# Metabolic targets for cancer therapy

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Abstract | Malignant cells exhibit metabolic changes, when compared to their normal counterparts, owing to both genetic and epigenetic alterations. Although such a metabolic rewiring has recently been indicated as yet another general hallmark of cancer, accumulating evidence suggests that the metabolic alterations of each neoplasm represent a molecular signature that intimately accompanies and allows for different facets of malignant transformation. During the past decade, targeting cancer metabolism has emerged as a promising strategy for the development of selective antineoplastic agents. Here, we discuss the intimate relationship between metabolism and malignancy, focusing on strategies through which this central aspect of tumour biology might be turned into cancer's Achilles heel.

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Although the tendency of malignant cells to metabolize glucose via aerobic glycolysis was first described by Otto Warburg as early as in 1924 (REFS 1,2), the first medical procedure based on these concepts, namely $^{18}$F-deoxyglucose positron emission tomography ($^{18}$FDG–PET), was not implemented in the clinic until the 1980s[3]. Furthermore, it is only during the past decade that the metabolic alterations of cancer cells have been rediscovered by researchers and clinicians. It has now become clear that the Warburg effect represents only the tip of the iceberg with regard to the metabolic rearrangements that accompany malignant transformation, which involve not only aerobic glycolysis but also an increased flux through the pentose phosphate pathway (PPP), elevated rates of lipid biosynthesis, high glutamine consumption, maintenance of redox homeostasis and — at least in the first steps of oncogenesis — limited levels of macroautophagy (hereafter referred to as autophagy)[4–6].

Hanahan and Weinberg have recently added a state of "deregulated cellular energetics" to the original hallmarks of cancer theorized in a seminal paper published in 2000 (REF. 7), reflecting the generalized consensus around the idea that cellular metabolism is substantially altered during oncogenesis and tumour progression[8]. In line with this notion, during the past decade considerable efforts have been devoted to the identification of agents that selectively kill neoplastic cells based on their metabolic alterations[9,10]. This approach has been relatively successful, leading to the development of several molecules that are now starting to enter clinical trials (see below). In addition, some antineoplastic agents that have been used in the clinic for a long time — such as 5-fluorouracil, methotrexate and gemcitabine — inhibit metabolic enzymes[11].

However, at least three profound misconceptions have frequently affected the consideration of cancer cell metabolism as a therapeutic target. First, metabolic alterations are generally viewed as a self-standing hallmark of cancer, rather than as a phenomenon that cannot be discerned from all other aspects of oncogenesis and tumour progression; second, it is believed that most neoplasms exhibit a common set of metabolic changes that precisely differentiate them from normal tissues; and third, tumours are often considered as relatively homogeneous entities composed of a limited range of cellular components, among which malignant cells numerically predominate (BOX 1). Carefully considering these points will allow for the development of safe and efficient metabolic inhibitors for cancer therapy. In this Review, we discuss the molecular mechanisms linking the principal metabolic alterations of neoplastic cells with other aspects of malignant transformation and present promising strategies for the development of clinically useful modulators of cancer metabolism.

## Systemic metabolism and cancer

Throughout the twenty-first century, clinical and epidemiological evidence has accumulated in support of the notions that: changes in whole-body metabolism influence oncogenesis, tumour progression and response to therapy; and some drugs that are currently licensed by the US Food and Drug Administration (FDA) for use in patients with metabolic disorders may exert antineoplastic effects[4,9].

Metabolic conditions including — but not limited to — obesity, hyperglycaemia, hyperlipidaemia and insulin resistance have all been associated with an increased risk of developing various types of cancer, accelerated tumour progression and poor clinical outcome[12,13]. In line with

this notion, retrospective clinical studies indicate that both metformin (a biguanide that is generally used for the treatment of type 2 diabetes) and statins (inhibitors of cholesterol synthesis that are currently used for the prevention of cardiovascular diseases) may reduce cancer-related morbidity and mortality[14–17].

Phenformin — another biguanide that was previously used to treat patients with diabetes — also appears to exert both prophylactic and therapeutic anticancer effects, at least in mice[18–20]. Although the clinical use of phenformin was discontinued in the late 1970s, owing to a relatively high incidence of fatal lactic acidosis (40–64

Box 1 | **Common misconceptions about oncometabolism**

Our progress towards an improved understanding of the metabolic alterations that occur in cancer, and hence towards the development of therapeutic measures targeting this important aspect of tumour biology, has been hindered by profound misconceptions.

First, metabolic alterations intimately accompany, mechanistically underpin and hence cannot be dissociated from other facets of malignant transformation. Indeed, cancer cells rewire their metabolic circuitries while acquiring phenotypic and behavioural traits of malignancy, including a virtually unrestricted proliferative potential and an increased resistance to stress conditions[8]. At least partially, this misconception reflects the misleading (but still largely accepted) view that signal transduction and metabolism constitute completely distinct entities. By contrast, accumulating evidence suggests that multiple metabolites and metabolic by-products such as ATP, acetyl-CoA, α-ketoglutarate (α-KG) and reactive oxygen species (ROS) can have a crucial role in cell-intrinsic and cell-extrinsic signalling pathways[259,264,265].

Various enzymes with key roles in metabolism may also participate in signal transduction. For instance, cytochrome *c* acts both as an electron shuttle of the mitochondrial respiratory chain and as a key regulator of mitochondrial apoptosis[265,266]. Similarly, the M2 isoform of pyruvate kinase, muscle (PKM2) has been suggested to operate as a signal transducer under some circumstances[267–269]. Whether the signalling activity of PKM2 is required for tumour progression remains controversial[177,178].

Referring to the metabolic alterations of malignant cells as a state of deregulated cellular energetics may also be misleading, as this implies that only the bioenergetic metabolism of cancer cells is altered and that neoplastic cells experience a state of metabolic deregulation. Instead, the situation appears to be more complex. Malignant cells exhibit alterations not only in bioenergetic processes such as glycolysis, mitochondrial respiration and glutaminolysis[198,270] but also in anabolic circuitries such as fatty acid synthesis and the mevalonate pathway[271,272]. Whether the metabolism of cancer cells and tumour-bearing organisms is deregulated remains a matter of perspective. Tumour growth is obviously abnormal for the host, but systemic metabolism is likely to adapt — at least initially — to the presence of neoplastic lesions. Moreover, accumulating evidence suggests that the metabolism of malignant cells is precisely tuned to sustain their needs in the face of changing environmental conditions[273]. Thus, the global metabolic rewiring that accompanies malignant transformation constitutes a continuum of the phenotypic and behavioural features of cancer[259,264].

Second, cancer-associated metabolic alterations are not a strict prerogative of malignant cells and are not the same across distinct neoplasms. Rather, with the exception of so-called 'oncometabolites' (see the main text), the metabolism of cancer cells closely resembles the metabolism of non-transformed highly proliferating cells[274,275]. Cancer cell metabolism (at least *in vitro*) is indeed centred around aerobic glycolysis, an elevated flux through the pentose phosphate pathway, high rates of lipid synthesis, increased glutamine consumption and low levels of autophagy (at least in the early stages of oncogenesis)[4–6]. Thus, agents targeting cancer-associated metabolic alterations may be intrinsically prone to also affect the metabolism of normal, highly proliferating cells. Notwithstanding this point, the clinical success of antimetabolites, which are toxic for highly proliferating tissues (see the main text), argues in favour of the existence of a therapeutic window that could allow for the implementation of chemotherapeutic regimens based on metabolic inhibitors, at least in some circumstances.

In addition, it has recently been demonstrated that the metabolic profile of tumours depends not only on the oncogenic driver but also on tissue type[276]. Indeed, although *MYC*-driven liver tumours exhibited increased glycolytic and glutaminolytic fluxes together with decreased levels of glutamine synthetase (GLUL) and a switch from glutaminase 2 (GLS2) to GLS1, *MET*-induced hepatic neoplasms utilized glucose to produce glutamine, and *MYC*-driven lung cancers displayed increased expression of both GLUL and GLS1, along with glutamine accumulation[276]. Therefore, the biochemical responses elicited by metabolic modulators may depend not only on tumour type but also on other context-dependent features such as tumour stage, vascularization, and so on.

Third, tumours contain not only malignant cells but also non-transformed stromal, endothelial and immune cells, which — in many cases — outnumber their neoplastic counterparts[277]. In fact, cancer cells modulate the tumour microenvironment to serve their own needs. Tumour-infiltrating leukocytes respond to cancer-derived signals by establishing an immunosuppressive milieu that promotes immune evasion[278]. Along similar lines, various stromal cells exert robust pro-tumorigenic functions by engaging in metabolic circuitries with their malignant counterparts. Normal human adipocytes stimulate the metastatic spread of ovarian cancer cells by secreting mediators such as interleukin-8, and directly transfer lipids to malignant cells, hence supporting their growth *in vitro* and *in vivo*[279]. Immortalized as well as primary breast carcinoma cells, which express the monocarboxylate transporter 1 (MCT1), stimulate fibroblasts to express MCT4 upon the establishment of oxidative stress[280,281]. In this setting, fibroblasts catabolize glucose mainly via aerobic glycolysis and secrete an excess of lactate and ketones (through MCT4), which may be taken up by cancer cells (through MCT1) and used to fuel oxidative phosphorylation[202,280]. Such a symbiosis closely resembles the lactate shuttle that normally operates in the brain and skeletal muscle[282], and may be modulated by the relative expression levels of pyruvate kinase isoforms[283]. Some subsets of patients with cancer might therefore benefit from agents that interrupt the metabolic coupling between neoplastic cells and their stroma[284].

$^{18}$F-deoxyglucose positron emission tomography ($^{18}$FDG–PET). An imaging procedure that is widely used in oncology for diagnostic, staging or monitoring purposes. $^{18}$FDG–PET relies on a radioactive glucose analogue that is preferentially taken up and retained by malignant cells in the context of the Warburg effect.

Pentose phosphate pathway (PPP). A metabolic circuitry (also known as phosphogluconate pathway or hexose monophosphate shunt) that converts glycolytic intermediates (mainly glucose-6-phosphate, fructose-6-phosphate and glyceraldehyde-3-phosphate) into pentoses (5-carbon sugars) and NADPH.

Macroautophagy
An evolutionarily conserved mechanism that targets intracellular components for lysosomal degradation. Macroautophagy has a major role in the maintenance of intracellular homeostasis as well as in the response of cells to adverse microenvironmental conditions, including nutrient deprivation and hypoxia.

Lactate shuttle
A cell-extrinsic metabolic circuitry that is based on the release of glycolytic lactate from one cell type (for example, astrocytes) and its uptake by another cell type (for example, neurons), which uses lactate to fuel oxidative phosphorylation.

cases per 100,000 patient years), metformin currently represents the most prescribed antihyperglycaemic agent worldwide[21]. Indeed, metformin displays an optimal pharmacokinetic profile (that is, 50–60% absolute oral bioavailability, slow absorption, negligible binding to plasma protein, broad tissue distribution with a slight preference for red blood cells and the small intestine, no hepatic metabolism, limited interaction with other drugs and rapid urinary excretion) as well as an exceptional safety profile (three cases of lactic acidosis per 100,000 patient years, mostly attributable to co-morbidities, and a limited range of mild gastrointestinal side effects)[21]. Statins (at least seven of which are currently approved by the FDA for use in patients) also display a good safety profile and are used by a large patient population[22].

The molecular mechanisms that underlie the reduced incidence of cancer among patients receiving metformin or statins remain a matter of debate. High circulating levels of glucose, insulin and insulin-like growth factor 1 (IGF1) have been shown to promote tumour growth by stimulating both mitogenic signalling pathways that emanate from IGF1 receptor (IGF1R)[13] and glucose uptake by malignant cells. However, the antineoplastic activity of metformin, which has cellular effects beyond 5′-AMP-dependent protein kinase (AMPK) activation[23], appears to be independent of glycaemia[24] and perhaps reflects the ability of this drug to preferentially kill cancer stem cells, to inhibit mitochondrial respiration, to aggravate glutamine addiction or to limit tumour-promoting inflammatory responses[25–28]. Along similar lines, statins may exert anticancer effects by interfering with the mevalonate pathway or by activating other stress response mechanisms in malignant cells rather than by normalizing systemic cholesterol metabolism[29,30]. Intriguingly, fibrates (antilipidaemic agents that reduce the rate of cardiovascular events in individuals at risk) are not associated with a clear reduction in the incidence of multiple neoplasms[31]. This is at odds with a large amount of preclinical data demonstrating a key role for fatty acid oxidation in oncogenesis and tumour progression[32], as well as with epidemiological data that convincingly link hyperlipidaemia to an increased risk of developing various neoplasms[12]. The reasons underlying such a discrepancy have not yet been elucidated.

The possibility that protracted caloric restriction or other long-term dietary modifications that lower circulating glucose levels (such as a ketogenic diet) would hinder tumour growth or specifically sensitize malignant cells to chemotherapy has recently generated considerable interest[33]. For instance, the combination of a ketogenic diet with hyperbaric oxygen has been shown to exert antineoplastic effects in a murine model of metastatic cancer, possibly reflecting a shift from a prevalently glycolytic to a predominantly oxidative metabolism in neoplastic cells (see below)[34]. Moreover, several short episodes of severe dietary restriction appear to increase the susceptibility of various tumour types to chemotherapy[35]. Although this approach is receiving attention from both clinicians and cancer patients[36], the actual clinical benefits of combining cycles of starvation with chemotherapy remain to be determined. Of note, the American Cancer Society currently recommends that patients with neoplasms who are undergoing chemotherapy increase their calorie and protein intake. Muscle wasting and cachexia have long been regarded as aetiological contributors of cancer-related morbidity and mortality[33]. Supporting this notion, the pharmacological inhibition of activin receptor 2B (a transmembrane receptor for transforming growth factor-like proteins that negatively regulates skeletal muscle mass) reverses cachexia in tumour-bearing mice and dramatically prolongs their survival, even in the absence of direct antineoplastic effects[37].

Interestingly, tumours carrying genetic alterations that cause constitutive signalling via phosphoinositide 3-kinase (PI3K) are resistant to the antineoplastic effects of dietary restriction, at least in mouse models[38]. Examples of such genetic alterations include point mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit α (*PIK3CA*) and deletions in phosphatase and tensin homolog (*PTEN*). Conversely, patients with *PIK3CA*-mutated colorectal tumours benefit from the regular use of aspirin[39], a non-steroidal anti-inflammatory drug that has been suggested to have anticancer effects[39,40]. Aspirin exerts its anti-inflammatory functions by inhibiting prostaglandin endoperoxide synthase 2 (PTGS2; also known as COX2), and this activity may also provide aspirin with antineoplastic properties as it results in the downregulation of PI3K signalling[39,41]. Indeed, retrospective evidence from a large clinical study suggests that the regular use of aspirin reduces the risk of developing colorectal carcinomas that overexpress PTGS2 but not similar lesions with weak or absent PTGS2 expression[41]. Moreover, the capacity of aspirin to limit the incidence of colorectal carcinoma appears to be influenced by the mutational status of *BRAF*, which also has an impact on PTGS2 activity[42]. Beyond its effects on PTGS2, aspirin directly stimulates AMPK, one of the most prominent regulators of intermediate metabolism[43], and thus may resemble metformin in its capacity to function as a dietary restriction mimetic under selected circumstances. However, the precise mechanisms that underlie the potential antineoplastic activity of aspirin remain elusive.

Taken together, these observations suggest that there is an intimate but poorly understood link between organismal metabolism and cancer that may offer several new therapeutic targets.

## Cancer and cellular metabolism

Accumulating evidence suggests that malignant transformation is associated with changes that affect several branches of metabolism (FIG. 1). A detailed compendium of these alterations exceeds the scope of this Review and has been covered elsewhere in the literature[4,5,44]. Cancer-associated metabolic rearrangements have been linked to the activation of proto-oncogenes and to the inactivation of tumour suppressor genes[45]. Moreover, the accumulation of specific metabolites such as succinate, fumarate and 2-hydroxyglutarate (2-HG) has been shown to drive oncogenesis, at least in part by affecting specific signal transduction cascades[46–48]. Altogether, these observations reinforce the notion that intermediate metabolism and signal transduction are intimately intertwined.

Lactic acidosis
A medical condition (also known as metabolic acidosis) that is characterized by a reduction in the pH of tissues and blood, and is often caused by the extracellular accumulation of lactate.

Ketogenic diet
A high-fat, adequate-protein, low-carbohydrate diet that forces an organism to produce energy mostly via fatty acid oxidation rather than via the catabolism of carbohydrates. This is generally associated with an increase in the levels of circulating ketone bodies, which have beneficial effects in some forms of epilepsy.

2-hydroxyglutarate
(2-HG). An oncometabolite originating from the reduction of α-ketoglutarate as catalysed by the neomorphic enzymatic activity associated with specific isocitrate dehydrogenase mutations.

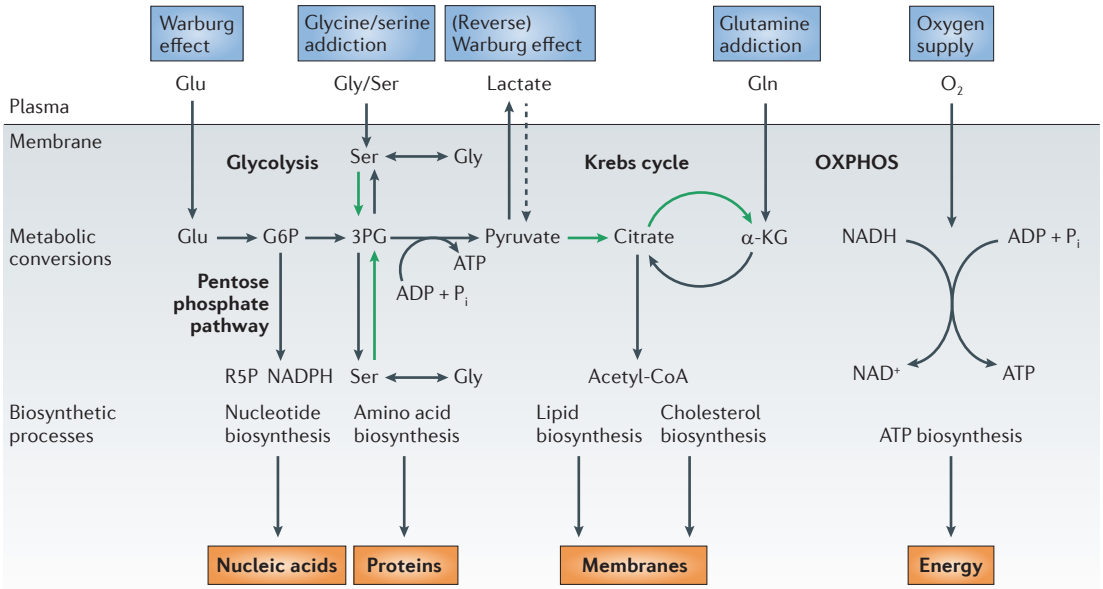



Figure 1 | **Metabolic alterations of cancer cells.** Similar to highly proliferating normal cells, malignant cells exhibit a profound imbalance towards anabolic metabolism. Owing to genetic and epigenetic alterations that intervene along with oncogenesis, cancer cells take up high amounts of glucose (Glu; underpinning the Warburg effect) and glutamine (Gln) and divert them to the phosphate pentose pathway and lipid biosynthesis, respectively. Coupled to an increased uptake of glycine (Gly) and serine (Ser), which are required for protein synthesis and sustain anaplerotic reactions that replenish Krebs cycle intermediates, this generates sufficient building blocks (that is, nucleic acids, proteins and membranes) for proliferation. In spite of long-standing views within the scientific community, neoplastic cells also produce ATP via oxidative phosphorylation (OXPHOS), which imposes an additional metabolic burden on the Krebs cycle. This perhaps explains the crucial importance of anaplerotic substrates in this context. In some instances, malignant cells take up (rather than secrete) lactate and use it to fuel OXPHOS via the Krebs cycle (this is known as the reverse Warburg effect). Moreover, oncogenesis is frequently associated with an increased generation of reactive oxygen species. This calls for appropriate levels of antioxidants, most of which originate from the pentose phosphate pathway. 3-PG, 3-phosphoglycerate; α-KG, α-ketoglutarate; G6P, glucose-6-phosphate; R5P, ribose-5-phosphate. Grey and green arrows indicate metabolic fluxes that are up- and downregulated, respectively, in malignant cells.

***Oncogenes and metabolism.*** The signalling pathways that emanate from several distinct oncogenic drivers have been mechanistically linked to cancer-associated metabolic alterations. For instance, MYC not only stimulates glucose uptake[49] and the expression of the M2 isoform of pyruvate kinase, muscle (PKM2)[50], which promotes the diversion of glycolytic intermediates towards anabolic metabolism, but also regulates a complex transcriptional and post-transcriptional programme that results in glutamine addiction[51,52]. Oncogenic *RAS* and *BRAF* mutations are associated with increased levels of glucose transporter 1 (GLUT1), endowing tumour cells with the ability to survive in microenvironments that are characterized by limited glucose availability[53,54]. Such an increased avidity for glucose is not only relevant for the maintenance of the oncogenic phenotype but might also constitute an early marker of the resistance of malignant cells to specific therapeutic interventions[55,56]. Indeed, although murine lung adenocarcinomas driven by mutant *PIK3CA* responded to a dual inhibitor of PI3K and mammalian target of rapamycin (mTOR) as their glucose intake dropped, *KRAS*-driven lung tumours neither responded to therapy nor manifested alterations in their avidity for glucose, irrespective of a robust inhibition of PI3K signalling[56]. The possibility that the avidity of neoplastic cells for glucose might predict their propensity to respond to metabolic modulators remains to be explored.

PI3K is often hyperactivated in malignant cells that express constitutively active receptor tyrosine kinases (RTKs). In turn, this drives the activation of AKT1 and mTOR complex 1 (mTORC1)[55]. AKT1 stimulates aerobic glycolysis in the following ways: by promoting the synthesis and incorporation of GLUT1 into the plasma membrane[57–59]; by stabilizing the association between hexokinase 2 (HK2) and mitochondria, hence increasing its enzymatic activity[60]; by activating 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3)[61]; and by triggering an ATP hydrolysis cycle that is centred around the endoplasmic reticulum (ER) enzyme ectonucleoside triphosphate diphosphohydrolase 5 (ENTPD5)[62]. In addition, AKT1 stimulates lipid biosynthesis by increasing the activity of ATP citrate lyase (ACLY)[63] and it inhibits beclin 1 (BECN1)[64], which is a haploinsufficient tumour suppressor and an essential component of the molecular machinery for autophagy[65].

Hexokinase 2
(HK2). A member of an enzyme family that catalyses the essentially irreversible phosphorylation of glucose to glucose-6-phosphate, de facto trapping it in the cytoplasm and rendering it available for metabolic processes including glycolysis or glycogen synthesis.

Active mTORC1 drives a complex transcriptional programme that sustains glycolysis, the oxidative arm of the PPP as well as nucleotide and lipid biosynthesis[66–68], and also stimulates protein synthesis, inhibits autophagy and promotes the anaplerotic conversion of glutamine into α-ketoglutarate (α-KG) via post-translational mechanisms[69,70]. Recent results suggest that the molecular pathways connecting RTKs to aerobic glycolysis do not completely overlap with those that link RTKs to cell proliferation[71]. In addition, some RTKs such as ERBB2 (also known as HER2), which is overexpressed by a sizeable proportion of breast carcinomas, stimulate glycolysis via both AKT1-dependent and -independent pathways. In particular, ERBB2 can promote the AKT1-independent, heat shock factor protein 1 (HSF1)-mediated transactivation of the gene encoding lactate dehydrogenase A (LDHA)[72].

Besides inhibiting cell death as triggered by multiple stimuli including oncogenic transformation, several anti-apoptotic members of the B cell lymphoma 2 (BCL-2) protein family — including BCL-2 itself, BCL-2-like 1 (BCL-2L1; also known as BCL-$X_L$) and myeloid cell leukaemia sequence 1 (MCL1)[73] — can influence metabolism, at least to some extent. In particular, BCL-2 and BCL-$X_L$ have an important role in the modulation of calcium fluxes at the ER[74]. Moreover, BCL-$X_L$ and MCL1 have recently been reported to physically interact with — and hence regulate the function of — the mitochondrial ATP synthase[75,76].

Finally, although none of the REL family members other than viral v-*rel* itself can be regarded as a bona fide oncogene, the nuclear factor-κB (NF-κB) system is frequently activated during malignant transformation, transducing crucial pro-survival signals. Such constitutive activation is thought to underpin a state of so-called non-oncogene addiction[77] (BOX 2). One of the transcriptional targets of NF-κB that is implicated in this phenomenon is *GLUT3* (REFS 78,79). Recent data indicate that NF-κB is required for robust mitochondrial metabolism as it transactivates the gene encoding synthesis of cytochrome *c* oxidase 2 (SCO2)[80], hence mediating oncosuppressive functions. Accordingly, the silencing of RELA (an NF-κB subunit) in murine tumours that heavily rely on NF-κB activation results in a metabolic reprogramming towards aerobic glycolysis, rendering these tumours especially sensitive to metabolic challenges including glucose deprivation and inhibition of mitochondrial respiration by metformin[80]. These observations suggest that neoplasms that exhibit relatively low rates of aerobic glycolysis may be particularly sensitive to the combined administration of metabolic inhibitors and NF-κB-targeting agents.

***Oncosuppressors and metabolism.*** Several oncosuppressor proteins have been shown to regulate cellular metabolism. In particular, inactivation of the tumour suppressor p53 — which occurs in more than 50% of all neoplasms — results in a plethora of metabolic consequences that potently stimulate the Warburg effect. Indeed, p53 can repress the transcription of *GLUT1* and *GLUT4* (REF. 81), in addition to stimulating the expression of TP53-induced glycolysis and apoptosis regulator (TIGAR; also known as C12orf5)[82], glutaminase 2 (GLS2)[83], SCO2 (REF. 84) and various pro-autophagic factors[85]. In addition, p53 can physically interact with glucose-6-phosphate dehydrogenase (G6PD), which is the rate-limiting enzyme of the PPP[86], and with RB1-inducible coiled-coil 1 (RB1CC1)[85,87].

On the one hand, SCO2 is crucial for the assembly of the cytochrome *c* oxidase (COX) complex, which partially explains the reduced baseline levels of mitochondrial respiration exhibited by p53-deficient cells[84]. On the other hand, TIGAR functions as a fructose-2,6-bisphosphatase and hence diverts glycolytic intermediates towards the PPP, whereas RB1CC1 is a crucial upstream regulator of autophagy[82,87]. Thus, although the cytoplasmic pool of p53 appears to limit autophagy as well as the PPP by interacting with RB1CC1 and G6PD, respectively, its nuclear counterpart mediates opposite effects by stimulating the synthesis of various pro-autophagic factors as well as that of TIGAR. This apparent discrepancy may reflect the dual ability of p53 to preserve intracellular homeostasis — a setting in which glucose is normally utilized to fuel mitochondrial respiration — and to orchestrate adaptive responses to adverse conditions in which antioxidants and autophagy are required for cell survival[88].

The p53 system also exhibits a substantial degree of crosstalk with key signal transducers such as PI3K, PTEN and AKT1, thus modulating their metabolic functions[45]. Of note, p53 has recently been shown to assist with the adaptation of cancer cells to serine and glutamine shortage[89,90], which indicates that p53-deficient tumours may be particularly dependent on ample supplies of these amino acids. Thus, if interventions resulting in the local or systemic depletion of serine or glutamine were feasible, they could exert robust therapeutic effects against a broad range of p53-deficient neoplasms. Additional research is required to further explore this possibility.

Other prominent oncosuppressor proteins are intimately connected with intermediate metabolism. By negatively regulating hypoxia-inducible factor 1 (HIF1), a transcription factor that controls the synthesis of several glycolytic enzymes and angiogenic factors in response to hypoxia and other stress conditions[91], the von Hippel–Lindau tumour suppressor E3 ubiquitin protein ligase (VHL) inhibits aerobic glycolysis[92]. Along similar lines, as PTEN directly antagonizes the enzymatic activity of PI3K (which promotes HIF1 synthesis)[93], the loss of PTEN results in increased HIF1 transcriptional activity[94]. Increased PI3K signalling following the loss of PTEN also promotes aerobic glycolysis via a signalling cascade that involves the mTORC1 substrate ribosomal protein S6 kinase β1 (RPS6KB1; also known as $p70^{S6K}$)[95].

Accordingly, cells obtained from mice that have been genetically engineered to overexpress PTEN at the whole-body level not only display reduced glucose and glutamine uptake that is coupled to increased oxidative phosphorylation but also resist oncogenic transformation[96,97]. Moreover, mice carrying additional genomic copies of *Pten* exhibit a statistically significant reduction in the incidence of both carcinogen-induced and spontaneous neoplasms, as well as an increase in lifespan[97].

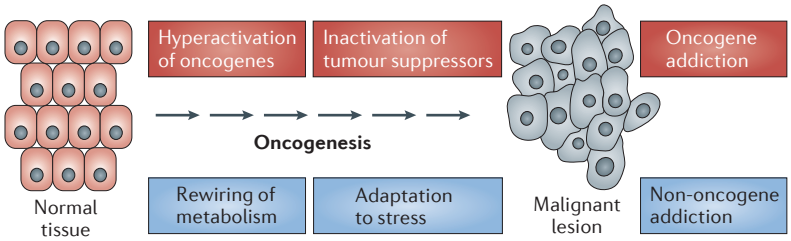
Anaplerotic conversion
Reaction that contributes to the replenishment of metabolic intermediates involved in a metabolic circuitry but does not pertain to the same circuitry. A classic example of anaplerosis refers to the replenishment of Krebs cycle intermediates via the direct conversion of pyruvate (or aspartate) into oxaloacetate, glutamate into α-ketoglutarate, or adenylosuccinate into fumarate.

Lactate dehydrogenase A
(LDHA). A member of the LDH family. LDH is an abundant cytosolic enzyme that catalyses the reversible conversion of pyruvate and NADH into lactate and $NAD^+$.

Box 2 | **Non-oncogene addiction**

Oncogenesis generally proceeds via the progressive acquisition of genetic and epigenetic alterations that together influence various cellular processes, including metabolic pathways. Such alterations, which generally involve either the inactivation of oncosuppressor genes or the hyperactivation of oncogenes, not only allow for malignant transformation but also support the survival of established tumours (see figure). This concept is widely known as 'oncogene addiction' and reflects a wealth of experimental data demonstrating that the inhibition of oncogenic drivers and/or the reconstitution of (previously lost) oncosuppressive functions normally results in robust antineoplastic effects, both *in vitro* and *in vivo*[260].

At least in part owing to the elevated levels of intracellular stress and to the adverse microenvironmental conditions that developing tumours must continuously endure, the survival of malignant cells also relies on an array of genes and functions that are not inherently tumorigenic (see figure). Such a 'non-oncogene addiction', which frequently involves stress response pathways, offers an attractive approach for the development of novel therapeutic strategies against cancer[260]. Indeed, targeting the molecular pathways that underpin non-oncogene addiction is proposed to affect the viability of malignant — but not normal — cells, as the latter are not exposed to a constant state of intracellular and extracellular stress. Preclinical data in support of this notion have begun to accumulate[261,285]. For instance, the stress-responsive transcription factor heat shock factor protein 1 (HSF1) appears to be required for oncogenesis as driven by *Kras* hyperactivation or *Trp53* loss-of-function mutations in mice[285]. Along similar lines, antioxidant defences have been shown to constitute a selective liability of malignant — as opposed to non-transformed — cells in xenograft tumour models[261]. Several metabolic alterations of cancer cells, such as their dependency on glutamine, glycine or serine, might also be viewed as examples of non-oncogene addiction.




Importantly, such a phenotype is paralleled by several metabolic improvements, including elevated insulin sensitivity, enhanced protection against the harmful effects of a high-fat diet and increased energy expenditure[97]. Taken together, these observations confirm the existence of an intimate link between oncosuppression and the preservation of an optimal metabolism at both cellular and systemic levels.

Liver kinase B1 (LKB1; also known as STK11), a serine/threonine kinase that is frequently lost or inactivated in sporadic tumours owing to somatic mutations (and in patients with Peutz–Jeghers syndrome owing to hereditary mutations), is required for the activation of AMPK[98], thus exerting a major control on metabolism. AMPK directly phosphorylates several metabolic enzymes, including acetyl-CoA carboxylase 1 (ACC1), ACC2 and 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR), thus inhibiting the mevalonate pathway and the synthesis of fatty acids. Moreover, AMPK can phosphorylate several signal transducers that affect metabolic pathways, such as tuberous sclerosis 2 protein (TSC2), which is a negative regulator of mTOR, and UNC51-like autophagy activating kinase 1 (ULK1; also known as ATG1), which is an autophagy-initiating kinase[99]. These observations indicate that AMPK functionally antagonizes several metabolic effects of AKT1.

Additional oncosuppressive factors such as ataxia telangiectasia mutated (ATM), which is a kinase that operates as a sensor of DNA damage, have been shown to regulate the catalytic activity of AMPK[100]. Thus, AMPK stands out as a key regulator of metabolism that collects signals from several oncosuppressive factors. ATM appears to phosphorylate several other signal transducers with metabolic connections, including p53 and AKT1 (REF. 100). Accordingly, the loss of ATM has been associated with increased HIF1 transcriptional activity and with the upregulation of GLUT1 (REF. 101). ATM has also been reported to phosphorylate HIF1 in response to hypoxia[102], thereby downregulating mTOR via a complex transcriptional circuitry[103]. There is no model available at present that reconciles these apparently discrepant observations on the metabolic activity of ATM.

Various other oncosuppressive proteins have been proposed to influence intermediate metabolism in some circumstances, including — but presumably not limited to — death-associated protein kinase 1 (DAPK1), sirtuin 6 (SIRT6) and several pro-apoptotic members of the BCL-2 protein family. DAPK1 exerts autophagy-regulatory functions and can stimulate the enzymatic activity of both PKM1 and PKM2 (REFS 104,105). By doing so, DAPK1 favours the production of lactate while limiting the metabolic flux through the PPP, mediating an antiproliferative effect[105]. These observations, which may sound counterintuitive, are in line with the findings that the reduced enzymatic activity of PKM2 is further decreased by the activation of growth signalling[106–109] as well as by the production of reactive oxygen species (ROS)[110]. Indeed, malignant cells appear to harness aerobic glycolysis mostly as a measure to boost anabolic metabolism and generate reducing equivalents rather than as a source of ATP.

The histone deacetylase SIRT6 has recently been suggested to mediate prominent oncosuppressive effects by regulating both aerobic glycolysis (via HIF1) and ribosome metabolism[111,112]. Although SIRT6 exerts other oncosuppressive functions — for instance, by contributing to the maintenance of genomic stability[113,114] and by repressing the synthesis of survivin, an inhibitor of apoptosis that is often overexpressed in the course of oncogenesis[115,116] — these observations lend further support to a general role for metabolic changes in malignant transformation. Several other sirtuins, including SIRT1 and SIRT2 (which are found in the cytosol and in the nucleus) as well as SIRT3, SIRT4 and SIRT5 (which are mainly localized to mitochondria), exert prominent metabolic functions, at both the cellular and organismal level[117]. Despite the conservation of their catalytic domain, sirtuins have an impact on oncogenesis and tumour progression in an isoform-specific manner[118]. Thus, although some members of the sirtuin family (such as SIRT2, SIRT3 and SIRT6) have mainly been ascribed with oncosuppressive functions, others (such as SIRT1 and SIRT7) have a more controversial role and can promote tumorigenesis, at least in some circumstances[118–120].

Finally, the pro-apoptotic BCL-2 family members BCL-2-associated X protein (BAX) and BCL-2-antagonist/killer 1 (BAK1), which have a crucial role in the tumour response to chemotherapy by executing mitochondrial apoptosis[73], may influence cellular metabolism as they cooperate with BCL-2 and BCL-$X_L$ in the regulation of calcium fluxes at the ER[74]. Vice versa, the pro-apoptotic functions of BAX and BAK1 appear to be regulated by sphingolipid metabolism[121]. The actual relevance of these effects for the oncosuppressive activity of BAX and BAK1 remains to be elucidated.

Intriguingly, the transcription factor promyelocytic leukaemia (PML), which has previously been ascribed with bona fide oncosuppressive functions[122], appears to mediate prominent pro-survival effects in breast carcinoma cells as it stimulates fatty acid oxidation[123,124]. In line with this notion, elevated expression levels of PML (as measured by immunohistochemistry in bioptic tumour specimens) were shown to correlate with reduced time to recurrence and a genetic signature of poor prognosis in patients with breast carcinoma[123]. These findings are in line with several recent reports indicating that fatty acid oxidation has an important role in the adaptation to metabolic and oncogenic stress[125–127]. Moreover, they suggest that, at least in some settings, PML exerts clinically relevant oncogenic (rather than oncosuppressive) functions that depend on metabolic alterations.

***Oncometabolites and oncoenzymes.*** The possibility that metabolites could directly contribute to oncogenesis first arose when mutations in succinate dehydrogenase (SDH) and fumarate hydratase (FH) were found to be associated with both familial and sporadic forms of cancer (including leiomyoma, pheochromocytoma, paraganglioma and renal cell carcinoma)[128]. These mutations disrupt the enzymatic activity of SDH and FH, resulting in the accumulation of succinate and fumarate, which are proposed to drive oncogenesis[128]. Initially, the oncogenic effects of succinate and fumarate were ascribed to their capacity to inhibit α-KG-dependent prolyl hydroxylases that tag HIF1 for proteasomal degradation in normoxic conditions, and hence to establish a tumorigenic pseudohypoxic state similar to that elicited by the loss of VHL[46,47]. This view has been challenged by recent studies demonstrating that the formation of renal cysts in FH-deficient mice does not require HIF1 but instead involves the non-enzymatic modification of cysteine residues on Kelch-like ECH-associated protein 1 (KEAP1), which abrogates its ability to repress antioxidant responses orchestrated by nuclear factor erythroid 2-related factor 2 (NRF2)[129]. Along similar lines, succinate has been suggested to promote oncogenesis by inhibiting α-KG-dependent enzymes that are involved in the epigenetic regulation of gene expression[130] (discussed below) or by favouring the production of potentially genotoxic ROS[131].

Mutations in the genes encoding two distinct isoforms of isocitrate dehydrogenase (that is, cytosolic *IDH1* and mitochondrial *IDH2*) occur in a high proportion of patients with glioma, glioblastoma and acute myeloid leukaemia[132,133], in a fraction of individuals affected by intrahepatic cholangiocarcinoma and cartilaginous tumours, as well as in sporadic cases of other malignancies (including melanoma, pheochromocytoma, paraganglioma and thyroid carcinoma)[134]. These mutations have been found to result in a neomorphic enzymatic activity, endowing IDH with the capacity to catalyse the NADPH-dependent reduction of α-KG to 2-HG[48,135]. These findings not only identified 2-HG as a novel oncometabolite but also established the concept of an oncoenzyme: that is, an enzyme that is generally involved in intermediate metabolism and — under specific circumstances — exerts bona fide tumorigenic functions.

Recently, the overexpression of glycine decarboxylase, which is paralleled by the accumulation of sarcosine (also known as *N*-methylglycine), has also been suggested to constitute an oncogenic event[136]. Although this derivative of glycine has previously been implicated in oncogenesis and tumour progression[137], it remains to be determined whether sarcosine truly represents a novel oncometabolite. Irrespective of how 2-HG and other oncometabolites drive malignant transformation, they may constitute tumour-specific biomarkers. In particular, elevations in 2-HG may be useful for identifying patients with *IDH1* or *IDH2* mutations (for example, R132H or R140Q substitutions), who may benefit from IDH-targeted interventions (see below). Of note, cancer-associated *IDH1* and *IDH2* mutations are most often heterozygous, presumably reflecting the advantage conferred to malignant cells by the capacity of wild-type IDH1 and IDH2 to generate NADPH (hence contributing to the maintenance of redox and metabolic homeostasis to some degree)[138].

Initially, 2-HG was thought to promote oncogenesis by acting as a competitive inhibitor of the α-KG-dependent prolyl hydroxylases that direct the degradation of HIF1 in physiological conditions, hence mimicking the oncogenic effects of *VHL* mutations[139,140]. However, it has become clear that the oncogenic pathways engaged by 2-HG are complex and may exhibit some degree of context dependency. For instance, 2-HG has recently been shown to drive the malignant transformation of human astrocytes along with the activation (rather than the inhibition) of prolyl hydroxylases of the EGLN family, de facto resulting in diminished HIF1 levels[141]. In addition, by impairing the function of other α-KG-dependent enzymes such as the methylcytosine dioxygenase TET2 (REF. 142) or the histone demethylase KDM4C[143], the accumulation of 2-HG can promote the establishment of a hypermethylated chromatin state that blocks cell differentiation[143–145]. Actually, these may not be the sole epigenetic effects of *IDH1* and *IDH2* mutations, as defects in the catalytic activity of these enzymes deplete cells of acetyl-CoA[146], hence inhibiting histone acetylation[143]. High levels of 2-HG have recently been shown to render the growth of haematopoietic cells independent from cytokines, hence mediating reversible oncogenic effects[147]. This may constitute an additional mechanism underpinning the oncogenic activity of 2-HG and perhaps other oncometabolites.

The reaction catalysed by wild-type IDH1 (that is, the conversion of isocitrate into α-KG) is highly reversible and hence can be exploited as a means to reductively

Mitochondrial apoptosis
A regulated signal transduction cascade leading to the apoptotic demise of cells upon the permeabilization of mitochondrial membranes, resulting in the functional impairment of mitochondria and in the release of cytotoxic proteins into the cytosol.

Succinate dehydrogenase
(SDH). An enzyme of the inner mitochondrial membrane that catalyses the oxidation of succinate to fumarate, which is coupled to the reduction of ubiquinone to ubiquinol, de facto being simultaneously involved in the Krebs cycle and in mitochondrial respiration.

Fumarate hydratase
(FH). An enzyme that catalyses the reversible hydration of fumarate to malate. The mitochondrial isoenzyme of FH is involved in the Krebs cycle.

Isocitrate dehydrogenase
(IDH). An enzyme that catalyses the reversible oxidative decarboxylation of isocitrate, producing α-ketoglutarate and carbon dioxide. The mitochondrial isoenzyme (IDH2) is involved in the Krebs cycle.

Oncometabolite
A small chemical produced in the context of intermediate metabolism that is sufficient to promote oncogenesis following its accumulation.

convert glutamine into acetyl-CoA for *de novo* lipid synthesis[148,149]. The IDH1-mediated reductive metabolism of glutamine contributes to lipogenesis more extensively than the oxidative catabolism of glucose in cancer cells that are exposed to hypoxic conditions or that bear defects in the mitochondrial respiratory chain[149]. This effect is partly mediated by the HIF1-dependent upregulation of pyruvate dehydrogenase kinase 1 (PDK1) and MYC[148,150], but it is primarily determined by the relative abundance of citrate and α-KG[150,151].

Kynurenine, a tryptophan metabolite that is constitutively generated by many neoplastic cells (but not by most healthy tissues other than the brain and liver) via indoleamine-2,3-dioxygenase, has also been suggested to be an oncometabolite[152]. In particular, kynurenine, which is well known for its robust immunosuppressive effects[153], appears to operate as an endogenous ligand for the aryl hydrocarbon receptor, which is a helix–loop–helix transcription factor that is implicated in the carcinogenic activity of environmental pollutants such as dioxin[152]. The relative contributions of the immunosuppressive and transcriptional activities of kynurenine to its oncogenic potential remain to be determined.

Taken together, these observations demonstrate the intimate connection between cancer and metabolism.

## Targeting cancer metabolism

During the past decade, the metabolic rewiring of cancer cells has been viewed as a promising source of novel drug targets. Several different approaches of this type have been explored, which has led to the identification of agents that are now close to clinical evaluation (TABLE 1). The relatively low number of metabolic inhibitors developed so far for use in cancer therapy partly reflects the recent rediscovery of the field, as well as concerns regarding the uniformity between the metabolism of malignant cells and that of non-transformed cells undergoing intensive proliferation (see above). Whether this truly constitutes a liability in therapeutic settings, however, remains to be determined.

***Targeting bioenergetic metabolism.*** Several cancer-associated alterations in bioenergetic metabolic circuitries — including glycolysis, the Krebs cycle, mitochondrial respiration, glutaminolysis and fatty acid oxidation — have been investigated as potential drug targets. The unselective inhibition of hexokinases with 2-deoxy-D-glucose has been associated with acceptable toxicity in patients with glioma who are concurrently treated with fractionated radiotherapy[154], although there are doubts as to whether these studies used clinically relevant doses of 2-deoxy-D-glucose. Currently, interest is being refocused on interventions that preferentially target HK2, the hexokinase isoform that is most often expressed by — and has a predominant role in — malignant cells[155], over HK1, which is found in the majority of normal tissues. In this sense, promising preclinical results have been obtained with 3-bromopyruvate and methyl jasmonate, which reportedly exert antineoplastic effects in a range of rodent tumour models[156–158]. However, the true specificity of 3-bromopyruvate for HK2 is limited, as this agent has been shown to inhibit additional enzymes that are involved in bioenergetic metabolism, including glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and LDHA[159,160]. The development of lonidamine, a cytotoxic agent that — among its multiple effects — has been suggested to inhibit hexokinases, seems to stand at an impasse, as a large number of clinical studies performed in the 1980–1990s failed to associate its use with unequivocal clinical benefits[9,161].

A large body of preclinical results suggest that several other glycolytic enzymes as well as substrate or product transporters may be targets for anticancer therapy, including PFKFB3 (REFS 162–164), GAPDH[159,165], PKM2 (REFS 108,166), LDHA[160,167,168], GLUT1 (REFS 169,170), GLUT4 (REF. 171) and monocarboxylate transporter 4 (MCT4; also known as SLC16A4)[172,173]. Small-molecule inhibitors of PFKFB3 limit the growth of human promyelocytic leukaemia and breast carcinoma cells implanted in immunodeficient mice, as well as the development of transplantable murine lung carcinomas in immunocompetent hosts[162,164]. Along similar lines, the pharmacological or genetic inhibition of GAPDH[159,165], PKM2 (REF. 108), LDHA[167,168], GLUT1 (REFS 169,170), GLUT4 (REF. 171) and MCT4 (REFS 172,173) has been associated with antineoplastic effects *in vivo* in several tumour models. Interestingly, recent data have indicated that glycolysis-targeting interventions such as the depletion of PFKFB3 may exert antineoplastic effects as they limit vessel sprouting, de facto operating as angiogenesis inhibitors[174]. Only a few of these approaches have entered clinical development. For instance, TLN-232 (a PKM2-inhibiting peptide) has been evaluated as a stand-alone therapeutic intervention in patients with recurrent melanoma or metastatic renal cell carcinoma (ClinicalTrials.gov identifiers: NCT00735332; NCT00422786). Of note, the activation of PKM2 is another therapeutic approach being evaluated (see below)[175,176]. However, emerging data suggest that at least some tumours do not require PKM2 (REFS 177,178), thus dampening the enthusiasm about the targeting of this enzyme as an anticancer therapeutic strategy.

Dichloroacetate (DCA) is an inexpensive, orally available drug that is used for the treatment of hereditary lactic acidosis[179]. By inhibiting PDK1, which is often hyperactivated in malignant cells as a result of MYC, RTK or HIF1 signalling[180–182], DCA indirectly stimulates the activity of pyruvate dehydrogenase, hence favouring the mitochondrial catabolism of pyruvate at the expense of glycolysis and lactate production[179]. However, it is unclear whether such a metabolic normalization truly accounts for the prominent antineoplastic activity of DCA in murine tumour models[183,184]. Indeed, DCA has also been reported to reactivate a signal transduction cascade that regulates the propensity of cancer cells to undergo mitochondrial apoptosis[183,] and to promote an increase in extracellular pH (as a consequence of reduced lactate secretion)[185], thereby limiting local invasion[186] and the establishment of an immunosuppressive microenvironment[187].

Irrespective of these incognita, preliminary clinical results indicate that DCA is well tolerated by patients with glioblastoma[188]. In addition, a durable complete remission (4 years) has been achieved with DCA in a patient with

Table 1 | **Examples of promising metabolic targets for cancer therapy**

| Targets | Pathways | Agents or approaches (company)* | Development stage | Observations | Refs |
|---|---|---|---|---|---|
| ***Bioenergetic metabolism*** | | | | | |
| CPT1 | β-oxidation | • Etomoxir<br>• Oxfenicine<br>• Perhexiline<br>• RNAi | Perhexiline is approved for use as an anti-angina agent in Asia, Australia and New Zealand | Inhibition of CPT1 exerts anticancer effects *in vitro* and *in vivo*, yet it remains unclear whether these stem from the blockade of β-oxidation | 213–215 |
| Complex I | Mitochondrial respiration | • Metformin<br>• Phenformin | Metformin is prescribed for the treatment of type 2 diabetes | The antineoplastic activity of metformin is independent of glycaemia and may reflect its capacity to inhibit mitochondrial respiration | 23,200 |
| GLUT1 | Glycolysis | • WZB117<br>• RNAi | Preclinical data | Pharmacological or genetic inhibition of GLUT1 exerts antineoplastic effects, both *in vitro* and *in vivo* | 169,170 |
| GLS1 | Glutamine metabolism | • 968<br>• BPTES<br>• RNAi | Preclinical data | Malignant cells expressing mutant IDH1 may be particularly sensitive to GLS1-targeting agents | 205,206 |
| Hexokinases | Glycolysis | • 2-DG<br>• 3-BP<br>• Lonidamine<br>• Methyl jasmonate<br>• RNAi | The clinical development of 2-DG, 3-BP and lonidamine has been discontinued | It remains to be determined whether the anticancer effects of 3-BP and lonidamine stem from the inhibition of hexokinases | 9, 154–157, 161 |
| MCT1 | Krebs cycle | • AR-C155858<br>• AR-C117977<br>• AZD3965 (AstraZeneca)<br>• CHC<br>• RNAi | AZD3965 is in clinical development | AZD3965 is currently being tested in a Phase I clinical trial enrolling patients with advanced solid tumours; these agents may be incompatible with the use of MCT1-transported drugs such as 3-BP | 159,202 |
| PDK1 | Krebs cycle | • DCA | DCA is a prescription drug for the treatment of lactic acidosis | DCA is well tolerated by patients with glioblastoma multiforme and provokes profound mitochondrial defects in cancer cells | 179 |
| PKM2 | Glycolysis | • TLN-232 (Thallion)<br>• RNAi | The clinical development of TLN-232 has been discontinued | Inhibition of PKM2 reverses the Warburg effect (at least in some tumour models), yet it may favour anabolism | 108,166, 286 |
| ***Anabolic metabolism*** | | | | | |
| Choline kinase | Lipid biosynthesis | • CK37<br>• TCD-717 (TCD Pharma)<br>• RNAi | TCD-717 is in clinical development | The safety and therapeutic profile of TCD-717 is currently being tested in patients with advanced solid tumours | 245,246 |
| HMGCR | Mevalonate pathway | • Statins | Statins are prescription drugs that are used to treat hypercholesterolaemia | The antineoplastic potential of statins is being investigated in multiple prospective clinical trials | 16,248 |
| IDHs | Lipid biosynthesis | • AGI-5198 (Xcessbio)<br>• AGI-6780 (Xcessbio)<br>• RNAi | Preclinical data | Inhibition of both wild-type and mutant IDH results in multipronged antineoplastic effects, presumably reflecting a decrease in 2-HG levels as well as an interference with glutamine metabolism | 48,135, 203,204 |
| MGLL | Lipid biosynthesis | • JZL184<br>• RNAi | Preclinical data | MGLL promotes the migration, invasion and survival of malignant cells, as well as *in vivo* tumour growth | 247 |
| PGAM1 | Pentose phosphate pathway | • PGMI-004A<br>• RNAi | Preclinical data | Pharmacological or genetic inhibition of PGAM1 attenuates tumour growth *in vitro* and *in vivo*, presumably owing to the 3PG-mediated inhibition of the pentose phosphate pathway | 222 |
| PHGDH | Anaplerosis | • RNAi | Preclinical data | PHGDH inhibition fails to affect serine availability, yet limits that of multiple intermediates of the Krebs cycle | 229,230 |
| PKM2 | Pentose phosphate pathway | • TEPP-46<br>• SAICAR<br>• Serine | Preclinical data | PKM2 activators reportedly limit the diversion of glucose toward the pentose phosphate pathway, hence mediating antitumour effects | 175,176, 226,227 |

Table 1 (cont.) | **Examples of promising metabolic targets for cancer therapy**

| Targets | Pathways | Agents or approaches (company)* | Development stage | Observations | Refs |
|---|---|---|---|---|---|
| *Other metabolic circuitries* | | | | | |
| HIF1 | Hypoxic responses | • Acriflavine<br>• PX-478 | Preclinical data | Most, if not all, HIF1-targeting agents have failed (or never reached) clinical development | 103 |
| IDO | Tryptophan metabolism | • RNAi | Preclinical data | IDO-derived kynurenine promotes tumour progression via cell-intrinsic and cell-extrinsic mechanisms | 152 |
| mTOR | Cell growth, autophagy | • Rapalogues<br>• Torins | Rapalogues are prescription drugs for the treatment of graft rejection and several tumours | Although mTOR inhibitors may limit tumour growth, they may also favour chemoresistance or neocarcinogenesis | 237,238 |
| PTGS2, AMPK? | Cell growth, autophagy | • Aspirin | Over-the-counter non-steroidal anti-inflammatory drug | Although aspirin has been shown to activate AMPK, its antineoplastic activity appears to stem from on-target effects | 39,41,43 |

2-DG, 2-deoxy-D-glucose; 2-HG, 2-hydroxyglutarate; 3-BP, 3-bromopyruvate; 3PG, 3-phosphoglycerate; 968, 5-[3-bromo-4-(dimethylamino)phenyl]-2,2-dimethyl-2,3,5,6-tetrahydrobenzo[a]; AMPK, 5′-AMP-activated protein kinase; BPTES, bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulphide; CHC, α-cyano-4-hydroxycinnamate; CK37, *N*-(3,5-dimethylphenyl)-2-[[5-(4-ethylphenyl)-1H-1,2,4-triazol-3-yl]sulfanyl] acetamide; CPT1, carnitine *O*-palmitoyltransferase 1; DCA, dichloroacetate; GLS1, glutaminase 1; GLUT1, glucose transporter 1; HIF1, hypoxia-inducible factor 1; HMGCR, 3-hydroxy-3-methyl-glutaryl-CoA reductase; IDH, isocitrate dehydrogenase; IDO, indoleamine-2,3-dioxygenase; JZL184, 4-nitrophenyl-4-[bis(1,3-benzodioxol-5-yl)(hydroxy)methyl]piperidine-1-carboxylate; MCT1, monocarboxylate transporter 1; MGLL, monoglyceride lipase; mTOR, mammalian target of rapamycin; TEPP-46, 6-[(3-aminophenyl) methyl]-4,6-dihydro-4-methyl-2-(methylsulfinyl)-5h-thieno[2′,3′:4,5]pyrrolo[2,3-d]pyridazin-5-one; PDK1, pyruvate dehydrogenase kinase 1; PGAM1, phosphoglycerate mutase 1; PGMI-004A, PGAM1 inhibitor 004A; PHGDH, phosphoglycerate dehydrogenase; PKM2, pyruvate kinase M2 (muscle) isoform; PTGS2, prostaglandin-endoperoxide synthase 2 (also known as COX2); PX-478, S-2-amino-3-[4′-*N*,*N*,-bis(2-chloroethyl)amino]phenyl propionic acid N-oxide dihydrochloride; RNAi, RNA interference; SAICAR, succinyl aminoimidazole carboxamide ribose-5′-phosphate; TLN-232, D-Phe-Cys-D-Trp-Lys-Cys-Thr-$NH_2$.
*Where company name is not indicated, this is not applicable, the agent is an academic compound or it is a generic drug. See also Supplementary information S1 (table).

non-Hodgkin's lymphoma who relapsed following conventional chemotherapy[189], prompting the initiation of further clinical studies. Other regulators of extracellular pH, such as the $Na^+/H^+$ exchanger 1 (NHE1; also known as SLC9A1)-targeting agent cariporide and several inhibitors of carbonic anhydrase (for example, acetazolamide and indisulam), have been shown to exert antineoplastic effects in murine tumour models[190]. The therapeutic profile of indisulam, which also acts as a cell cycle inhibitor, has been extensively investigated in cohorts of cancer patients, including individuals with head and neck cancer[191], melanoma[192] and non-small-cell lung carcinoma[193], but with relatively disappointing results. Only one clinical trial is currently investigating the antineoplastic profile of indisulam in patients with cancer (ClinicalTrials.gov identifier: NCT01692197), which indicates that the interest of clinicians in this sulphonamide derivative has generally decreased.

Neoplastic cells exhibit alterations in mitochondrial bioenergetics that were initially proposed to be the prime aetiological determinants of the Warburg effect[194]. Although such a direct cause–effect relationship now appears to be a simplistic interpretation, mutations in mitochondrial DNA can indeed accumulate during the course of oncogenesis and tumour progression, resulting in partial defects in oxidative phosphorylation[194]. Notably, such defects have a role in the initiation or maintenance of the malignant state, at least in some settings, presumably as they are accompanied by the overproduction of ROS[195,196]. Irrespective of these partial defects, cancer cells produce a considerable amount of ATP via oxidative phosphorylation[194], which allows them to divert glycolytic intermediates towards anabolic reactions, rather than using them as a source of energy[54,86]. In these conditions, the anaplerotic replenishment of Krebs cycle intermediates may provide building blocks for anabolic metabolism or constitute a source of reducing equivalents for oxidative phosphorylation[148,149,151]. Glutamine is an abundant amino acid that is well suited for these purposes, perhaps explaining the state of profound glutamine addiction exhibited by the vast majority of cancer cell lines[197,198]. The oxidation of fatty acids, which generates acetyl-CoA as well as reducing equivalents in the form of NADH and $FADH_2$, can also provide cancer cells with fuel for oxidative phosphorylation or support anabolic metabolism, at least under some circumstances[32].

Both the Krebs cycle and mitochondrial respiration have been proposed as targets for the development of novel anticancer drugs[199]. In line with this notion, several agents have been shown to mediate anticancer effects as they inhibit mitochondrial metabolism. These drugs include metformin (see above), whose antineoplastic potential is currently being assessed in dozens of cohorts of patients with breast, pancreatic and prostate cancer (source: ClinicalTrials.gov). Metformin interferes with mitochondrial complex I, and this may constitute the mechanism through which it activates AMPK[200]. The inhibition of mitochondrial respiration by metformin might contribute to its antineoplastic activity. Indeed, the ability of this antidiabetic agent to reduce cancer-related morbidity and mortality[14,15] appears to be unrelated to the pharmacological effects of metformin on glycaemia[24], which are mediated (for the most part) by the AMPK-dependent and -independent inhibition of hepatic gluconeogenesis[23,201].

Carbonic anhydrase
One of several zinc-containing enzymes that catalyses the reversible conversion of carbon dioxide and water into carbonic acid ($H_2CO_3$), which — in physiological conditions — rapidly dissociates into $H^+$ and $HCO_3^-$, thus exerting a major pH-regulatory function.

The blockade of lactate import via MCT1 (a major transporter that takes up extracellular lactate; see above) has been shown to induce tumour cell death *in vivo* under hypoxic conditions[202]. However, such an approach may be incompatible with the use of 3-bromopyruvate, as MCT1 is required for the uptake of this agent by cancer cells[159]. The genetic or pharmacological inhibition of wild-type IDH1, mutant IDH1 or mutant IDH2 exerts antineoplastic effects in preclinical models[48,135,203,204]. However, it remains to be clarified whether this activity only originates from a reduction in the intracellular levels of 2-HG or whether it also involves the reversal of other functions of wild-type or mutant IDH. In line with the notion that malignant cells rely on glutamine for survival and proliferation[197,198], GLS1-targeting agents have been shown to selectively inhibit the oncogenic transformation of murine fibroblasts as induced by GTPases of the RHO family, and to arrest the growth of human breast carcinoma, B lymphoma cells and *IDH1*$^{R132H}$-expressing glioma cells[205,206].

Moreover, RNA interference (RNAi)-mediated depletion as well as chemical inhibition of glutamate dehydrogenase 1 (GLUD1) converts the glutamine addiction of cultured glioblastoma cells into glucose dependence[207], and this adaptation appears to rely on the activity of pyruvate carboxylase[208]. Vice versa, by inhibiting glucose catabolism, metformin can exacerbate the dependence of prostate cancer cells on glutamine[28]. The antineoplastic potential of phenylacetate and its precursor phenylbutyrate, which lower circulating levels of glutamine and are used for the treatment of hyperammonaemia[209], has been explored in paediatric patients with neurological cancers[210] as well as in individuals with advanced solid tumours[211,212]. Nonetheless, the clinical development of phenylacetate and phenylbutyrate as antineoplastic agents has stalled. Conversely, AZD3965 (a chemical inhibitor of MCT1) is currently being tested in patients with advanced neoplasms (ClinicalTrials.gov identifier: NCT01791595).

Although fatty acids constitute a prominent source of anabolic substrates and reducing equivalents, relatively little attention — with a few exceptions — has been given to the possibility that inhibitors of fatty acid oxidation may exert antineoplastic effects. The carnitine *O*-palmitoyltransferase 1 (CPT1)-targeting agent etomoxir, which inhibits the mitochondrial import of fatty acids mediated by the carnitine shuttle, decreases intracellular ATP levels as well as the viability and resistance to chemotherapy of glioblastoma and acute myeloid leukaemia cells[213,214]. In line with this notion, CPT1C-depleted cancer cells exhibit increased sensitivity to hypoxia and glucose deprivation as well as a limited tumorigenic potential *in vivo*[215]. Unfortunately, the clinical development of etomoxir has been terminated because of severe hepatotoxicity associated with therapy[216]. To our knowledge, the antineoplastic potential of alternative CPT1 inhibitors such as oxfenicine and perhexiline (which is currently approved in Asia, Australia and New Zealand as an anti-angina drug) has not yet been investigated.

Trimetazidine (Vastarel; Servier) and ranolazine (Ranexa; Gilead Sciences), which are currently approved for use in patients as anti-angina medications, target the α-subunit of the trifunctional protein HADHA (hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase) and hence inhibit fatty acid oxidation at the mitochondrial level[217]. A few reports suggest that these compounds may synergize with other metabolic modulators as well as with BCL-2 and BCL-$X_L$ antagonists in the killing of cultured cancer cells[214,218]. However, the literature on the cancer-modulatory effects of these agents is scarce, and ranolazine has been suggested to accelerate — rather than inhibit — intestinal oncogenesis in *Apc*$^{min/+}$ mice[219]. Thus, the actual antineoplastic potential of HADHA inhibitors remains unexplored. Importantly, as the inhibition of CPT1 and HADHA considerably impairs NADPH production, hence facilitating the accumulation of ROS[213], it remains to be determined whether the potential antineoplastic effects of etomoxir and other CPT1 inhibitors truly reflect the bioenergetic consequences of a blockade in fatty acid oxidation.

***Targeting anabolic metabolism.*** Rapidly proliferating cells, be they normal or malignant, must continuously generate new biomass. To cope with this need, the anabolic metabolism of cancer cells is coordinately boosted to increase the output from lipid, protein and nucleotide biosynthesis pathways[5].

A high metabolic flux through the PPP is instrumental to neoplastic cells as it generates ribose-5-phosphate (a precursor for the synthesis of purines and pyrimidines) and NADPH. NADPH is required for the synthesis of lipids and nucleotides, and also has a key antioxidant function[5]. The ectopic overexpression of G6PD suffices to transform murine NIH-3T3 fibroblasts[220], and the RNAi-mediated depletion of transketolase-like protein 1 (TKTL1) — one of the enzymes that mediates the cross-talk between glycolysis and the PPP — limits the proliferation of malignant cells *in vitro* and *in vivo*[221]. Along similar lines, the pharmacological or genetic inhibition of phosphoglycerate mutase 1 (PGAM1) reduces tumour growth *in vitro* and *in vivo*, perhaps owing (at least in part) to the G6PD-inhibitory effects of 3-phosphoglycerate[222]. That said, genetic defects that have an impact on the enzymatic activity of G6PD are common among individuals living in geographical areas with a history of endemic malaria[223]. However, these genetic defects do not appear to influence the risk of the development of various tumours in these populations[224,225].

Activators of PKM2, promoting the glycolytic flux at the expense of the PPP, have also been shown to limit tumour growth in xenograft models[175,176]. Importantly, both serine and succinyl aminoimidazole carboxamide ribose-5′-phosphate (SAICAR; a precursor of purines generated by the PPP) appear to operate as endogenous activators of PKM2 (REFS 226,227), thus limiting the diversion of glycolytic intermediates towards anabolic reactions when the latter are not strictly required[226,228]. The gene encoding phosphoglycerate dehydrogenase (PHGDH), the enzyme that catalyses the first reaction in the multistep conversion of 3-phoshoglycerate into serine, is amplified in a percentage of human breast carcinomas and melanomas[229,230]. Malignant cells with

Glutamate dehydrogenase 1
(GLUD1). A mitochondrial enzyme that catalyses the essentially irreversible conversion of α-ketoglutarate into glutamate and ammonia. The reverse (anaplerotic) reaction is highly unfavoured in mammals owing to the very low affinity of GLUD1 for ammonia.

Carnitine shuttle
A multi-enzymatic system that relies on carnitine as a recyclable vehicle for the import of cytosolic fatty acids into the mitochondrial matrix.

*Apc*$^{min/+}$ mice
Mice harbouring a heterozygous mutation that results in the expression of a truncated form of adenomatosis polyposis coli (APC). Owing to this alteration, *Apc*$^{min/+}$ mice can develop up to 100 polyps in the small intestine as well as colorectal tumours.

*PHGDH* amplifications are sensitive to the depletion of the enzyme, which suggests that this enzyme critically contributes to the progression of some neoplasms[229,230]. Still, the mechanisms whereby PHGDH exerts oncogenic effects remain unclear. One possibility is that the increased availability of serine may favour the anaplerotic conversion of glutamate into α-KG[230]. Irrespective of this unresolved issue, PHGDH is a potential target for the development of novel anticancer drugs. Of note, the selectivity of PPP-targeting agents for neoplastic cells may not be optimal, as highly proliferating cells of all types are expected to have an increased anabolic demand[9]. Whether a therapeutic window for the clinical application of these compounds exists or not remains to be determined.

Amino acid deprivation is sensed by mTOR and generally results in a proliferative arrest that is coupled to the inhibition of protein translation and the activation of autophagy[228]. Malignant cells of different origins have been suggested to be auxotrophic for non-essential amino acids other than glutamine, including asparagine[231], arginine[232] and possibly glycine[233] and serine[90,230]. A bacterial variant of L-asparaginase (which reduces the availability of circulating asparagine) was approved by the FDA for the treatment of acute lymphoblastic leukaemia in 1978 (REF. 234), but it still remains unclear whether the antineoplastic effects of L-asparaginase stem from the reduced availability of asparagine (as opposed to glutamine)[9].

The therapeutic potential of a pegylated variant of arginine deiminase (which converts circulating L-arginine into L-citrulline) is currently being investigated in clinical trials, with promising preliminary results[235,236]. In particular, the systemic administration of pegylated arginine deiminase was shown to be well tolerated and to promote disease stabilization in a fraction of patients with melanoma and hepatocellular carcinoma[235,236]. Pharmacological inhibitors of mTOR have also been investigated as a means to arrest the proliferation of malignant cells[237]. Two of these agents, everolimus (Afinitor; Novartis) and temsirolimus (Torisel; Wyeth/Pfizer), were originally licensed by the FDA for the prevention of allograft rejection, but their clinical use has now been extended to several oncological indications[238]. Concurrently, clinical trials testing the antineoplastic potential of everolimus, temsirolimus and other rapalogues (such as ridaforolimus) continue to be initiated at an elevated pace (source: ClinicalTrials.gov). Nonetheless, the therapeutic benefits provided by mTOR inhibitors may be limited by the intrinsic ability of these compounds to stimulate autophagy and hence render established tumours more resistant to therapy-elicited and metabolic stress[6,239].

The metabolic circuitries underpinning nucleic acid synthesis were recognized long ago as attractive targets for the development of anticancer drugs. Thus, inhibitors of folate metabolism (for example, methotrexate and pemetrexed), thymidine synthesis (for example, 5-fluorouracil), deoxynucleotide synthesis (for example, hydroxyurea) and nucleic acid elongation (for example, gemcitabine and fludarabine), which are collectively referred to as antimetabolites, are all part of standard chemotherapeutic regimens against many human neoplasms[11]. All of these agents are associated with some toxicity, which mainly affects highly proliferating tissues such as the bone marrow and intestinal epithelium. This well-known toxicological profile further substantiates the similarity between the metabolism of malignant cells and that of rapidly proliferating but normal cells. However, the clinical success of these compounds points to the existence of a therapeutic window through which metabolic inhibitors can be successfully used as antineoplastic agents, at least in some cases.

As high proliferation rates entail a considerable demand for the generation of novel phospholipid bilayers, targeting *de novo* lipogenesis or steroidogenesis also represents a rational approach for anticancer therapy[240]. Several enzymes involved in these molecular circuitries, including fatty acid synthase (FASN)[241,242], ACLY[243], ACCs[244], choline kinase[245,246], monoglyceride lipase (MGLL)[247] and HMGCR[248], have been ascribed critical roles in oncogenesis or tumour progression *in vivo*. Nonetheless, the use of lipogenesis inhibitors as anticancer agents has not been tested in clinical settings, although some of these inhibitors, such as orlistat (Xenical/Alli; Roche/GlaxoSmithKline), are currently approved for the treatment of obesity[249]. Conversely, the antineoplastic potential of several HMGCR inhibitors of the statin family is being intensively investigated in preclinical settings[30,250] and in prospective clinical trials, reflecting the interest in statins generated by the results of multiple retrospective studies (see above)[16,17]. Although statins have failed to exert objective anticancer effects in the prospective clinical trials concluded to date, it remains possible that these studies were not conducted on the patient subset (or subsets) that are most likely to obtain a clinical benefit from HMGCR inhibitors.

***Targeting other metabolic pathways.*** Additional pathways that are involved in the adaptation to metabolic stress may harbour drug targets for anticancer therapy. This applies to NAD metabolism, HIF1-orchestrated responses and autophagy. FK866, a specific non-competitive inhibitor of nicotinamide phosphoribosyltransferase (NAMPT), has been shown to exert antineoplastic effects in murine tumour models, both as a stand-alone agent and in combination with the poly(ADP-ribose) polymerase inhibitor olaparib[251,252]. However, the clinical development of FK866 has been hampered by dose-limiting thrombocytopenia, which was first documented in a cohort of patients with advanced solid malignancies who were treated with escalating doses of FK866 as a continuous, 96-hour infusion every 28 days[253].

Similarly, several HIF1 inhibitors such as acriflavine or PX-478 have generated promising results as investigational agents, yet never entered clinical development or (in the case of PX-478) were unexpectedly discontinued for undisclosed reasons, despite showing promising results in a Phase I study[103,254]. Finally, the pharmacological or genetic inhibition of autophagy may exacerbate the response of established neoplasms not only to

Auxotrophic
The state of cells or organisms that are unable to synthesize a metabolite that is strictly required for their own survival or growth.

Rapalogue
Any of several chemical agents that resemble rapamycin in its capacity to inhibit the enzymatic activity of mammalian target of rapamycin.

Antimetabolites
Any of several antineoplastic drugs that operate, at least in part, by inhibiting the metabolism of nucleic acids. Several antimetabolites are currently approved for use in patients with cancer.

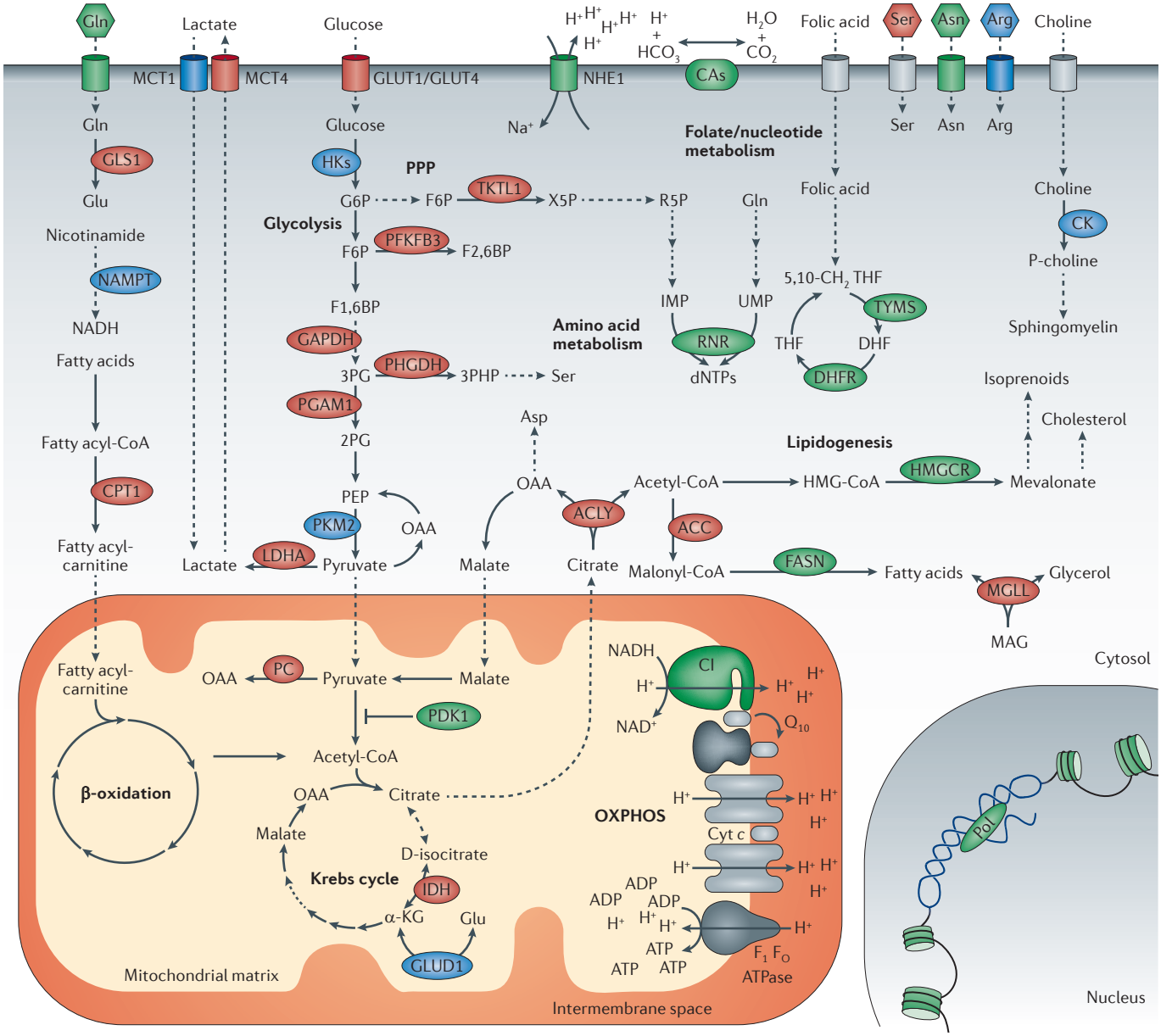



Figure 2 | **Metabolic targets for cancer therapy.** Several branches of the bioenergetic and anabolic metabolism of malignant cells offer targets that can be drugged to inhibit oncogenesis or tumour progression. Although interfering with the metabolism of cancer cells is also expected to affect highly proliferating normal cells, this notion is substantiated by a large amount of preclinical evidence (targets shown in red), which in some instances has prompted the initiation of prospective clinical studies (targets shown in blue), as well as by an increasing degree of clinical experience (targets shown in green). For illustrative purposes, only prominent metabolic conversions are depicted. An exhaustive list of metabolic targets for cancer therapy can be found in Supplementary information S1 (table). 2PG, 2-phosphoglycerate; 3PG, 3-phosphoglycerate; 3PHP, 3-phosphohydroxypyruvate; 5,10-$CH_2$-THF, 5,10-methylene tetrahydrofolate; α-KG, α-ketoglutarate; ACC, acetyl-CoA carboxylase; ACLY, ATP citrate lyase; CA, carbonic anhydrase; CI, complex I; CK, choline kinase; CPT1, carnitine *O*-palmitoyltransferase 1; Cyt *c*, cytochrome *c*; DHF, dihydrofolate; DHFR, DHF reductase; dNTP, deoxynucleotide triphosphate; F1,6BP, fructose-1,6-bisphosphate; F2,6BP, fructose-2,6-bisphosphate; F6P, fructose-6-phosphate; FASN, fatty acid synthase; G6P, glucose-6-phosphate; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GLS1, glutaminase 1; GLUD1, glutamate dehydrogenase 1; GLUT, glucose transporter; HK, hexokinase; HMG-CoA, 3-hydroxy-3-methyl-glutaryl coenzyme A; HMGCR, HMG-CoA reductase; IDH, isocitrate dehydrogenase; IMP, inosine monophosphate; LDHA, lactate dehydrogenase A; MAG, monoacylglycerol; MCT, monocarboxylate transporter; MGLL, monoglyceride lipase; NAMPT, nicotinamide phosphoribosyltransferase; NHE1, $Na^+/H^+$ exchanger 1; OAA, oxaloacetate; OXPHOS, oxidative phosphorylation; PC, pyruvate carboxylase; PDK1, pyruvate dehydrogenase kinase 1; PEP, phospho-enolpyruvate; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PGAM1, phosphoglycerate mutase 1; PHGDH, phosphoglycerate dehydrogenase; PKM2, pyruvate kinase, muscle, M2 isoform; Pol, DNA polymerase; PPP, pentose phosphate pathway; $Q_{10}$, coenzyme $Q_{10}$; R5P, ribose-5-phosphate; RNR, ribonucleotide reductase; THF, tetrahydrofolate; TKTL1, transketolase-like protein 1; TYMS, thymidylate synthase; UMP, uridine monophosphate; X5P, xylulose 5-phosphate.

chemo- and radiotherapy[6] but also to specific dietary restrictions[255]. That said, autophagy sometimes promotes — rather than inhibits — the death of malignant cells exposed to chemotherapy[256], and it is currently viewed as a major mechanism of oncosuppression, which is presumably linked to its crucial role in the maintenance of intracellular homeostasis[6,257] or in the elicitation of anticancer immune responses[258]. Thus, autophagy inhibitors may limit — rather than increase — the beneficial effects of chemotherapy, at least in some scenarios, and/or stimulate neo-oncogenesis[6].

## Concluding remarks

As discussed above, the extensive metabolic rewiring of malignant cells offers a large number of potential drug targets (FIG. 2). Multiple agents targeting metabolic enzymes have been used in the clinic for decades, and several others are currently being developed.Thus, even if the use of metabolic modulators is complicated by the similarities between the metabolism of malignant cells and that of highly proliferating normal cells, a therapeutic window may exist for harnessing the antineoplastic activity of these agents in clinical settings[9].

So far, considerable efforts have been focused on combining metabolic modulators with conventional therapies or targeted anticancer agents, reflecting the common view that signal transduction and metabolism are largely independent — if not entirely separate — entities[259]. Simultaneously targeting oncogene and non-oncogene addiction, which often manifests at the level of metabolism or stress responses[260,261], is also a promising approach. In this context, it is tempting to speculate that attacking the metabolic alterations of cancer cells at distinct nodes may bring about consistent benefits to patients with cancer. This hypothesis is strongly supported by the observations that malignant cells display elevated sensitivity to the concomitant deprivation of glutamine and inhibition of pyruvate carboxylase[208] as well as to the simultaneous depletion of glucose and blockade of GLUD1 (REF. 207), but they are generally not sensitive to any of these interventions alone.

Future studies will need to elucidate the extent to which the metabolic functions of oncogenic and oncosuppressive systems contribute to their biological activity. FH and SDH appear to mediate oncosuppressive functions mainly as they ensure a normal metabolic flux through the Krebs cycle, thus preventing the accumulation of oncometabolites such as succinate and fumarate[128]. Along similar lines, p53 has recently been shown to prevent tumorigenesis even in the presence of mutations that abolish its capacity to trigger cell cycle arrest, cell senescence and apoptosis[262]. Thus, although in some settings the oncosuppressive functions of p53 may impinge on a cell-extrinsic mechanism involving innate immunity[263], the metabolic functions of oncogenes and oncosuppressor genes may modulate tumorigenesis in ways that are not yet completely understood. Further insights into this aspect of cancer cell biology are expected to boost the development of a novel generation of increasingly more selective and efficient antineoplastic agents.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### Competing interests statement
The authors declare no competing financial interests.

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