Published in final edited form as:

Trends Cancer. 2016 July ; 2(7): 365–377. doi:10.1016/j.trecan.2016.06.002.

Oncogene-directed alterations in cancer cell metabolism

Arvindhan Nagarajan¹, Parmanand Malvi¹, and Narendra Wajapeyee^{1,2,*}

¹Department of Pathology, Yale University School of Medicine, New Haven, CT, USA, 06510

²Yale Cancer Center, Yale University School of Medicine, New Haven, CT, USA, 06510

Abstract

Oncogenes are key drivers of tumor growth. Although several cancer-driving mechanisms have been identified, the role of oncogenes in shaping metabolic patterns in cancer cells is only beginning to be appreciated. Recent studies show that oncogenes directly regulate critical metabolic enzymes and metabolic signaling pathways. Here, we present evidence for oncogene-directed cancer metabolic regulation and discuss the importance of identifying underlying mechanisms that can be targeted for developing precision cancer therapies.

Keywords

Oncogene; metabolic pathways; tumor growth; precision cancer therapies

Cancer as a metabolic disease: the role of oncogenes

Altered metabolism is a hallmark of cancer [1, 2]. In almost all solid and hematological malignancies, metabolic pathways involved in energy production or the biosynthesis of carbohydrates, lipids, amino acids, or nucleotides are hijacked to meet the tumor's specific nutritional and growth requirements. These alterations often favor the growth of rapidly dividing cancer cells and inhibit metabolic signaling that prevents tumor initiation or attenuates tumor progression and metastatic dissemination. Thus, cancer can be thought of as a metabolic disease. The drivers of cancer metabolic changes remain unclear, and different models attempt to explain them. For example, changes can be attributed to stochastic events, following a Darwinian selection. According to this model, metabolic alterations occur randomly in cancer cells and are selected based on the growth advantage they confer. An alternative model suggests that metabolic alterations are the result of genetic and epigenetic alterations in cancer cells, with the activation of oncogenes being a prime example. However, both models may operate in conjunction, and many metabolic pathways can be subject to both stochastic and oncogene-driven metabolic alterations. For instance, almost all cancer cells use glucose in aerobic glycolysis to rapidly generate ATP irrespective of oncogenic mutation or the absence thereof. Aerobic glycolysis provides a survival and

*Correspondence: Narendra.Wajapeyee@yale.edu (N. Wajapeyee).

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growth advantage, indicating a tendency towards need-based selection of metabolic alterations independent of tissue or genetic background. This review focuses on the role of oncogenes in rewiring cancer metabolism (Figure 1; Table 1).

MYC

Deregulation of MYC oncogene is common in human cancers [3–5]. The MYC proteins (c-MYC, N-MYC, and L-MYC) are transcription factors that bind to enhancer box (E-box) sequences in gene promoters and can activate or repress transcription, thereby controlling various aspects of cellular transformation and tumor growth [6]. A potential role for MYC in the regulation of cancer metabolism was initially suggested by studies of pediatric advanced neuroblastoma that found an inverse relationship between amplification of N-MYC and catecholamine metabolism [7–9]. However, two decades passed before it was formally shown that MYC regulates key metabolic enzymes, such as thymidine kinase (TK; involved in DNA synthesis) and lactate dehydrogenase A (LDHA; an enzyme of the glycolytic pathway) [10, 11]. Although the functional implications of TK regulation by MYC were not addressed, the studies showed that LDHA is required for MYC-mediated transformation in a variety of cellular systems, including rat fibroblasts, Burkitt lymphoma cells, and human lymphoblastoid cells. This was the first study linking MYC to increased lactate production (a measure of aerobic glycolysis) and its consequences in cell transformation [11]. Subsequent studies identified several other metabolic pathways and enzymes as MYC targets [12–18]. For example, MYC regulates the glutaminolytic pathway in renal cell carcinoma, and targeting glutamine metabolism inhibits tumor growth [18].

In *Drosophila*, increased Myc activity confers a “supercompetitor” status to cells, which enhances cellular fitness and viability [14]. In these cells, the boost in glycolytic flux triggers the elimination of nearby wild type cells in a p53-dependent manner. Consequently, loss of p53 in Myc-expressing cells impairs metabolism and the ability to induce apoptosis in neighboring wild type cells. Although this phenomenon of cell competition was not studied in cancer, a similar mechanism may exist between pre-cancerous and cancerous cells and could potentially contribute to oncogene-directed metabolic changes. In fact, cancer cell metabolism may be regulated, in part, through paracrine or cell-autonomous mechanisms.

MYC can also indirectly regulate metabolism via microRNAs (miRNAs) [15, 16]. For instance, MYC represses the transcription of miR-23a and miR-23b, which results in the activation of mitochondrial glutaminase, upregulated conversion of glutamine to glutamate, and production of glutamate-derived ATP (via the tricarboxylic acid [TCA] cycle) or glutathione. Thus, MYC regulates both energy production and levels of reactive oxygen species in cells.

RAS and BRAF

The Cancer Genome Atlas (TCGA) and other genome-scale sequencing initiatives have revealed that oncogenic mutations in *RAS* genes (*KRAS*, *NRAS*, and *HRAS*) are present in a majority of cancers. More than 90% of pancreatic cancers, 50% of colorectal cancers, and up to 30% of lung cancers harbor *KRAS* mutations. *NRAS* mutations are present in approximately 20% of melanomas [19] and acute lymphoblastic leukemias (ALL) [20] and

in about 10% of acute myeloid leukemias (AML) [21]. *HRAS* mutations are present in about 20% of bladder cancers [22] and 10% of head and neck cancers [23]. In addition, more than 50% of melanoma and thyroid cancers harbor *BRAF* mutations, as does a smaller fraction of colorectal and lung cancers [24]. *RAS* and *BRAF* mutations are mutually exclusive, which highlights the fact that these genes regulate overlapping pathways to initiate and promote cancer. Both oncogenes activate mitogen-activated protein kinase (MAPK) pathways, and *NRAS* activates the phosphoinositide 3-kinase (PI3K) and Ral guanine nucleotide dissociation stimulator (RalGDS) pathways [25]. *RAS* and *BRAF* can also directly regulate metabolic pathways in cancer cells. An early study reported that uptake and interconversion of polyamine spermidine was higher in *RAS*-transformed NIH-3T3 fibroblasts [26]. Subsequent studies showed that *RAS*-transformed cells had significantly higher phosphatidylinositol and phosphatidylinositol-4-phosphate kinase activity, suggesting increased inositol phospholipid metabolism [27–29]. *RAS* was also directly linked to aerobic glycolysis [30]. In pancreatic ductal adenocarcinoma (PDAC), oncogenic *KRAS*^{G12D} controls pancreatic tumor metabolism by stimulating glucose uptake and channeling of glucose intermediates into the hexosamine biosynthesis pathway [31]. This study also showed that *KRAS*^{G12D} drives glycolysis intermediates into the non-oxidative pentose phosphate pathway (PPP), decoupling ribose biogenesis from NADP/NADPH-mediated redox control.

Non-canonical glutamine pathways were also reported in PDAC. Although most cells utilize glutamate dehydrogenase to convert glutamine-derived glutamate into α -ketoglutarate in the mitochondria and fuel the TCA cycle, in PDAC cells glutamine-derived aspartate is transported into the cytoplasm, where it is converted into oxaloacetate by aspartate transaminase. Oxaloacetate is then further converted to malate and subsequently to pyruvate, increasing the NADPH/NADP⁺ ratio to maintain the cellular redox state. This study also showed that aspartate transaminase is directly regulated by *KRAS*. Knockdown of enzymes along these pathways suppressed tumor growth *in vitro* and in mouse models, indicating that glutamine is essential for PDAC progression [32]. *RAS*-transformed cells can also be supplied with amino acids through macropinocytosis [33], a highly conserved process by which extracellular fluid and its contents are taken up into cells through vesicles known as macropinosomes [34]. Inhibiting macropinocytosis impairs the growth of *RAS*-transformed pancreatic xenograft tumors.

BRAF can also regulate glucose and glutamine metabolism [35, 36], as well as other distinct pathways. For example, *BRAF*^{V600E} upregulates the ketogenic enzyme 3-hydroxy-3-methylglutaryl-CoA lyase (HMGCL) in human primary melanoma and hairy cell leukemia cells, and inhibition of HMGCL attenuates cell growth [37]. Acetoacetate, the product of HMGCL, specifically enhances the binding of *BRAF*^{V600E} to MEK1 to promote MEK-ERK signaling [38]. Pyruvate dehydrogenase (PDH) is a mediator of *BRAF*^{V600E}-induced senescence [39], which is accompanied by suppression of pyruvate dehydrogenase kinase 1 (PDK1; PDH-inhibitory enzyme) and induction of pyruvate dehydrogenase phosphatase 2 (PDP2; PDH-activating enzyme). Enforced normalization of either PDK1 or PDP2 blocked PDH and prevented *BRAF*^{V600E}-induced senescence. Interestingly, PDK1 inhibition impaired the growth of melanoma cells resistant to targeted *BRAF*^{V600E} inhibition and caused the regression of established melanoma.

Taken together, these studies suggest that RAS and BRAF regulate different metabolic pathways; however, future studies in cancers that harbor both *RAS* and *BRAF* mutations will be needed to better understand their roles in metabolism.

The role of other oncogenes

A description of the role of oncogenes in regulating cancer metabolism would be incomplete without the mention of isocitrate dehydrogenase 1 and 2 (IDH1, IDH2), which catalyze the oxidation of isocitrate to 2-oxoglutarate. Although IDH1 is localized primarily in the cytoplasm and peroxisomes, IDH2 is localized to the mitochondria. Mutations in *IDH1* and *IDH2* were identified in gliomas [40] and AML [41]. Because all tumors with *IDH1/2* mutations are heterozygous, and *IDH1* and *IDH2* mutations are mutually exclusive, it was initially believed that these mutations inhibited the activity of wild type IDH proteins. However, knockdown of *IDH1* and *IDH2* in glioma cells inhibits tumor growth, ruling out a tumor suppressor-like role [42]. Recent studies indicated that these genes may in fact be proto-oncogenes and also revealed new and surprising neomorphic functions for *IDH1* and *IDH2* mutants. In glioma, *IDH1*^{R132}, *IDH2*^{R172}, and *IDH2*^{R140} mutations lead to the production of 2-hydroxyglutarate, which inhibits the enzymatic function of many α -ketoglutarate-dependent dioxygenases, including histone and DNA demethylases. Thus, widespread changes in histone and DNA methylation caused by *IDH1* and *IDH2* mutations may promote tumorigenesis.

Oncogene-directed biochemical alterations

The impact of oncogene-directed metabolic alterations can be pervasive, and multiple metabolic pathways may be simultaneously altered, even in single cancer types. In this section, we discuss the dysregulation of biochemical pathways that control the production and use of lipids, sugars, and amino acids, and describe how oncogenes modulate enzymes within these pathways. We also briefly discuss other metabolic pathways (Figure 2).

Carbohydrate metabolism

Cancer cells significantly alter their energy metabolism by using glucose and glutamine as the main energy sources and diverting other amino acids and lipids into biosynthetic processes [43]. A well-documented yet poorly understood metabolic alteration is the *Warburg effect*: the observation that cancer cells have increased glycolysis and lactate production, even in the presence of oxygen [44, 45]. Increased lactate production creates an acidic microenvironment around cancer cells that facilitates extracellular matrix remodeling [46], tumor invasion [47, 48], angiogenesis [49], and immune evasion [50]. Furthermore, diverting pyruvate into lactate decreases mitochondrial oxidation of pyruvate, leading to a decrease in mitochondrial activity, which may increase stemness and decrease differentiation [51]. Glycolysis, the major contributor of energy in cancer cells, generates ATP, NADH, and pyruvate, which feed into the TCA cycle. The major regulatory nodes in the glycolytic pathway are glucose transporter 1 (GLUT1), hexokinase 2, LDHA, pyruvate dehydrogenase, and phosphofructokinase [52]. Oncogene-directed activation of glycolysis occurs primarily through hypoxia-inducible factor 1 α (HIF-1 α), which induces the expression of several enzymes in the glycolysis pathway [53]. HIF-1 α is stabilized by oncogenic signaling, such

as MAPK signaling downstream of RAS or BRAF, through the degradation of the Von Hippel–Lindau E3 ubiquitin ligase [54]. The Warburg effect results from the coordinated deregulation of multiple genes, starting with the upregulation of GLUT1 and GLUT3, which leads to increased glucose uptake [55–57]. GLUT1 is a target of MYC and an indirect target of the RAS/RAF pathway via HIF-1 α . The oncometabolite 2-hydroxyglutarate stabilizes HIF-1 α by inhibiting prolyl hydroxylases [58].

The TCA cycle utilizes pyruvate, fumarate, succinate, α -ketoglutarate, and oxaloacetate derived from glycolysis and amino acid pathways [59]. In cancer cells, the TCA cycle is driven primarily by glutaminolysis, as pyruvate from glycolysis is shunted into lactic acid production. The PPP pathway utilizes glucose-6-phosphate generated by hexokinase and in turn generates NADPH and ribonucleotides. The PPP consists of an oxidative branch and a nonoxidative branch. Glucose-6-phosphate dehydrogenase (G6PDH) catalyzes the rate-limiting step in the oxidative branch. This enzyme is highly regulated and is overexpressed in cancer cells by transcriptional and post-translational mechanisms [60, 61]. Transcription of *G6PDH* is induced by sterol regulatory element-binding protein 1 (SREBP1) in a mammalian target of rapamycin (mTOR) complex 1-dependent manner; epidermal growth factor receptor signaling increases G6PDH activity by the release of bound G6PDH to a soluble fraction. Both RAS and PI3K pathways are essential for this process. Along this pathway, 6-phosphogluconate dehydrogenase, an enzyme that mediates the production of ribulose-5-phosphate, is also deregulated. Ribulose-5-phosphate inhibits AMPK activation by disrupting the active liver kinase B1 complex, thereby activating acetyl-CoA carboxylase 1 and lipogenesis [62].

Lipid metabolism

Lipids—fatty acids, phospholipids and cholesterol—are a major source of energy and building blocks for plasma membranes. Cancer cells have increased synthesis of fatty acids, which are diverted into membrane phospholipids or stored as neutral lipids. SREBP1 is the master transcription factor for fatty acid synthesis [63], upregulating ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), fatty acid synthase, stearoyl-CoA desaturase-1, and glycerol-3-phosphate acyltransferase. ACLY links the TCA cycle to fatty acid synthesis by converting citrate and CoA to oxaloacetate and acetyl-CoA. Acetyl-CoA is then converted into malonyl-CoA by ACC, which is the first step of fatty acid synthesis. Targeting ACLY or ACC decreases fatty acid synthesis and suppresses cancer cell growth [64, 65]. Fatty acid synthase catalyzes the condensation reaction of malonyl-CoA and acetyl-CoA, resulting in the production of long-chain fatty acids. Enzymes that modify fatty acids also play a role in cancer progression. These include acyl-CoA synthetase, which activates fatty acids prior to oxidative degradation, and stearoyl-CoA desaturase, which introduces double bonds at C9.

Amino acid metabolism

High protein synthesis rates in cancer cells increase the overall need for amino acids. A major signaling pathway involved in amino acid metabolism is mTOR, a pathway activated by multiple oncogenic insults. The mTOR pathway is directly activated by AKT [66] and suppressed by LKB1-AMPK signaling [67]. Intracellular amino acid levels also activate

mTOR through RAG GTPase and the Ras homolog enriched in brain (RHEB) pathway [68, 69]. Cancer cells have a high requirement for serine and glycine, which are required for nucleotide biosynthesis [70]. Serine hydroxymethyltransferase 1, which is upregulated in ovarian and other cancers, couples the conversion of serine to glycine with the conversion of tetrahydrofolate to 5,10-methylene tetrahydrofolate to provide one-carbon units for the synthesis of methionine, thymidylate, and purines.

Deregulated amino acid metabolism also plays a role in immune tolerance in cancer. For example, T cells require sufficient tryptophan to proliferate. Tryptophan is degraded by indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase, which catalyze the conversion of tryptophan to kynurenine. In addition, tryptophan hydroxylase-1 (TPH-1) converts tryptophan to 5-hydroxytryptophan. IDO is highly upregulated in cancer cells and in the tumor microenvironment, which causes the depletion of tryptophan and allows tumor cells to evade the immune response by limiting the T cell response [71]. Cancer cells also downregulate argininosuccinate synthetase 1, an enzyme that catalyzes the final step of arginine biosynthesis. Thus, some cancers such as melanoma, hepatocellular carcinoma, and prostate cancer are auxotrophic for arginine, which is needed to produce nitric oxide, urea, ornithine, and citrulline [72]. Accordingly, arginine deiminase and bacterial arginase can suppress the growth of certain cancer cells through arginine depletion [73]. Cancer cells also have a high requirement for asparagine and consequently show elevated expression of asparagine synthetase. A portion of the glutamine taken up by cancer cells is diverted for asparagine synthesis [74].

Other metabolic pathways

Several other pathways, which are offshoots of the three major metabolic pathways described above, are also dysregulated in cancer and promote tumor growth. Among these are glycosylation pathways, which attach carbohydrate side chains (glycans) to proteins and lipids. Glycosylation affects cell adhesion and motility, modifies cell signaling, and influences the stability, localization, and function of proteins. Cancer cells show increased levels of sialylated glycans. The overexpression of sialylated antigens promotes cell detachment from the tumor mass and attachment to the endothelium, a step that is needed for metastatic spread. Heparan sulfate proteoglycans are also overexpressed in cancers. These glycosylated proteins act as co-receptors for various tyrosine kinase-type growth factor receptors and lower their activation threshold or change signal duration [75]. Sphingolipid metabolism contributes to cancer cell growth primarily by causing an anti-apoptotic response. This occurs, in part, by the ability of this pathway to prevent accumulation of pro-apoptotic ceramides [76]. Overexpression of glucosylceramide synthase confers resistance to doxorubicin, suggesting that inhibiting ceramide metabolism or catabolism can enhance chemotherapy. In addition, several anticancer agents, including the cytotoxic retinoid fenretinide (4-hydroxy[phenyl]retinamide), exert their effects, at least in part, by causing the accumulation of ceramide in tumor cells via de novo synthesis [77].

Targeting cancer metabolic pathways for precision therapy

Targeting metabolic pathways is viewed as a promising approach in cancer therapy for multiple reasons. First, the dependence of cancer cells on altered metabolism makes these cells vulnerable to metabolic perturbations, whereas most of these altered pathways are not essential in normal cells. Second, metabolic enzymes are good candidates for drug development. Third, oncogenic activation of specific metabolic nodes allows the use of oncogene-targeted therapies. Potential metabolic targets are listed in Table 2 and described below.

Targeting signaling pathways

Oncogenes regulate gene expression directly, as in the case of MYC [11], or regulate the localization or stability of specific transcription factors through phosphorylation, as in the case of the RAF-BRAF-MEK-ERK signaling [78]. Cancer therapies targeting driver oncogenes do not completely reset metabolic deregulation. However, targeting the signaling pathways downstream of oncogenes (e.g., AMPK or mTOR), alone or in combination, has proven effective in various cancers [79]. AMPK activators block both nucleotide and fatty acid biosynthetic pathways [79] and induce apoptosis and autophagy by activating the FOXO pathway [80]. The AMPK agonist metformin, used to treat type 2 diabetes, inhibits cancer cell proliferation [81], and its ability to prevent cancer, alone or in combination with other therapies, is under investigation in clinical trials [82, 83]. Inhibitors of mTOR, such as rapamycin, are effective in colon cancer and glioblastoma [84, 85]. Rapamycin has been approved for the treatment of a number of cancers. Its anticancer actions include inhibiting protein, nucleotide, and lipid biosynthesis and blocking glycolysis and glutaminolysis by preventing mTORC1-mediated HIF-1 α activation.

Targeting metabolic enzymes with selective and non-selective inhibitors

Because of its similarity to glucose and the inability of mammals to metabolize it, 2-deoxyglucose (2-DG) can serve as a non-selective inhibitor for various steps in glycolysis. 2-DG is a competitive inhibitor for glucose and reduces the activity of GLUT1 and GLUT3; it is also phosphorylated by hexokinase 2, which is in turn inhibited by phosphorylated 2-DG [86]. The starvation response caused by 2-DG due to ATP depletion can activate the AMPK pathway. Studies with 2-DG have provided proof of concept that targeting cancer cell metabolism is viable [87].

The development of selective and specific inhibitors is helping to overcome toxicity. A list of drugs and their metabolic targets, current stage of development, and indicated cancer types is presented in Table 2. Besides blocking deregulated metabolic pathways, these drugs can alter oncogenic signaling. Examples include statins, which target cholesterol biosynthesis and also inhibit RAS signaling by blocking farnesylation, and heparin, which blocks heparin sulfate-modifying enzymes such as heparanases and sulfatases, and also reduces growth factor receptor signaling by fibroblast growth factor 2 [88].

Metabolite depletion

Metabolite depletion refers to the use of enzymes to reduce a specific oncogenic metabolite and prevent its use by another downstream enzyme to inhibit a specific metabolic pathway. Enzymes of non-human origin, which have lower K_M and higher K_{cat} , can quickly degrade a metabolite before it is available in its specific cellular compartment. Examples are recombinant arginine deiminase and arginase I, which deplete arginine [89, 90], and L-asparaginase, which depletes asparagine and is effective in childhood and adolescent hematopoietic tumors [91].

Concluding Remarks

Cellular homeostasis is sustained by an intricate web of interconnected metabolic pathways. However, the complexity of the metabolic pathways and redundancy in some aspects, such as the ability to produce energy via different sources (carbohydrates, lipids, and proteins), provides substantial flexibility. This flexibility allows the dysregulation of multiple metabolic pathways without compromising cell survival. Oncogenes target these metabolic flexibilities and redundancies to promote cancer growth and metastatic dissemination. There is now substantial evidence that one of the major activities of an oncogene is the alteration of cell metabolism. However, several questions still remain unanswered (see Outstanding Questions). For example, most studies have focused on cell-intrinsic mechanisms of oncogene-directed metabolic alterations; thus little is known about cell-extrinsic mechanisms of metabolic alterations in cancer. However, recent studies have highlighted the important role of the tumor microenvironment in tumor growth and metastasis. These studies are important for several reasons. The development of immunotherapies for cancer treatment requires an understanding of the interactions between the tumor and its microenvironment and the way in which oncogene-mediated metabolic alterations lead to immune evasion. This knowledge will enable a more effective use of immunotherapies and aid in the development of other promising cancer therapies. In summary, although we have made substantial progress towards understanding oncogene-directed cancer cell metabolism regulation and its role in cancer, there is much to learn. A comprehensive grasp of cancer metabolism is needed to better understand tumor biology and improve therapeutic responses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge grants from the National Institutes of Health: R21CA197758-01 (N.W.), R21CA191364-01 (N.W.), R21CA195077-01A1 (N.W.), R01CA200919-01 (N.W.), R01CA196566-01A1 (N.W.), and 1R41CA195908-01A1 (N.W.). N.W. is also supported by a Research Scholar Grant from the American Cancer Society (128347-RSG-15-212-01-TBG).

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Outstanding Questions

- How do oncogenes rewire metabolism in cancer cells?
- Does the tumor microenvironment play a role in determining how oncogenes shape cancer metabolism?
- Do metastatic tumors have unique metabolic requirements different from those of primary tumors?
- Do different cancer types have distinct metabolic requirements?
- How do oncogene-induced metabolic alterations promote cancer initiation and progression?
- Which metabolic alterations represent viable clinical targets for precision cancer therapy and how to discover such alterations?

Trends Box

- Metabolic regulation by oncogenes is a key hallmark of cancer and is necessary for tumor growth, survival, immune evasion, and metastasis.
- Oncogenes reprogram cancer metabolism by directly regulating key metabolic enzymes and pathways.
- Oncogene-induced metabolic alterations result from the activation of specific transcription factors that deregulate energy sensor pathways and macromolecule uptake, and alter autocrine and paracrine mechanisms.
- Metabolic requirements specific to cancer cells have been identified. Targeting these metabolic requirements provides a unique therapeutic opportunity in cancer.

Figure 1. Regulation of cancer metabolism by oncogenes
A. Stages of cancer progression and contributions of major metabolic alterations to different cancer stage-specific phenotypes. **B.** Nodes of deregulation in major metabolic pathways and transcription factors regulating key metabolic enzymes. **C.** Major oncogenic alterations and their downstream signaling pathways activating specific transcription factors that regulate key metabolic enzymes. Events that lead to oncogenic activation are highlighted in red.

Major steps and genes involved in key metabolic pathways that are altered in cancer cells. Enzymes directly altered in cancer cells are shown in bold. A wide variety of metabolic enzymes and pathways are altered that, alone or in conjunction with each other, facilitate cancer cell-specific phenotypes such as tumor initiation, growth, and metastasis.

Table 1

Databases, tools and software to study cancer metabolism

Databases	URL
Oncomine	https://www.oncomine.org/resource/login.html
Gene Expression Omnibus (GEO) database	http://www.ncbi.nlm.nih.gov/geo/
Human Metabolome Database	http://www.hmdb.ca/
Cancer Cell Metabolism Gene Database (ccmGDB)	http://bioinfo.mc.vanderbilt.edu/ccmGDB/
Kyoto Encyclopedia of Genes and Genomes (KEGG) database	http://www.genome.jp/kegg/kegg1.html
MASCOT database	http://www.matrixscience.com/search_form_select.html
Cancer Cell Metabolism Research Database	http://bioinfo.mc.vanderbilt.edu/ccmGDB/
Pathway Commons	http://www.pathwaycommons.org/about/
Tools and software	URL
MetaboAnalyst	http://www.metaboanalyst.ca/
Flux balance analysis (FBA)	http://www.bioinformatics.org/fasimu/
Genome-scale metabolic models (GEMs)	http://link.springer.com/protocol/10.1007%2F978-1-61779-346-2_7
Metabolic Context-specificity Assessed by Deterministic Reaction Evaluation (mCADRE)	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3576361/
Metabolite set enrichment analysis (MSEA)	http://bioinformatics.ca/links_directory/tool/10635/msea
Metabolite pathway enrichment analysis (MPEA)	http://ekhidna.biocenter.helsinki.fi/poxo/mpea/
CellNetAnalyzer	https://www2.mpi-magdeburg.mpg.de/projects/cna/cna.html
MetaboAnalyst	http://www.metaboanalyst.ca/
Constraint-Based Reconstruction and Analysis (COBRA) software	http://cobramethods.wikidot.com/

Table 2

Targeting cancer metabolism (Signaling pathways/Metabolic enzymes/Metabolite depletion)

Signaling pathways			
Pathway	Drug/Compound	Cancer type	Clinical development stage
mTOR	Rapamycin (Sirolimus) Everolimus (Afinitor) Temsirolimus (Torisel) Ridaforolimus AZD8055 XL388	Kaposi sarcoma, renal angiomyolipomas Advanced neuroendocrine tumours, breast cancer, and renal cell carcinoma (RCC) Advanced RCC Breast cancer and advanced solid tumors Recurrent gliomas and advanced solid tumors Various xenograft models	FDA approved FDA approved FDA approved Phase I /II/III Phase I Preclinical
AMPK	Metformin AICAR	Many cancer types Many cancer types	FDA approved Preclinical
Metabolic enzymes			
Carbohydrate metabolism enzyme	Drug/Compound	Cancer type	Remarks
GLUT1	Phloretin WZB117	Colon cancer and leukemia Lung cancer and breast cancer	Preclinical Preclinical
GLUT4	Ritonavir	Multiple myeloma	
Hexokinase	2-deoxyglucose (2-DG) Lonidamine (LND) 3-bromopyruvate (3-BrPA)	Leukemia, cervical cancer, hepatocarcinoma, breast cancer, small lung cancer, lymphoma and prostate cancer Leukemia and lymphoma Leukemia, multiple myeloma, colon cancer and leukemia	Phase I/II Phase III Preclinical
Pyruvate kinase	TLN-232	Metastatic melanoma and renal cell carcinoma	Phase II
PDK1	Dichloroacetate (DCA)	colon cancer, lung cancer, squamous cell carcinoma and prostate cancer	Preclinical
Lactate dehydrogenase (LDH)	Oxamate	Breast cancer	Preclinical
Mitochondrial Complex I	Metformin	Solid tumors and lymphoma	FDA approved
IDH1/IDH2	Dasatinib	Liver cancer	Phase II
Lipid metabolism enzyme	Drug/Compound	Cancer type	Remarks

Signaling pathways			
Pathway	Drug/Compound	Cancer type	Clinical development stage
Fatty acid synthase (FASN)	Cerulenin C75 Orlistat	Breast cancer Breast cancer Breast and pancreatic cancer	Preclinical Preclinical Preclinical
ACC	Soraphen-A TOFA (5-(tetradecyloxy)-2-furoic acid) A-769662	Breast cancer Ovarian and prostate cancer Breast cancer	Preclinical Preclinical Preclinical
ACLY	SB-204990 LY294002	Solid and hematologic cancers Various cancer types	Phase II Preclinical
ACS	Triascin C Thiazolidinediones (TZDs)	Breast and colon cancer Various cancer types	Preclinical FDA approved
AGPAT	CT-32501	Lung cancer	Preclinical
CKα	TCD-717 MN58B	Advanced Solid Tumors Various cancer types	Phase I Preclinical
CPT1	Etomoxir Ranolazine	Myeloma and prostate cancer Leukemia	Preclinical FDA approved
MAGL	JZL184	Colorectal and prostate cancer	Preclinical
SCD	BZ36 A939572	Prostate cancer Kidney cancer	Preclinical Preclinical
SREBP	Fatostatin FGH10019	Prostate and breast cancer Various cancer types	Preclinical Preclinical
Amino acid metabolism enzyme	Drug/Compound	Cancer type	Remarks
ASS1	ADI-PEG20	Hepatocellular carcinoma	Phase II/III
IDO	Indoximod 1-D-MT	Different metastatic solid tumors Different metastatic solid tumors	Phase I Phase I
TDO	Indole LM10	Various TDO expressing cancer cells	Preclinical
PHGDH	shRNA	Melanoma and breast cancer cell lines (SkBr3, MCF7) Murine mammary fat pad tumors with MDA- MB-468 cells expressing PHGDH-shRNA	Preclinical
SHMT1	shRNA	Lung cancer and lymphomagenesis	Preclinical
Glutamine – dependent enzymatic steps	L-DON Azaserin Acivicin	Various animal and human xenografted tumors Pancreatic cancer Mant cancers and high grade astrocytoma	Preclinical Preclinical Phase II

Signaling pathways			
Pathway	Drug/Compound	Cancer type	Clinical development stage
Metabolite depletion	Drug/Compound	Cancer type	Remarks
Glutamine	Phenylacetate	Brain tumors	Phase II
Asparagine	Asparaginase and pegasparaginase	Acute lymphoblastic leukaemia (ALL), T-cell lymphoma (TCL) and B-cell lymphoma (BCL)	Phase II/III
Arginine	Arginine deiminase	Metastatic melanoma and hepatocellular carcinoma	Phase I/II