or *FH* mutations (that is, a truncated TCA cycle) are still able to generate the TCA cycle metabolites necessary for growth. These include succinyl-CoA for haem synthesis, as well as oxaloacetate, which is produced via PC or glutamine-dependent reductive carboxylation, for nucleotide synthesis[9,71].

Thus, metabolic reprogramming such as PC activation must have taken place to adapt to these mutations and to ensure the synthesis of the macromolecules needed for cancer cell proliferation. It is likely that most tissues are tolerant to these mutations, and tumour initiation and progression only occurs under the right context, such as the presence of additional mutations coupled with environmental factors.

Active-site mutations in the genes encoding IDH1 or IDH2 provide the neomorphic ability to reduce the TCA cycle intermediate α-ketoglutarate (α-KG) to D-2HG, instead of the canonical interconversion of isocitrate and α-KG[72,73]. Of note, phosphoglycerate dehydrogenase (PHGDH) can also generate D-2HG in breast cancer[74]. These mutations occur in cholangiocarcinoma, chondrosarcoma, gliomas and acute myeloid leukaemias. To date, treatment with inhibitors specific for mutant IDH1 or mutant IDH2 has shown efficacy in reducing tumour progression only in patients with acute myeloid leukaemia. The metabolite 2HG also exists as the enantiomer L-2HG, which is produced from α-KG by the promiscuous activity of various dehydrogenases, including malate dehydrogenases and lactate dehydrogenases. The FAD-linked enzyme L-2HG dehydrogenase (L2HGDH) converts L-2HG back to α-KG[75]. L-2HG is at low levels under normal conditions but accumulates in hypoxic and acidic conditions, in cells with disrupted ETC function and in human renal cell carcinoma displaying epigenetic silencing of the gene encoding L2HGDH (REFS[76,77]). Notably, decreasing L-2HG levels by overexpression of L2HGDH in human renal cell carcinoma diminishes tumour growth in mice[76]. The severity of hypoxia correlates with tumour progression and metastasis, leading to the speculation that L-2HG might causally link hypoxia to tumour aggressiveness.

One outstanding question is how the accumulation of succinate, fumarate and D-2HG or L-2HG exerts tumorigenic effects in certain tissues. A feature shared between these metabolites is their ability to competitively inhibit α-KG-dependent dioxygenases (α-KGDDs) through their structural similarity to α-KG[77] (FIG. 2b). These dioxygenases include prolyl hydroxylases (negative regulators of HIFs), histone demethylases, RNA demethylases and the Ten–eleven translocation (TET) family of 5-methylcytosine hydroxylases that participate in DNA demethylation. All of these oncometabolites have been shown to inhibit dioxygenases involved in regulating epigenetic modifications, which directly influence gene expression by promoting a hypermethylation phenotype that blocks cell differentiation[78]. However, the specific mechanism linking oncometabolite accumulation to the observed undifferentiated state is not fully understood. Additionally, how any oncometabolite alters particular histones or DNA methylation at specific loci to modify gene expression is largely unknown. One provocative idea is that TCA cycle enzymes can be found within the nucleus to generate oncometabolites to alter the chromatin landscape[79], but how these mitochondrial enzymes localize to nucleus is perplexing. Beyond cancer, these oncometabolites have been linked to various tissue functions including immune functions and control of organismal metabolism[80]. For example, lactate, an abundant metabolite in the TME, can cause histone lactylation to modulate gene expression[81]. Thus, there continue to be discoveries of metabolites that, beyond their role in supporting biomass production, can determine cell fate and function.

ROS in tumour progression

The major species of ROS generated in cancer cells are superoxide (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (^-OH) and lipid hydroperoxide (LOOH)[25]. Cancer cells have a high rate of superoxide production from the mitochondrial ETC and NADPH oxidases, which is rapidly converted to H_2O_2 by superoxide dismutase 1 (SOD1) or SOD2 (REF.[25]). This localized H_2O_2 oxidizes specific cysteine residues in proteins to alter their function, that is, redox signalling to promote proliferation, survival and invasion of cancer cells (FIG. 3). Reactive cysteine residues in PTEN, SHP2 and MAP kinase phosphatases are known targets of H_2O_2 linked to cancer[82–84]. Decreasing H_2O_2 levels in cancer cells by inhibiting mitochondrial ETC or NADPH oxidase activity has been shown to decrease tumorigenesis[85–87]. There is much interest in deciphering the key cysteine residues that undergo H_2O_2-dependent oxidation or antioxidant-dependent reduction, that is, reductive stress, to alter their function[88,89]. H_2O_2, which is primarily a signalling molecule, can be detoxified to water by peroxiredoxin enzymes, but other forms of ROS such as LOOH, ^-OH and O_2^- can cause oxidation of proteins, lipids, and mitochondrial and nuclear DNA to incur toxicity. H_2O_2 can become ^-OH in the presence of iron by the Fenton reaction, and ^-OH can become LOOH in the presence of polyunsaturated fatty acids (PUFAs), that is, oxidative stress can occur[25]. Metals including selenium[90] and iron[91] are necessary for the function of ETC and antioxidant proteins as well as ROS

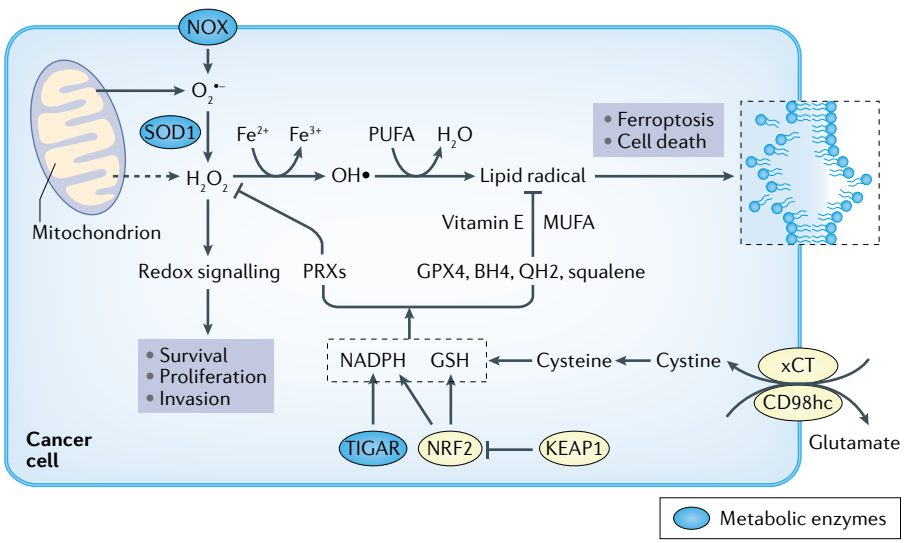

Fig. 3 | **Biology of ROS in cancer cells.** Cancer cells generate superoxide from the mitochondrial electron transport chain (ETC) and NADPH oxidases that is rapidly converted to hydrogen peroxide (H_2O_2) by superoxide dismutase 1 (SOD1) in the cytosol. Localized H_2O_2 promotes proliferation, survival and invasion. H_2O_2 can be detoxified to water by PRXs. H_2O_2 can also be converted into hydroxyl radical (^-OH), which in the presence of polyunsaturated fatty acids (PUFAs) becomes lipid hydroperoxide (LOOH) to induce ferroptosis. Cancer cells utilize the cyst(e)ine–glutathione (GSH)/GPX4, CoQ_{10}–FSP1, squalene and BH_4–DHFR systems to reduce LOOH to harmless lipid alcohols (LOH) to prevent ferroptosis. TP53-induced glycolysis regulatory phosphatase gene (TIGAR) and nuclear factor erythroid 2-related factor 2 (NRF2) promote antioxidant capacity. MUFA, monounsaturated fatty acid; PRX, peroxiredoxins; ROS, reactive oxygen species.

generation but are relatively understudied in the context of cancer in vivo. Interestingly, metals such as copper can modulate autophagy flux to control tumour growth[92]. LOOH can induce ferroptosis, a form of cell death caused by peroxidation of phospholipids[93]. Monounsaturated fatty acids (MUFAs), which compete with PUFAs for incorporation into phospholipids, ameliorate ferroptosis. Additionally, cancer cells utilize the cyst(e)ine–glutathione (GSH)–GPX4, CoQ_{10}–FSP1, squalene and BH_4–DHFR systems to reduce LOOH to harmless lipid alcohols (LOH), which prevents ferroptosis[93] (FIG. 3).

At steady state, measuring the levels of any type of ROS is determined by the rate of ROS production relative to the rate of ROS scavenging. Thus, inhibition of antioxidant proteins in normal and cancer cells can expose an increase in ROS in cancer cells compared with normal cells at steady state[25]. This indicates that the rate of ROS production in cancer cells is much higher compared with normal cells. To limit the damaging effects of ROS, cancer cells utilize the transcription factor NRF2 to upregulate antioxidant proteins, as well as pathways that support NADPH and GSH production, which are necessary to maintain the function of certain antioxidant proteins[25,94,95] (FIG. 3). Mutations in KEAP1, the negative regulator of NRF2, and gain-of-function mutations in NRF2 are observed in NSCLC and drive tumour progression[26]. Activation of NRF2 or dietary antioxidants can also increase metastasis, in part, by inhibiting the degradation of the pro-metastatic factor BACH1 (REFS[96,97]). Additionally, expression of the TP53-induced glycolysis regulatory phosphatase gene (TIGAR), which boosts antioxidant capacity by activating the oxidative pentose phosphate pathway (PPP) and enhancing NADPH production, is elevated in many cancer types[98]. TIGAR expression levels increase during pancreatic tumour initiation, but subsequently decrease to support migration, invasion and metastatic capacity through MAPK signalling[99]. This would suggest that limiting ROS is necessary for initiation, whereas sustaining ROS levels promotes metastasis. By contrast, limiting ROS levels with dietary antioxidants or preventing ferroptosis promotes metastasis of melanoma cells[100,101]. Although these results seem contradictory, they likely reflect the type of ROS that is being affected by TIGAR at different stages of tumour progression. We speculate that high levels of toxic ROS (that is, $O_2^{\cdot-}$, $^{\cdot}OH$, LOOH) may be a barrier to tumour initiation; thus, initiation requires elevated expression of both TIGAR and NRF2 activation to support toxic ROS scavenging. Indeed, immortalized cells can become tumorigenic in vivo by exogenous supplementation with antioxidants[40]. On the other hand, the metastatic phenotype could require high levels of localized H_2O_2 to promote redox signalling[99] but prevention of toxic ROS production to avert ferroptosis when traversing the blood to colonize a distant site[102,103]. In fact, H_2O_2 can promote epithelial–mesenchymal transition (EMT)[104], which is associated with a metastatic phenotype. Once the EMT phenotype is established, these cells express high levels of GPX4, which prevents ferroptosis[105]. We propose a model to understand the role of ROS in the context of tumour progression in which cancer cells allow for localized H_2O_2 for pro-tumorigenic signalling but maintain high levels of antioxidant capacity to detoxify damaging ROS molecules such as $O_2^{\cdot-}$, $^{\cdot}OH$ and LOOH. The development of specific probes to measure different types of ROS as well as genetic interventions that specifically modulate different types of ROS during tumour progression are needed to bring clarity to the biology of ROS in the context of cancer.

Nutrient availability

Whereas the intrinsic effects of reprogrammed metabolism in cancer cells have been extensively characterized, the mechanisms by which cancer cells rewire their metabolism in vivo to thrive in a low-nutrient and acidic milieu of the TME are not fully understood. Tumour type, anatomical location and host diet together affect local nutrient availability[106]. Moreover, how changes in metabolism determine the interplay between different cell types that coexist within the TME, including stromal and immune cells, is beginning to be understood[33]. During tumour evolution, accessibility to nutrients within solid tumours is often challenged by their proximity to the vasculature or by the perturbed tissue architecture[107]. Tumour vasculature, unlike normal blood vessels, branches irregularly, and therefore delivers nutrients poorly and causes considerable nutrient heterogeneity within the TME[108]. Autophagy is one of the key pathways that allows cell survival and proliferation when nutrients or growth factors are scarce[30,109,110] (FIG. 4). AMPK activation in nutrient-depleted conditions maintains both autophagy and lysosomal function in cancer[65]. Genetic studies in models of autochthonous pancreatic and lung cancers demonstrated that inhibition of autophagy impairs tumour progression[111,112]. In addition, inhibition of systemic autophagy decreased tumour growth through the release of arginase 1 (ARG1) from the liver, resulting in degradation of circulating arginine, which is essential for tumour growth in cancer cells lacking the ability to make intracellular arginine due to loss of ASS1 (REF.[113]). Interestingly, mTORC1, which prevents autophagy and supports anabolism, is activated on the lysosomal surface, a finding that has led to a resurgence of research into lysosomal biology[14]. Macropinocytosis is another pathway that supports cellular adaptation to nutrient deprivation by allowing cells to internalize proteins[114,115] and necrotic cell debris (necrocytosis) in the extracellular milieu and deliver them for degradation in the lysosome, thus supporting macromolecule synthesis and feeding into central carbon metabolic pathways[116] (FIG. 4). Oncogenic Kras-driven pancreatic cells display robust macropinocytosis in nutrient-limiting conditions[115]. Importantly, macropinocytosis allows cells to overcome therapies that target intracellular nucleotide synthesis in vivo[117]. There are ongoing efforts to find a specific protein that controls macropinocytosis in cancer cells as this would make for a promising therapeutic target. The importance of these nutrient scavenging pathways has been revealed only in conditions that mimic the in vivo TME and not in the artificial nutrient-repleted conditions that are common in cell culture. There has been considerable progress in designing media that reflect the metabolite composition of human plasma and the tumour interstitial fluid using mass spectrometry to better mimic TME conditions in vitro[106,118,119].

Metabolism in the TME

A hallmark of the in vivo TME beyond changes in nutrient availability and acidic conditions is its composition by distinct cell types that contribute to controlling tumour progression[33] (FIG. 4). A simplified model is that endothelial cells and stromal cells support tumour growth whereas cytotoxic T cells (CTLs) can diminish tumour progression, although CTLs can be inhibited by certain myeloid cells and regulatory T cells in order to sustain tumour growth (FIG. 4). Central carbon pathways such as one-carbon metabolism, glycolysis and the TCA cycle are not only essential for cancer cell proliferation but also critical for the function of endothelial cells, stromal cells, CTLs, regulatory T cells and myeloid

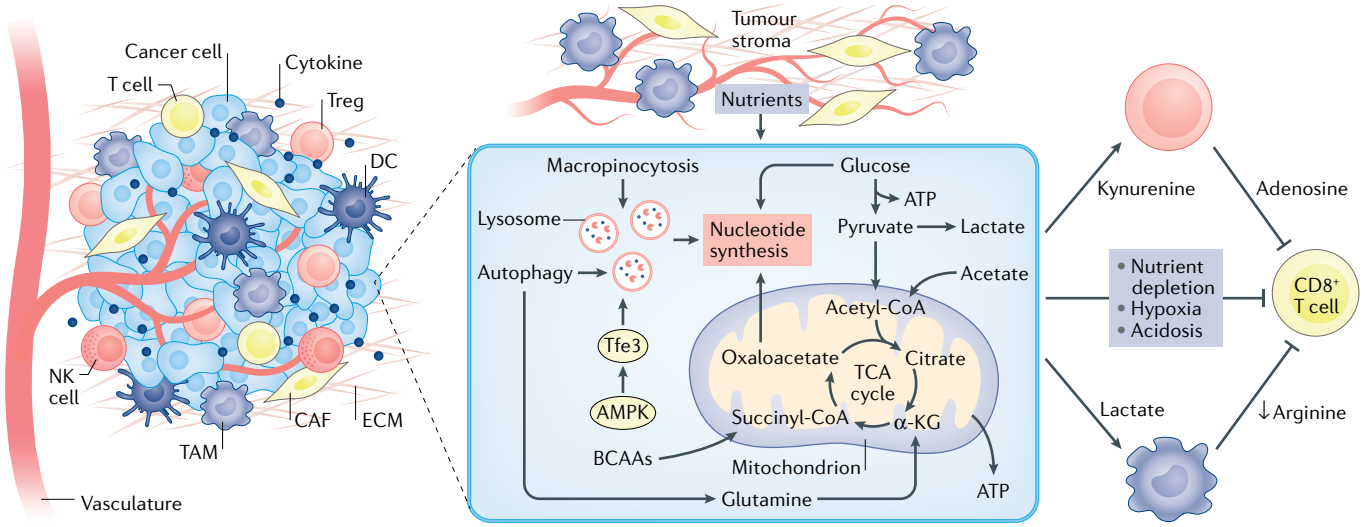

Fig. 4 | **Metabolic crosstalk of cells within the TME.** Different cell types that coexist within the tumour microenvironment (TME), including stromal and immune cells, have distinct metabolic demands. The TME is nutrient limited and acidic. Macropinocytosis or activation of autophagy using lysosomes as well as adjacent stromal cells can provide metabolites to sustain nucleotide synthesis and survival of cancer cells when nutrient availability is low. AMPK activation promotes lysosomal biogenesis. Cancer cells release metabolites that can promote immunosuppressive immune cells as well as inhibit the function of cytotoxic $CD8^+$ T cells, in part, by limiting nutrients, particularly amino acids. α-KG, α-ketoglutarate; BCAAs, branched-chain amino acids; TAM, tumour-associated macrophage; TCA, tricarboxylic acid.

cells[108,120,121]. Thus, cancer cells must compete for nutrients with the various other cell types in the TME. For example, higher consumption of methionine by cancer cells due to increased levels of its transporter (SLC43A2) restricts methionine metabolism in CTLs, leading to impaired CTL function because of modified histone methylation patterns[122]. Ultimately, it will be important to determine which particular nutrients are limiting for each cell type within a certain TME. It is often assumed that oxygen and glucose would be limiting for tumour growth in vivo. Yet mitochondrial respiration can effectively work at oxygen levels as low as 0.5%[7], and glucose concentrations as low as 0.5 mM are sufficient for cell proliferation[123]. A recent study highlighted that glucose is not limiting within the TME[124]. Therefore, low oxygen and glucose levels in the TME likely do not limit metabolism per se but, rather, affect changes in gene expression (for example, activation of HIFs) to alter signalling pathways that are necessary for metabolic adaptation. However, certain amino acids can be limiting for metabolism within the TME, including arginine, tryptophan, alanine, serine and glycine, which are needed not only for cancer cell proliferation but also for CTL function[106]. Beyond its cell autonomous role as a survival mechanism for nutrient-starved cancer cells, autophagy controls how cancer cells increase local immunosuppression within the TME[34,125] as well as systemic organismal-dependent immune-suppressive mechanisms[126].

Aside from nutrient competition, there is also metabolic crosstalk between different cell types in the TME, a strategy that cancer cells use to continuously grow under unfavourable conditions. For example, in pancreatic tumours, stroma-associated pancreatic stellate cells[127] and cancer-associated fibroblasts can provide carbon sources such as alanine and glutamine, respectively, to support TCA cycle metabolism in cancer cells[128]. Additionally, adipocytes surrounding epithelial ovarian cancer cells provide fatty acids for tumour progression[129]. By contrast, cancer cells evade CTL-mediated killing through various mechanisms including the release of metabolites such as kynurenine and lactate, which boost regulatory T cell and myeloid cell-dependent immune-suppressive functions[130]. Finally, chronic antigen stimulation and immune inhibitory receptors, such as PD1, also contribute to metabolic impairment of T cells in the TME[131]. Currently, we do not fully understand the breadth of metabolite crosstalk between distinct cells within the TME. Furthermore, the metabolic phenotype of many cell types within the TME, including neurons, dendritic cells and natural killer T cells, is not fully understood.

A current limitation in examining in vivo cancer metabolism is the inability to determine whether the metabolite signals detected are coming from the cancer cells or other cells present within the TME, such as immune cells. Thus, it is critical to have cell type-specific metabolic profiling in cancers with heterogenous cell compositions. Furthermore, cancer cell clones with divergent metabolism likely have different growth or metastatic trajectories[102] and their existence requires development of new technologies to assess this metabolic heterogeneity. Emerging technologies such as matrix-assisted laser desorption ionization–imaging mass spectrometry enable in situ metabolic profiling in complex tissue samples[132]. The recognition that the TME has distinct cell types with divergent metabolism has increased our appreciation that therapeutically targeting a particular metabolic pathway in cancer cells could have similar or distinct effects on other cells in the TME, which in turn might determine therapeutic efficacy.

Metabolic control of metastasis

A burgeoning area of cancer metabolism research in the past few years has been research into metastasis, which is a major contributor to the death of patients with cancer[32]. There are relatively few papers in this arena, and it will be critical for the field to decipher the metabolic vulnerabilities of cells that metastasize and colonize distal sites. Metastasis is an inefficient process in disseminating primary cancer cells to secondary sites and metabolic constraints are now being recognized as a barrier to the metastatic potential of cancer cells.

Metabolic changes are linked to each of the sequential multistep processes involved in metastasis: invasion of the basement membrane and cell migration into the surrounding vasculature or lymphatic system (that is, intravasation); survival in the circulation; and extravasation from the vasculature and colonization of secondary tumour sites (FIG. 5). Intravasation is linked to a change in cell state of cancer cells from a proliferative to an invasive and migratory phenotype often associated with EMT, which is, in part, regulated by TGFβ-dependent transcriptional changes. There is likely metabolic heterogeneity linked to metastatic potential within the primary tumour as exemplified by the observation that, within a primary tumour, cells with high MCT1 expression go on to metastasis[102]. The use of non-invasive technologies with spatial resolution could assess metabolic heterogeneity that is causally linked to metastatic potential.

In the coming years, there will be much focus on cataloguing metabolic pathways that are dispensable for primary growth but become essential for metastasis. We are excited about the possibility of discovering metabolites and types of ROS that are not part of anabolic or catabolic programmes but support cell state transition into a metastatic phenotype with properties of invasion and migration. Multiple studies have demonstrated that metastatic potential is linked to mitochondrial function, potentially through the production of ROS as signalling molecules[133,134]. Loss of TIGAR can also increase mitochondrial ROS, thereby promoting EMT and metastatic potential[99]. Additionally, TGFβ, a dominant inducer of the EMT phenotype, can increase mitochondrial ROS[135]. Besides ROS, certain metabolites have been linked to promoting EMT by acting as signalling molecules. For example, studies in FH-deficient tumours have demonstrated that excess fumarate can increase the EMT phenotype through epigenetic changes[136]. Hyaluronidase induction of glycolysis is required for concomitant acceleration of cell migration in cancer cells[137]. The cytoskeleton tethers glycolytic enzymes and releases them during growth factor signalling to increase flux through glycolysis[138]. We surmise that changes in the cytoskeleton that occur during the transition to a metastatic phenotype could be another mechanism to control flux through glycolysis or other metabolic pathways. In addition, normal ageing, which is associated with an increased risk of cancer, coincides with elevated levels of the metabolite methylmalonic acid (MMA), a by-product of propionate metabolism that increases the EMT phenotype and cancer cell aggressiveness[139]. Thus, we are continuing to decipher a myriad of potential metabolites that are able to induce EMT and promote metastatic potential in vivo.

Metastatic cells need to survive in the circulatory or lymphatic system in order to reach and colonize distal sites. During their 'journey', cancer cells are not in an anabolic state but, rather, enter a catabolic state in order to survive the changing environment. The specific metabolic barriers imposed by the circulatory and lymphatic systems are just beginning to be addressed[140]. Loss of attachment to the extracellular matrix increases oxidative stress-induced death of cancer cells[141]. This mechanism of cell death can be mitigated by cell clustering, which induces hypoxia, resulting in a HIF1-mediated decrease in oxidative stress[142]. This might explain why increased HIF1 stabilization correlates with high metastatic potential[143]. The oxidative stress-induced cell death that occurs in the circulation is likely to be mediated by LOOH-induced ferroptosis. Accordingly, metastatic melanoma cells have been shown to increase their antioxidant capacity through upregulation of enzymes that control NADPH production as well as lactate uptake, which diverts glucose carbon into the oxidative PPP[102]. Interestingly, the lymphatic system provides a different microenvironment to traversing melanoma cells than the circulatory system. For example, the MUFA oleic acid in lymphatic vessels mitigates oxidative stress, which might explain the propensity for cancer cells to circulate through the lymphatic system for metastatic dissemination[103]. In mouse models of lung adenocarcinoma and melanoma, mitigation of oxidative stress by dietary antioxidants, which is known to decrease ferroptosis, increases metastasis[100,144]. Beyond oxidative stress, it will be of interest to determine which other metabolic barriers are imposed on cancer cells 'travelling' through the circulatory and lymphatic systems.

The colonization at distal sites requires metabolic adaptation based on the distinct nutrient availability in the new TME compared with the primary tumour site. A salient example comes from examining tumour metastases in the brain. Two limiting nutrients in the TME of the brain are serine and fatty acids; thus, breast cancer cells that colonize to the brain have high expression of PHGDH to allow for glucose-dependent serine and glycine production[145]. Accordingly, genetic and pharmacologic inhibition of PHGDH attenuated brain metastasis, but not primary tumour growth. Metastatic breast cancer cells colonizing the brain are also more dependent on de novo lipogenesis compared with primary tumours[146,147]. Moreover, overcoming barriers to support anabolism in the new metastatic niche requires the specialized role of metabolites such as pyruvate and serine to drive collagen hydroxylation of the extracellular matrix and mTORC1 signalling, respectively[148,149]. Current efforts will continue to focus on cataloguing the nutrient compositions and metabolic liabilities within distinct

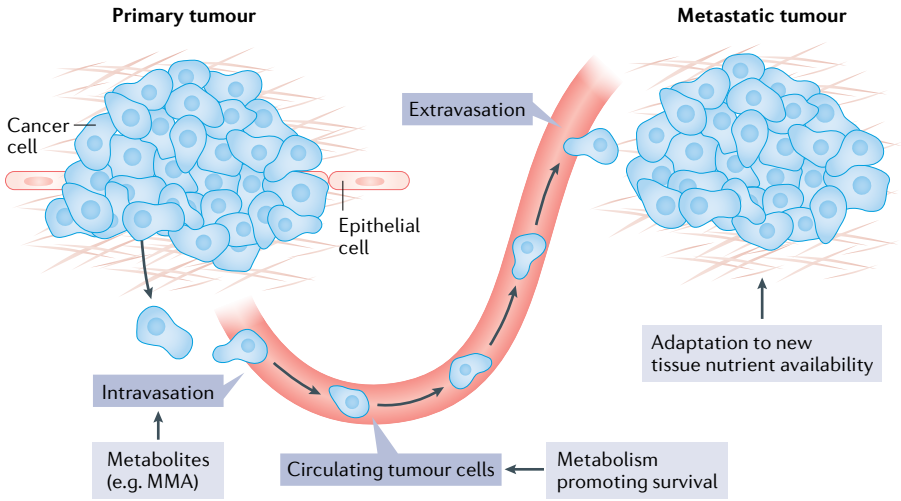

Fig. 5 | **Metabolism regulates multisteps of metastasis.** Metabolites such as methylmalonic acid (MMA) that are not directly connected to anabolism control invasion and migration into surrounding circulatory system (that is, intravasation). Metabolic pathways such as those that mitigate ferroptosis promote survival in the circulation. Extravasation from the vasculature and colonization of secondary tumour sites require changes in metabolism that allow cancer cells to adapt to a new nutrient milieu.

metastatic niches (for example, bone, liver, brain, lung), as it is unlikely that there is only one metabolic programme that allows for efficient colonization across tissues. Rather, it will be reflective of the nutrient availability of different tissues and the capacity of cancer cells to scavenge the necessary nutrients to support tumour growth, as well as their ability to generate de novo metabolites that are limiting in the microenvironment. Furthermore, it is not fully understood which metabolites control signalling pathways that support growth in the distal metastatic niche compared with the primary tumour. An understudied area is metastatic dormancy, where metastatic cancer cells stop proliferating but survive in a quiescent state after extravasation into a secondary site[150]. It is not known whether metabolites exert control in the transition of these dormant cells to reinitiate proliferation, which sometimes happens years after treatment of the primary tumour. Thus, much remains to be discovered about how metabolism promotes distinct steps of metastasis (FIG. 5).

Targeting metabolism for therapy

At first glance, metabolic enzymes are attractive therapeutic targets for cancer therapy, but there has been a paucity of new drugs targeting metabolism for numerous reasons. Nucleoside analogues were among the first chemotherapeutic agents to be introduced for cancer therapy; however, they were found to affect not only cancer cells but also normal proliferating cells[151]. Similarly, targeting other metabolic complexes or enzymes is limited due to toxicity in normal tissues. Tumours that relapse after acquiring resistance to standard of care therapies are more vulnerable to ETC inhibitors[5,28], but these inhibitors undoubtedly cause toxicity to non-cancer cells. Moreover, the metabolic plasticity of cancer cells, whereby cells can either upregulate alternative pathways or acquire nutrients from the environment to adapt to changes in metabolism, would require the challenging task of targeting both metabolic pathways and nutrient scavenging pathways[117]. It is not clear whether targeting biomass production is able to induce cytotoxicity in most cancer cells. This strategy is likely anti-proliferative or could induce differentiation[152]. Therefore, we propose identifying specific, driver mutation-dependent metabolic vulnerabilities within a particular cancer, targeting of which would synergize with radiation, chemotherapy or immunotherapy to induce cytotoxicity. For example, mutant IDH1 or mutant IDH2 inhibitors are not effective in gliomas harbouring mutations in the encoding genes, yet these gliomas have metabolic vulnerabilities due to the accumulation of D-2HG (REF.[153]). An interesting, newly discovered function of oncometabolites is their ability to inhibit homology-dependent repair resulting in increased DNA damage[154] (FIG. 2). This discovery has led to the use of poly(ADP-ribose) polymerase (PARP) inhibitors in clinical trials for gliomas that are refractory to mutant IDH inhibitors and could also be used in FH and SDH null tumours[155].

Multiple studies have suggested that a diverse set of cancers are 'addicted' to particular antioxidants for tumour progression and metastasis in vivo[94,96,97], which is analogous to the idea of 'oncogene addiction'. Moreover, persister cancer cells after therapy rely on GPX4 for survival[156]. A big challenge is to determine whether there is a therapeutic window that exists to allow selective targeting of a particular antioxidant protein with minimal toxicity to normal tissues. Pharmacologic targeting of the NRF2 network in KEAP1-null NSCLC is one promising approach[157]. In addition, certain tumours import extracellular cysteine to maintain antioxidant capacity in order to avoid ferroptosis and promote tumour progression[25]. Administration of cyst(e)inase, which depletes extracellular cysteine and cystine, has been shown to diminish tumour progression in mouse models of leukaemia and pancreatic cancer[158,159]. Interestingly, cyst(e)inase treatment of mice has been shown to synergize with T cell-mediated antitumour immunity to enhance ferropotosis[160]. CTLs can become exhausted in the TME, in part, due to impaired mitochondrial metabolism[161,162]. Furthermore, targeting glutamine metabolism increased antitumour immunity in mouse models, in part, by upregulating mitochondrial metabolism of CTLs[130,163]. These findings have encouraged efforts to investigate whether the metabolic preconditioning of therapeutic T cells in vitro prior to adoptive transfer might be beneficial to improve T cell performance for cancer immunotherapy. Interestingly, targeting glutamine metabolism in mouse models of oncogenic KRAS-driven NSCLCs harbouring *Keap1* mutations, which have increased antioxidant capacity due to activated NRF2, is more effective than in other subtypes of NSCLC[164]. It will be of interest to see the outcome of clinical trials using glutaminase inhibitors in NSCLC with *KEAP1* mutations, especially in conjunction with immunotherapy or radiation therapy. Moreover, glutamine uptake in KEAP1-null NSCLC could be assessed with the glutamine analogue 4-^{18}F-(2*S*,4*R*)-fluoroglutamine (^{18}F-FGln) to assess whether therapeutic targeting of glutamine metabolism is on target[165]. Ultimately, we speculate that there might be a therapeutic window for targeting antioxidant pathways, leading to increased susceptibility to ferroptosis in conjunction with radiation or immunotherapy.

In addition to cellular metabolism within cancer cells and other cell types in the TME, it is now recognized that organismal metabolism is critical for determining the efficacy of cancer therapies[166]. There is a resurgence in manipulating dietary serine or methionine as well as a ketogenic diet to modulate tumour progression[122,167,168]. For example, the PI3K signalling pathway is potently activated by insulin, and the efficacy of PI3K inhibitors is improved by the ketogenic diet or SGLT2 inhibitors, both of which lower insulin levels, in mouse models of pancreatic, endometrial, bladder and breast cancer as well as acute myeloid leukaemia[169]. Additionally, there is a link between obesity and the incidence of certain cancers[170]. In mouse models, the administration of a high-fat diet increases both primary tumour growth and metastasis[170]. Metastatic cells have high expression of proteins that facilitate fatty acid uptake[171], but the composition of the fatty acids in a high-fat diet and how these impact tumour and immune cell biology are often overlooked. It is possible that diets rich in MUFAs are not beneficial as they may be able to prevent ferroptosis[172] to potentially increase tumour growth and metastasis. Furthermore, systemic autophagy inhibition, another modulator of host metabolism, has been shown to be effective in conjunction with immunotherapy in tumours lacking ASS1 (REF.[113]). Autophagy inhibition is also

Glossary

Autophagy
A highly regulated process through which proteins and organelles are delivered to the lysosome and degraded.

Ferroptosis
A distinct form of programmed cell death that requires reactive oxygen species (ROS) and iron accumulation to cause lethal lipid peroxidation.

Hyaluronidase
An enzyme that degrades hyaluronic acid into monosaccharides.

Peroxiredoxin enzymes
Cysteine-dependent peroxidases that convert hydrogen peroxide (H2O2) to water.

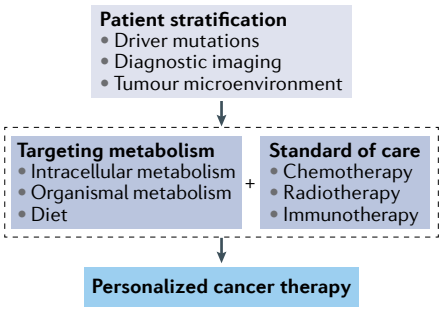

Fig. 6 | **Personalized medicine approach to targeting cancer metabolism.** A proposed 'personalized medicine' approach that involves combining standard of care therapy with targeting cell autonomous and/or organismal metabolic pathways in a particular subset of cancers defined by their genetics.

synthetic lethal with *Lkb1*-deficiency in a mouse model of oncogenic Kras-driven NSLC[173]. Thus, ongoing clinical trials could examine the ASS1 and LKB1 status of tumours and, potentially, combine autophagy inhibition with checkpoint blockade[126]. Finally, the combination of MEK inhibitors with autophagy inhibitors demonstrates remarkable results in preclinical models of pancreatic, melanoma and colon cancer[174,175].

Metformin continues to be invoked as a cancer-preventive and therapeutic agent by inhibiting mitochondrial complex I and modulating tumour immunity[5]. Factors that govern sensitivity to metformin include whether the cancer cells have robust ETC function and express organic cation transporters (OCTs), which allow efficient uptake of metformin in cancer cells[5]. Furthermore, metformin treatment can decrease intracellular asparagine levels, and its efficacy is enhanced in mouse models of cancer by the addition of L-asparaginase, which diminishes extracellular asparagine[4]. Interestingly, a genetic screen identifying the genes required for metastasis demonstrated that intracellular asparagine availability within breast cancer cells determined the metastatic potential. We speculate that tumours with high expression of OCTs would likely benefit from metformin treatment with the addition of L-asparaginase. Again, this would have to be combined with immunotherapy or other standard of care therapy to induce cytotoxic effects. Collectively, these studies indicate that targeting metabolism requires a 'personalized medicine' approach to define the correct cancer cell or organismal metabolism target, combined with standard of care therapy, in a particular subset of cancers defined by their genetics (FIG. 6).

Conclusions

The field of cancer metabolism has evolved from the simplistic model of the Warburg effect to our current knowledge of the vast metabolic complexity of tumours, and there are key questions that need addressing in the coming years (BOX 1). There is now an appreciation of how the metabolic constraints imposed by the TME and the distinct cell composition within the TME influence tumour progression. The use of technology has enabled the discovery of new metabolic proteins and pathways used by cancer cells during tumour initiation, progression and metastasis. Furthermore, research is now focusing on the relevant human cancer biology of metastasis and exploring a 'personalized medicine' approach to target metabolism for cancer therapy. An area that is grossly understudied, but will likely blossom over the next years, is the study of how changes in metabolism increase the risk of cancer during ageing. A legacy of the field is that some of the technologies and ideas that originated from studying cancer metabolism have made an impact in the burgeoning fields of immunometabolism, stem cell metabolism and organismal metabolism. Additionally, the cancer metabolism field has facilitated the next generation of scientists to examine metabolism in these distinct fields. Over the next decade, metabolism, once relegated to the backwaters of the modern revolution in molecular biology and genetics, will continue to make inroads in our understanding of how human physiology and pathology occurs. After all, several of the drugs that have had a huge impact on human health and disease in the past decades have targeted metabolism, including statins, metformin and recent SGLT2 inhibitors.

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