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DRUG DISCOVERY

Metabolic targets for cancer therapy

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Malignant cells exhibit metabolic changes when compared to their normal counterparts, owing to both genetic and epigenetic causes. Many of these alterations are in place to support intensive cell proliferation, which implies that the metabolic profile of cancer cells resembles that of non-transformed, rapidly dividing cells. Recent evidence also suggests that the metabolic rewiring of each neoplasm is specific and supports all facets of malignant transformation, rather than constituting yet another general hallmark of cancer. During the past decade, the metabolic circuitries of cancer cells have been characterized with increasing precision, and the therapeutic potential of strategies to target these pathways has been intensively investigated. Moreover, several conventional chemotherapeutics operate as de facto metabolic inhibitors, which suggests that a therapeutic window for approaches that target cancer cell metabolism can exist. A number of novel metabolic inhibitors are about to enter clinical trials for cancer therapy. Such a strategy has the potential to convert a central aspect of tumour biology into the Achilles heel of malignant cells.

Facts on oncometabolism

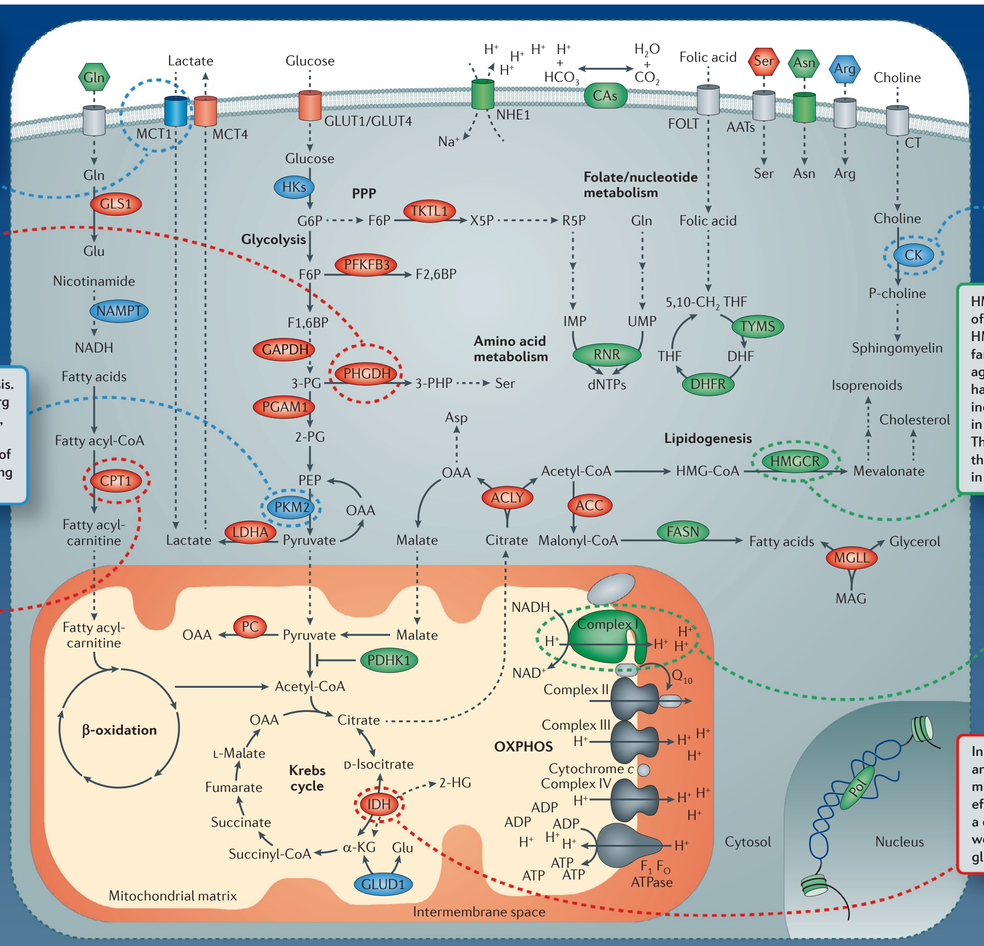
- The metabolism of cancer cells is rewired to allow for malignant transformation. Oncogenesis and tumour progression are accompanied by alterations of bioenergetic as well as anabolic processes that are finely tuned to adapt to changing environmental conditions.
- Signal transduction and metabolism are closely interlinked. Multiple metabolites and metabolic by-products such as ATP, acetyl-CoA, α-KG and ROS, as well as enzymes with key roles in metabolism, such as cytochrome c and AIFM1, can participate in signal transduction.
- A wide panel of cancer cell-intrinsic factors (such as oncogenic drivers and tissue type) and cell-extrinsic factors (such as oxygen availability, pH and vascularization) influence the metabolic profile of a developing neoplasm.
- Tumours contain large numbers of non-transformed stromal, endothelial and immune cells, which respond to signals from neoplastic cells to support oncogenesis and disease progression, establishing heterologous metabolic circuitries. For instance, lactate and ketones secreted by fibroblasts through MCT4 can be taken up by cancer cells (through MCT1) and fuel oxidative phosphorylation. Such metabolic circuitries may offer targets for the development of novel anticancer agents.

MCT1 is required for the uptake of extracellular lactate. It is targeted by AZD3965, which is currently being tested in a Phase I clinical trial in patients with advanced solid tumours. Agents targeting MCT1 may be incompatible with drugs that enter the cell via MCT1.

PHDGH mediates a major role in the anaplerotic replenishment of Krebs cycle intermediates. PHDGH inhibition fails to affect serine availability, yet limits the abundance of multiple inter-mediates of the Krebs cycle.

PKM2 catalyses the last step of glycolysis. Inhibition of PKM2 reverses the Warburg effect (at least in some tumour models), yet it may favour anabolism. PKM2 activators reportedly limit the diversion of glucose towards the PPP, hence mediating antitumour effects.

CPT1 is involved in the mitochondrial import of fatty acids, and is hence required for β-oxidation. Inhibition of CPT1 exerts anticancer effects *in vitro* and *in vivo*, yet it remains unclear whether these indeed stem from the blockade of β-oxidation.



CK is a critical enzyme for the synthesis of phospholipids. The safety and therapeutic profile of the CK inhibitor TCD-717 are currently being tested in patients with advanced solid tumours.

HMGCR is the rate-limiting enzyme of the mevalonate pathway. HMGCR inhibitors of the statin family, which are routinely used against hypercholesterolaemia, have been shown to limit the incidence of several tumours in retrospective clinical trials. The actual therapeutic potential of these agents is under investigation in prospective studies.

Complex I is the first multi-subunit component of the mitochondrial respiratory chain. It is targeted by metformin, which has been found to exert antineoplastic activity.

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.

Metabolic modulators with antineoplastic effects

Several chemotherapeutics de facto operate as metabolic inhibitors. These chemicals, which are collectively referred to as 'antimetabolites', include (but are not limited to) inhibitors of: folate metabolism, such as methotrexate and pemetrexed; thymidine synthesis, such as 5-fluorouracil; deoxynucleotide synthesis, such as hydroxyurea; and nucleic acid elongation, such as gemcitabine and fludarabine. Many of these agents are also used for the treatment of non-malignant conditions characterized by cellular hyperproliferation, including psoriasis, rheumatoid arthritis and myeloproliferative disorders such as polycythaemia vera, essential thrombocytosis and systemic mastocytosis. Various drugs originally developed for the treatment of metabolic conditions, such as dichloroacetate, metformin and statins, can also exert antineoplastic effects, possibly as a result of the normalization of tumour-specific metabolic alterations. Of note, regular intake of the non-steroidal anti-inflammatory drug aspirin, which has recently been suggested to operate as a metabolic modulator, limits the incidence of some forms of cancer, notably colorectal carcinoma. However, this is thought to be mediated via on-target effects on cyclooxygenase 2, and therefore not to constitute a direct metabolic effect.

Metabolic targets for cancer therapy

Pathway	Target(s)	Agent(s)	Phase of development for oncological indications
Anaplerosis	PHGDH	RNAi	Preclinical
Arginine metabolism	Arginine	Arginine deiminase	Phase I–III
β-oxidation	CPT1	Etomoxir, oxfenicine, perhexiline*, RNAi	Preclinical
Glutamine metabolism	GLS1	968, BPTES, RNAi	Preclinical
	GLUD1	EGCG, RNAi	EGCG is in Phase II–III; RNAi is preclinical
Glycolysis	GLUT1	WZB117, RNAi	Preclinical
	HKs	2-DG, 3-BP, lonidamine, methyl jasmonate, RNAi	Clinical development of 2-DG, 3-BP and lonidamine has been discontinued; the other agents are preclinical
	MCT4	*CD44* RNAi, *CD147* RNAi	Preclinical
Krebs cycle	MCT1	AR-C155858, AR-C117977, AZD3965, CHC, RNAi	AZD3965 is in Phase I; the other agents are preclinical
	PDHK1	DCA‡	Phase I–II
Lipid biosynthesis	CK	CK37, TCD-717, RNAi	TCD-717 is in Phase I; the other agents are preclinical
	IDHs	AGI-5198, AGI-6780, RNAi	Preclinical
	MGLL	JZL184, RNAi	Preclinical
Mevalonate pathway	HMGCR	Statins§	Phase 0–III
Mitochondrial respiration	Complex I	Metformin, phenformin‖	Phase 0–II
PPP	PGAM1	PGMI-004A, RNAi	Preclinical
	PKM2	TEPP-46, SAICAR, serine, TLN-232, RNAi	Clinical development of TLN-232 has been discontinued; the other agents are preclinical

*Approved for use as antianginal agent in Asia, Australia and New Zealand. ‡Approved for the treatment of lactic acidosis. §Approved for hypercholesterolaemia. ‖Approved for the treatment of type 2 diabetes.

Metabolic targets in cancer cells

Figure | Cancer cells tend to catabolize glucose via glycolysis rather than through mitochondrial respiration in spite of normal levels of oxygen (aerobic glycolysis), resulting in the abundant secretion of lactate. This is known as the Warburg effect. They also have an increased flux through the PPP, intense rates of lipid biosynthesis, an abnormally high consumption of glutamine, a strict control of redox homeostasis and (at least in the initial steps of oncogenesis) a limited propensity to activate macroautophagy. Moreover, in some cases, oncogenesis can be driven by the accumulation of specific metabolic intermediates (known as 'oncometabolites'), including fumarate, succinate and 2-HG, which is produced by mutant (not wild-type) IDH. Here, the targets of drugs in preclinical development are shown in red, the targets of drugs in clinical studies are shown in blue, and the targets of drugs that are currently used in the clinic are shown in green. For illustrative purposes, only prominent metabolic conversions are depicted.

Milestones

1920 **(1920s)** Otto Warburg proposes that the metabolic phenotype of malignant tissues differs from that of their normal counterparts; he shows that cancer cells use fermentation over respiration regardless of oxygen levels, and that fermentation is associated with increased glucose uptake (Warburg effect)
- (1929) Crabtree shows the variability in the respiration/fermentation ratio of various malignant tissues, casting doubts on whether all tumours display the same metabolic profile
- (1929) Lohmann, Fiske and Subbarow isolate ATP

1930 **(1920s–1930s)** Characterization of the glycolytic pathway

1940 **(1940s)** Demonstration of the anticancer activity of antifolate drugs
- (1941) Lipmann argues that ATP is an important carrier of biological energy

1950 **(1950s)** First clinical tests of 2-DG in cancer patients
- (1955) Eagle defines the first set of nutrient conditions that are required to grow cancer cells in culture
- (1956) Warburg's review in *Science* articulates the hypothesis that oncogenesis is caused by defects in mitochondrial respiration

1960 **(1950s–1960s)** Complete description of central carbon metabolism. Demonstration that many cancer cells retain functional mitochondria, questioning the 1956 Warburg hypothesis
- (1961) Mitchell proposes the chemiosmotic theory to explain mitochondrial respiration

1970 **(1970s)** Development of ^{18}F-FDG as a metabolic tracer, leading to the wide-spread use of FDG–PET as a clinical tool

1980 **(1960s–1980s)** Use of antifolates and 5-FU in the clinic, demonstrating that metabolic inhibitors can contribute to the cure of some patients with cancer

1990 **(1990s)** Demonstration that mitochondria control intrinsic apoptosis, which can be deregulated in cancer

2000 **(2000s)** First demonstration that specific metabolic enzymes (such as SDH and FH) can be tumour suppressors
- (2008–2009) Establishment of a link between gain-of-function mutations in IDH, the consequent accumulation of 2-HG and tumorigenesis

(1990s–2000s) Establishment of direct links between primary oncogenic events (such as the activation of oncogenes like *RAS* and the loss of tumour suppressor genes like *VHL*) and specific metabolic alterations (for example, increased glutamine uptake, the Warburg effect, and the activation of a HIF1-dependent pseudohypoxic state)

2010 **(2010s)** Development and preclinical characterization of novel metabolic inhibitors for cancer therapy. First modern clinical trials testing some of these agents in patients with cancer

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Abbreviations
^{18}F-FDG, ^{18}F-fluorodeoxyglucose; 2-DG, 2-deoxy-D-glucose; 2-HG, R(−)-2-hydroxyglutarate; 2-PG, 2-phosphoglycerate; 3-BP, 3-bromopyruvate; 3-PG, 3-phosphoglycerate; 3-PHP, 3-phosphohydroxypyruvate; 5,10-CH$_2$-THF, 5,10-methylene THF; 5-FU, 5-fluorouracil; 968, 5-[3-bromo-4-(dimethylamino)phenyl]-2,2-dimethyl-2,3,5,6-tetrahydrobenzo[a]; α-KG, α-ketoglutarate; AAT, amino acid transporter; ACC, acetyl-CoA carboxylase; ACLY, ATP citrate lyase; AIFM1, apoptosis-inducing factor, mitochondrial-associated 1; BPTES, *bis*-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulphide; CA, carbonic anhydrase; CHC, α-cyano-4-hydroxycinnamate; CK, choline kinase; CK37, *N*-(3,5-dimethylphenyl)-2-[[5-(4-ethylphenyl)-1*H*-1,2,4-triazol-3-yl]sulfanyl] acetamide; CPT1, carnitine *O*-palmitoyltransferase 1; CT, choline transporter; DCA, dichloroacetate; 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; FH, fumarate hydratase; FOLT, folate transporter; G6P, glucose-6-phosphate; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GLS1, glutaminase 1; GLUD1, glutamate dehydrogenase 1; GLUT1, glucose transporter 1; HIF1, hypoxia-inducible factor 1; HK, hexokinase; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; HMGCR, HMG-CoA reductase; IDH, isocitrate dehydrogenase; IMP, inosine monophosphate; JZL184, 4-nitrophenyl-4-[bis(1,3-benzodioxol-5-yl)(hydroxy)-methyl]piperidine-1-carboxylate; 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; PDHK1, pyruvate dehydrogenase kinase 1; PEP, phosphoenolpyruvate; PET, positron emission tomography; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; PGAM1, phosphoglycerate mutase 1; PGMI004A, PGAM1 inhibitor 004A; PHGDH, phosphoglycerate dehydrogenase; PKM2, pyruvate kinase (muscle) M2 isoform; Pol, DNA polymerase; PPP, pentose phosphate pathway; Q_{10}, co-enzyme Q_{10}; R5P, ribose-5-phosphate; RNAi, RNA interference; RNR, ribonucleotide reductase; SAICAR, succinyl aminoimidazole carboxamide ribose-5′-phosphate; SDH, succinate dehydrogenase; TEPP-46, 6-[(3-aminophenyl)methyl]-4,6-dihydro-4-methyl-2-(methylsulfinyl)-5*H*-thieno[2′,3′:4,5] pyrrolo[2,3-*d*]pyridazin-5-one; THF, tetrahydrofolate; TKTL1, transketolase-like protein 1; TLN-232, D-Phe-Cys-D-Trp-Lys-Cys-Thr-NH$_2$; TYMS, thymidylate synthase; UMP, uridine monophosphate; VHL, Von Hippel–Lindau protein; X5P, xylulose-5-phosphate.

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Further reading
1. *Nat. Rev. Drug Discov.* **12**, 829–846 (2013).
2. *Nat. Rev. Cancer* **13**, 227–232 (2013).
3. *Nat. Rev. Cancer* **12**, 401–410 (2012).
4. *Nat. Rev. Cancer* **12**, 685–698 (2012).
5. *Nature* **491**, 364–373 (2012).
6. *Cell* **149**, 274–293 (2012).
7. *Nat. Rev. Mol. Cell Biol.* **13**, 225–238 (2012).
8. *Nat. Rev. Cancer* **11**, 393–410 (2011).
9. *Nat. Rev. Drug Discov.* **10**, 671–684 (2011).
10. *Cell Metab.* **14**, 443–451 (2011).
11. *Cell* **144**, 646–674 (2011).
12. *Nat. Rev. Cancer* **11**, 85–95 (2011).
13. *Nat. Rev. Cancer* **10**, 267–277 (2010).
14. *Science* **330**, 1340–1344 (2010).
15. *Cell* **136**, 823–837 (2009).