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Understanding the intersections between metabolism and cancer biology

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Abstract

Transformed cells adapt metabolism to support tumor initiation and progression. Specific metabolic activities can participate directly in the process of transformation or support the biological processes that enable tumor growth. Exploiting cancer metabolism for clinical benefit requires defining the pathways that are limiting for cancer progression and understanding the context specificity of metabolic preferences and liabilities in malignant cells. Progress towards answering these questions is providing new insight into cancer biology and can guide the more effective targeting of metabolism to help patients.

Changes in cell metabolism can contribute to transformation and tumor progression. Metabolic phenotypes can also be exploited to image tumors, provide prognostic information, and treat cancer. Thus, understanding cancer metabolism has implications for understanding basic cancer pathophysiology and for clinical oncology.

CELL-AUTONOMOUS REPROGRAMMING OF CANCER METABOLISM

Many recent cancer metabolism studies have focused on the cell-autonomous effects of cancer-promoting mutations. This has uncovered new principles in metabolic regulation and in crosstalk between signaling and metabolic networks. No pathway has received more

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attention than aerobic glycolysis (the Warburg effect) (Vander Heiden et al., 2009). This phenomenon involves the propensity for proliferating cells, including cancer cells, to take up glucose and secrete the carbon as lactate even when oxygen is present. Principles governing glycolytic regulation in cancer cells have been extensively reviewed (Cairns and Mak, 2016).

Warburg interpreted tumor lactate secretion as an indication that oxidative metabolism (i.e. respiration) was damaged. However, numerous studies, including Warburg's original work, fail to demonstrate defective respiration as a general feature of malignant cells (Koppenol et al., 2011). Instead, respiration and other mitochondrial activities are required for tumor growth (DeBerardinis and Chandel, 2016). Furthermore, in non-transformed cells the Warburg effect is a reversible phenomenon tethered to proliferation, indicating that it reflects proliferation-associated changes in metabolism rather than a unique feature of malignancy.

Proliferating cells tend to express glucose transporters and glycolytic enzymes out of proportion to the machinery required to oxidize pyruvate (Curi et al., 1988), consistent with preferential conversion of glucose to lactate without loss of respiration. This distinction is important because intermediates generated by the tricarboxylic acid (TCA) cycle are precursors for lipids, amino acids, and nucleotides. These precursors complement precursor metabolites from glycolysis and other pathways and are necessary to support proliferation (DeBerardinis et al., 2007).

Fuels besides glucose also contribute to core metabolic functions of cancer cells: energy formation, biomass assimilation and redox control. Glutamine is a prominent example (Altman et al., 2016); however, recent work has revealed that a diversity of nutrients and pathways support these functions. The expanding metabolic repertoire of cancer cells has been reviewed extensively, with acetate and other fatty acids, lactate, branched chain amino acids, serine, and glycine representing some of the nutrients that are needed to fuel different cancers (DeBerardinis and Chandel, 2016; White, 2013).

The growing list of cancer fuels contrasts with prevailing views from just a few years ago, which suggested oncogenic signaling imposed a rigid dependence on specific nutrients (Vander Heiden et al., 2009). The current picture is more logical when one considers that cancer cells must compete for fuels in a crowded, nutrient-limited tissue environment. The ability to use a panoply of fuels is advantageous, with some cancer cells even relying on autophagic degradation or scavenging of macromolecules (Commisso et al., 2013; Guo et al., 2016; Palm et al., 2015).

This review builds on the increasingly sophisticated understanding of cancer metabolism derived from work over the last decade. Our goal is to convey emerging paradigms and questions in order to guide future research so altered metabolism can be exploited to improve patient care.

FUNCTIONAL CLASSIFICATION OF REPROGRAMMED METABOLIC ACTIVITIES IN CANCER CELLS

Not all reprogrammed metabolic activities contribute equally to cancer. With many metabolic activities under oncogenic control, categorizing them based on whether they are transforming, enabling, or neutral can clarify the role of each activity in cancer biology and predict how it might be exploited in basic research and clinical oncology (Figure 1).

Transforming activities

These activities directly contribute to cell transformation, and blocking them might prevent tumorigenesis in susceptible patients or antagonize disease progression. At present, only a handful of metabolic activities can be considered as transforming based on genetic evidence. These include metabolic perturbations caused by enzyme mutations that either arise somatically in a recurrent fashion; and/or are inherited in the germline of patients with heritable cancer predisposition syndromes. Three examples of these types of mutations have been intensely studied: mutations in the genes encoding isocitrate dehydrogenases-1 and −2 (IDH1, IDH2); mutations in components of the succinate dehydrogenase (SDH) complex; and mutations in fumarate hydratase (FH) (Losman and Kaelin, 2013).

Somatic mutations in *IDH1* and *IDH2* occur in several tumor types (Losman and Kaelin, 2013). These monoallelic mutations generate an enzyme with neomorphic ability to convert α-ketoglutarate (αKG) to (D)-2-hydroxyglutarate (D-2HG) (Dang et al., 2009). D-2HG accumulates to high levels in IDH-mutant tumors and interferes with the function of several αKG-dependent dioxygenases, including the prolyl hydroxylases that target HIF-a subunits for degradation and epigenetic enzymes that regulate the methylation status of histones and DNA (Losman and Kaelin, 2013). This interferes with expression of genes required for differentiation.

SDH and FH catalyze sequential reactions in the TCA cycle (Figure 2). Both enzymes act as tumor suppressors in familial cancer syndromes where patients inherit one loss-of-function allele and lose expression of the other allele in tumors (Baysal et al., 2000; Tomlinson et al., 2002). Consequently, tumors accumulate high levels of succinate and/or fumarate. Like D-2HG, these dicarboxylic acids interfere with dioxygenase function (Sciacovelli et al., 2016; Selak et al., 2005; Xiao et al., 2012).

In mouse models, mutations in these metabolic enzymes do not transform cells on their own, but cooperate with other mutations to promote neoplasia. Loss of *FH* in the kidney leads to cyst formation, and hyperproliferation results when p21 is also deleted (Zheng et al., 2015). *Idh2* mutations synergize with oncogenic *Kras* to produce intrahepatic cholangiocarcinoma (Saha et al., 2014). IDH mutations increase the number of hematopoietic progenitor cells (Sasaki et al., 2012), and cooperate with increased HoxA9 and Meis1a expression or with mutant *Flt3* or *Nras* to cause AML (Chen et al., 2013; Kats et al., 2014).

An important concept emerged from these studies. In all cases, an accumulated metabolite inhibits enzymes using αKG as a co-substrate to promote tumorigenesis (Kaelin and McKnight, 2013). Thus, a unifying feature of D-2HG, succinate and fumarate as

"oncometabolites" is causing non-metabolic effects that promote transformation in receptive contexts. Interestingly, modestly elevated levels of the L-enantiomer of 2HG might also contribute to malignancy (Shim et al., 2014). Given the importance of dioxygenases in regulating epigenetics, fluctuations in metabolite levels may also play functional roles in normal development. Consistent with this idea, extreme abnormalities in metabolite levels observed in monogenic metabolic diseases, such as deficiency in the dehydrogenases converting L- and D-2HG to αKG, are associated with developmental abnormalities (Erez and DeBerardinis, 2015).

Enabling activities

These activities are altered in cancer cells but are not involved in transformation. They carry out conventional metabolic tasks like supporting energetics, generating macromolecules and maintaining redox state and are required for tumor progression (Figure 1). In many cases they are effectors of oncogenes and tumor suppressor genes. For example, oncogene expression is sufficient to enhance glucose uptake in fibroblasts (Flier et al., 1987). Transcriptional targets of c-MYC include metabolite transporters and enzymes required for glucose metabolism, glutaminolysis and biosynthesis, and inhibiting these activities suppresses growth of c-MYC-driven tumors (Altman et al., 2016). Oncogenic *KRAS* also regulates nutrient acquisition, macromolecular synthesis and redox homeostasis, and inhibiting these pathways suppresses oncogenic *KRAS*-driven tumor growth (White, 2013). Activation of mTORC1, an essential component of growth factor signaling networks, enables protein, lipid and nucleic acid synthesis through a variety of mechanisms (Howell et al., 2013). Genetic suppression of metabolic activities may also enable tumor growth. For example, somatic deletion of genes involved in arginine synthesis allows aspartate to be diverted towards nucleotide synthesis, thereby supporting cell proliferation (Rabinovich et al., 2015). Most existing and investigational metabolic therapies are directed against enabling activities (Table 1).

Neutral activities

Many metabolic features of cancer cells are dispensable for tumor growth (Figure 1). In a given context, these activities are predicted to be poor therapeutic targets. Fluctuating nutrient access may cause activities to be required in some contexts and dispensable in others. Thus, confidently classifying an activity as neutral is challenging and requires definitive proof that loss of the activity does not impair tumor progression.

Pyruvate kinase M2 (PKM2) provides an example of an enzyme dispensable for tumor growth. PKM2 is an isoform of the glycolytic enzyme pyruvate kinase that is expressed in most cancers (Figure 2) and is regulated by oncogenic signaling (Israelsen and Vander Heiden, 2015). PKM2 expression is not required for growth of breast tumors, liver tumors, leukemia, or xenograft tumors from various human cancer cell lines in mice (Dayton et al., 2016; Israelsen and Vander Heiden, 2015). However, studies of PKM2 still provide insight into cancer metabolic regulation. PKM2 loss promotes cancer in some mouse models, and characterizing these models has argued that how glucose is metabolized can influence tumor progression (Dayton et al., 2016; Israelsen et al., 2013). In fact, activating PKM2 can slow growth of some tumors, but the ability of tumors to lose pyruvate kinase expression argues

against PKM2 being a good therapeutic target for most cancers (Israelsen and Vander Heiden, 2015).

WHAT PRODUCTS OF METABOLISM ARE LIMITING FOR PROLIFERATION?

One approach to identify enabling activities is to determine which aspects of metabolism are limiting for cancer cell proliferation. Targeting activities that supply limiting materials for proliferation is therapeutically attractive, especially if the pathways used are less important in normal proliferative tissues. Although several metabolic products have been proposed as critical outputs of cancer metabolism, which are rate limiting for proliferation remains controversial.

Is ATP limiting for proliferating cells?

ATP plays a critical role in all cells to enable otherwise unfavorable processes. Aerobic glycolysis has been historically interpreted as a shift from oxidative phosphorylation toward fermentation to generate ATP (Gatenby and Gillies, 2004; Vander Heiden et al., 2009). This route of ATP production yields less ATP per mole of glucose, but allows fast ATP generation even in low oxygen (Koppenol et al., 2011). Energy is derived from ATP hydrolysis to ADP (or AMP), and thus depends on the ATP/ADP (or ATP/AMP) ratio. Therefore, cells must continuously oxidize nutrients to regenerate ATP to maintain homeostasis. Although many proliferative processes also require ATP hydrolysis, the additional ATP needed for proliferation is small relative to the requirements for homeostasis (Vander Heiden et al., 2009). Thus, while producing ATP is critical for survival, it may not always be limiting for proliferation.

Little evidence supports ATP limitation as a reason cells use aerobic glycolysis. First, many proliferating cells use aerobic glycolysis regardless of nutrient and oxygen availability (Vander Heiden et al., 2009). Second, cancer cells retain the capacity to increase fermentation when respiration is inhibited, and also can increase respiration when mitochondria are uncoupled (Andrzejewski et al., 2014; Birsoy et al., 2014). The existence of “spare respiratory capacity” argues that the ATP/ADP ratio is sufficiently high to limit electron transport, and substrates are available in excess of the demand for ATP synthesis. Finally, increasing ATP consumption can promote proliferation (Fang et al., 2010), providing further evidence that the ability to generate ATP is greater than what is needed by proliferating cells.

Is NADPH limiting for proliferating cells?

Cells store energy as reduced carbon in carbohydrates and lipids, and the anabolic reactions used to synthesize these materials requires electrons from NADPH (Figure 3), leading to the hypothesis that NADPH may be limiting for proliferation (Vander Heiden et al., 2009). However, the fact that some cancers like clear cell renal cell carcinoma accumulate lipids (Qiu et al., 2015) argues that these cancers have sufficient NADPH to produce lipids in excess of those needed for cell membranes. Most macromolecular biosynthesis occurs in the cytosol where several enzymes can produce NADPH including malic enzyme 1, IDH1, and folate metabolism; however, the oxidative pentose phosphate pathway (oxPPP) is a major

source of cytosolic NAPDH (Fan et al., 2014; Lewis et al., 2014) (Figure 2). Despite this, most ribose is produced via the non-oxidative pentose phosphate pathway, which does not produce NAPDH (Boros et al., 2000; Ying et al., 2012). A major regulator of oxPPP flux is the NADP+/NADPH ratio, and exposing cells to oxidative stress increases oxPPP flux (Kuehne et al., 2015) arguing cells have excess capacity to produce NADPH even when ROS levels increase. Thus, while NADPH is important to help cancer cells cope with ROS, generating enough cytosolic NADPH for competing metabolic pathways may not be limiting for proliferation. This assertion is supported by both classic literature (Reitzer et al., 1980) and the fact that reduced oxPPP flux resulting from G6PD deficiency has no impact on human cancer risk (Cocco, 1987).

Products of the TCA cycle can be limiting for proliferation

Clues to which aspects of metabolism are most limiting for proliferation come from studies where proliferation arrest from metabolic disruption is rescued by re-supplying metabolites. A classic example is glutamine metabolism for TCA cycle anaplerosis (DeBerardinis et al., 2007; Yuneva et al., 2007). Most cultured cells require glutamine, and providing cells with αKG or other TCA cycle intermediates can rescue proliferation in low glutamine conditions (Yuneva et al., 2007). Activating pyruvate carboxylase to allow anaplerosis from glucose can also enable proliferation in low glutamine and contexts where glutamine is not used (Figure 2) (Cheng et al., 2011; Davidson et al., 2016b; Sellers et al., 2015).

The TCA cycle carbon requirement suggests a product of this cycle can be limiting for proliferation. TCA cycle intermediates are precursors for several biosynthetic intermediates, but production of amino acids accounts for the dominant disposition of TCA cycle carbon in biomass (Hosios et al., 2016). Aspartate, asparagine, proline and glutamate can all be produced from TCA cycle intermediates, and cells synthesize these amino acids from glutamine even when they are present in the environment (Hosios et al., 2016). Indeed, synthesis of both aspartate (Birsoy et al., 2015; Sullivan et al., 2015) and proline (Loayza-Puch et al., 2016) can be limiting under some conditions.

Nucleotide synthesis can be limiting for proliferation

Supplying nucleotide bases can rescue proliferation of glutamine-deprived cells and cells with high pyruvate kinase activity suggesting nucleotide base production is important downstream of major nutrient pathways (Gaglio et al., 2009; Lunt et al., 2015). Acquiring deoxyribonucleotide bases is limiting in other cancer contexts (Aird et al., 2013), and nucleotide synthesis is the target of several chemotherapeutics (Table 1), arguing that acquiring nucleotides might be a metabolic bottleneck for diverse cancers. Why might nucleotide base synthesis be limiting on a biochemical level? One important factor is that unlike lipids and proteins, nucleotides may not be provided in sufficient quantities or proportions by the tumor microenvironment and synthesis of these complex molecules requires the integrated metabolism of non-essential amino acids, ribose and one-carbon donors.

The DHODH step of pyrimidine biosynthesis is directly coupled to the mitochondrial electron transport chain and oxygen consumption (Figure 2) and is important for both AML

and melanoma progression (Sykes et al., 2016; White et al., 2011). While oxygen is abundant in standard tissue culture, oxygen levels in even the best perfused tissues are 9% or less (Bertout et al., 2008), a value closer to the oxygen levels used to study hypoxia responses in culture. Oxygen delivery can be more limiting than glucose for normal tissue physiology, as evidenced by lactic acid build-up in muscle during exercise, by increased hematocrit enhancing the performance of elite athletes, and by the fact that angiogenesis is regulated by oxygen levels rather than by nutrients even though tissue delivery of both relies on the vasculature. Oxygen can also be limiting for tumor growth. Individuals living at high altitude have lower cancer incidence (Burtscher, 2014), and increasing oxygen delivery to tissues with erythropoietin promotes cancer progression (Szenajch et al., 2010).

Cancer cells require oxidative metabolism to form tumors (Davidson et al., 2016b; Weinberg et al., 2010). Oxygen consumption is coupled to ATP synthesis, but maintaining an adequate ATP/ADP ratio may not be why respiration is limiting for proliferation. Respiration also regenerates NAD+ for oxidation reactions (Figure 3), which are required for aspartate synthesis (Birsoy et al., 2015; Sullivan et al., 2015), providing another link between oxygen consumption and nucleotide synthesis. Nucleotide base carbon is more oxidized than the carbon in most nutrients. Aspartate is a key oxidized precursor for both purines and pyrimidines (Figure 2), blood aspartate levels are low, and most cells are unable to take up aspartate from the environment (Birsoy et al., 2015). Thus, stoichiometric reduction of oxygen or another molecule is required for aspartate and nucleotide base synthesis (Sullivan et al., 2015). The ability to produce aspartate can be limiting for some tumors (Gui et al., 2016), and respiration also supports production of folate species for purine synthesis (Bao et al., 2016; Meiser et al., 2016). Taken together, these studies argue access to oxygen or alternative electron acceptors limits nucleotide synthesis for some cancer cells.

Consequences of electron acceptor limitation in cancer

The notion that chemical disposal of excess electrons to synthesize nucleotides is limiting for proliferation is attractive because it explains several cancer metabolism phenotypes. First, it provides an explanation for the propensity of cancer cells to produce lactate. NAD+ regeneration from NADH requires electron disposal (Figure 3). Conversion of pyruvate to lactate is driven by the NAD+/NADH ratio, and decreasing this ratio in proliferating cells because of increased nucleotide production may be sufficient to drive increased lactate production. All proliferating cells must replicate DNA, so the accompanying reduction in NAD+/NADH ratio could also explain the use of fermentation by many proliferating cells across organisms and conditions. Cancer cells have a very low NAD+/NADH ratio (Hung et al., 2011), and changes in NAD+/NADH ratio correlate better with tumor growth rate than changes in ATP/ADP ratio (Gui et al., 2016). Regenerating NAD+ via orthogonal pathways can also increase cell proliferation when respiration is impaired (Birsoy et al., 2015; Sullivan et al., 2015; Titov et al., 2016), and disposal of excess electrons can limit proliferation in prokaryotic systems (Dietrich et al., 2013).

A low NAD+/NADH ratio also could explain increased ROS in cancer. ROS levels might increase because cells are deficient in electron donors to detoxify ROS. However, electron acceptor deficiency leading to inefficient mitochondrial electron transport chain function

will also lead to increased ROS (Figure 2). The latter explanation is consistent with angiogenesis and oxygen delivery being a limitation for tumor growth (Gatenby and Gillies, 2004).

WHAT DETERMINES HOW DIFFERENT TUMORS USE METABOLISM?

Pathways downstream of oncogenes and tumor suppressors regulate cancer cell metabolism. Genomic alterations can also result in copy number gains and losses of genes encoding metabolic enzymes, and this may induce vulnerabilities (Li et al., 2014; Locasale et al., 2011; Possemato et al., 2011). However, the extent to which metabolic preferences are hard-wired by the tumor genotype is less clear, because many non-genetic factors also influence tumor metabolism (Figure 2). As in all tissues, tumor metabolism is dictated by a variety of intrinsic and extrinsic factors (Figure 4). We need to understand how these factors are integrated to create metabolic dependencies.

The environment can affect cancer cell metabolism

Cancer cells in culture have a different metabolic phenotype from tumors. While many cancer cell lines quantitatively convert glucose to lactate, glucose oxidation is prevalent in tumors (Davidson et al., 2016b; Hensley et al., 2016; Maher et al., 2012; Marin-Valencia et al., 2012). Cultured lung cancer cells use glutamine to supply TCA cycle carbon, while lung tumors in mice prefer glucose as a TCA cycle fuel (Davidson et al., 2016b; Hensley et al., 2016; Sellers et al., 2015). These differences translate into altered vulnerabilities, as lung cancer cell lines require glutaminase for proliferation while tumors derived from these same cells do not; the converse is true for enzymes involved in glucose oxidation (Davidson et al., 2016b).

The environment can also affect the efficacy of drugs targeting metabolism. Metformin and other biguanides are mitochondrial complex I inhibitors that slow tumor growth by preventing complex I-mediated NAD+ regeneration (Wheaton et al., 2014). Thus, alternative NAD+ regeneration pathways decrease complex I dependence and promote metformin resistance (Gui et al., 2016). Lipid depletion potentiates the effect of acetyl-coA carboxylase inhibitors in culture, but the same drugs affect lung tumor growth in vivo despite the presumed availability of fatty acids (Svensson et al., 2016). Tumors vary in the fraction of actively proliferating cells, which influences metabolic dependency (Coloff et al., 2016). Both genetic and drug screens have identified context-specific metabolic liabilities, implying that the tumor environment can influence sensitivity to metabolic inhibitors (Possemato et al., 2011; Wenzel et al., 2014).

Cell lineage can also affect cancer metabolism

Most cytotoxic chemotherapies, including those that target nucleotide metabolism, are only effective against select cancers. A genetic predictor of response is lacking for most of these drugs, with sensitive cancer types defined instead by the cancer tissue of origin. This suggests some metabolic dependencies might be defined by tumor lineage. Indeed, acute lymphoblastic leukemia (ALL) cells are auxotrophic for asparagine and are sensitive to asparagine depletion by L-asparaginase. DHODH activity is a lineage-specific requirement

of myeloid cells that impacts differentiation (Sykes et al., 2016). MYC induces distinct metabolic phenotypes in mouse liver and lung tumors, with liver tumors displaying enhanced glutamine catabolism and lung tumors retaining the ability to synthesize glutamine from glucose (Yuneva et al., 2012). Mouse lung and pancreatic tumors initiated by the same driver mutations also exhibit differences in amino acid metabolism with lung tumors relying on uptake of free amino acids from the blood (Mayers et al., 2016), while pancreatic tumors obtain amino acids from extracellular protein (Davidson et al., 2016a). These differences in amino acid metabolism translate into a differential dependency of lung and pancreatic tumors on branched chain amino acid nitrogen for nucleotide synthesis (Mayers et al., 2016).

An explanation for how lineage influences tumor metabolism is suggested by metabolic gene expression studies. The metabolic network of tumors is more similar to the normal tissue from where the cancer arose than it is to the metabolic network of tumors arising from another tissue (Hu et al., 2013), and normal tissues wire metabolism differently to support their unique functions. Mechanistically, tissue identity is established through epigenetic regulation of gene expression, and despite altered gene expression in cancer, many aspects of tissue identity are maintained (Gaude and Frezza, 2016). Metabolism can also influence epigenetic state, but the fact that tumors retain metabolic features from their parental normal tissue argues cancers adapt existing tissue metabolism to support abnormal proliferation rather than converging on a universal proliferation program. This distinction is critical, because it suggests that drugs targeting proliferative metabolism may not be effective against all tumors.

Tumor lineage also modifies the penetrance of transforming mutations. The restricted tumor spectrum in patients with familial cancer syndromes caused by SDH and FH mutations indicates an exquisite context-dependence for these events to cause malignancy. Why specific mutations cause lineage-restricted cancers is not understood, but one might speculate that some metabolic alterations are only tolerated in the context of a specific metabolic network.

Tissue-specific differences in nutrient availability impose further constraints on metabolism. How cancer cells generate aspartate in different contexts illustrates how such constraints can affect production of a key metabolite for nucleotide synthesis. Cells in culture where oxygen is in excess produce aspartate from glutamine via the TCA cycle, a pathway that involves multiple oxidation steps (Birsoy et al., 2015; DeBerardinis et al., 2007; Sullivan et al., 2015) (Figure 2). However, in lung tumors where oxygen is less abundant, aspartate is produced from glucose via a series of reactions with fewer oxidation steps (Davidson et al., 2016b; Hensley et al., 2016; Sellers et al., 2015). Pancreatic tumors are particularly oxygen-limited and use yet another strategy, scavenging amino acids from extracellular protein through *KRAS*-dependent macropinocytosis and circumventing any need to synthesize aspartate from other nutrients (Commisso et al., 2013; Davidson et al., 2016a; Kamphorst et al., 2015).

Interactions with benign cells can affect cancer cell metabolism

Tumors consist of a complex milieu of malignant and non-malignant cell types with distinct metabolic preferences. Specific nutrients might be available to cancer cells because they are produced in a given tissue, and differential consumption of nutrients by cancer and non-cancer cells might further affect metabolite levels. In the brain, astrocytes metabolize glucose and secrete lactate to be used by neurons as a source of energy (Bittar et al., 1996). A similar symbiotic relationship may exist within tumors, where some cells ferment glucose to lactate, which is then used as a respiratory substrate for other cells (Sonveaux et al., 2008). Alanine produced by pancreatic stellate cells can promote pancreatic cancer cell proliferation (Sousa et al., 2016) and bone marrow stromal cells provide cysteine to promote survival of chronic lymphocytic leukemia cells (Zhang et al., 2012). Similar relationships likely exist in all cancers, but dissecting how cell populations share nutrients within tumors remains a challenge.

ROLES FOR METABOLIC REPROGRAMMING DURING CANCER PROGRESSION

Most cancer-related deaths occur after therapy resistance has emerged and/or after tumor cells have spread from the primary site. Whether specific metabolic activities acquired during tumor progression promote therapy resistance or metastasis is being investigated.

Role of metabolism in metastasis

Epithelial-mesenchymal transition (EMT) is a transdifferentiation program associated with metastasis and chemotherapeutic resistance (Ye and Weinberg, 2015). Enforcing an EMT-like phenotype in lung cancer cells reduces lipogenesis and increases respiration (Jiang et al., 2015). Silencing fatty acid synthase in these cells induces EMT and enhances metastatic seeding in mice. Similarly, in a breast cancer model cellular invasion, migration and metastasis correlate with enhanced respiration and mitochondrial biogenesis driven by the transcriptional co-activator PGC1α (LeBleu et al., 2014). Silencing PGC1α reduced metastasis without altering tumor growth at the primary site. In this model, PGC1α was required for cancer cell invasion but not proliferation, perhaps explaining its role in metastasis and dispensability for primary tumor growth.

Several studies have examined metabolic transitions accompanying detachment from extracellular matrix, an early step in metastasis. In breast epithelial cells, loss of matrix attachment results in oxidative stress and cell death (Schafer et al., 2009). Treating detached cells with antioxidants or enhancing NAPDH production by the oxPPP promotes survival. In lung cancer cells, detachment suppresses pathways required to maximize cell growth and induced shuttling of cytosolic reducing equivalents into the mitochondria to combat ROS (Jiang et al., 2016). Specifically, reductive carboxylation of cytosolic αKG is induced to produce citrate, which then enters the mitochondria to produce NADPH. This pathway is dispensable in monolayer culture but required in the anchorage-independent state.

Additional bottlenecks can prevent metastasis after cells enter the circulation. Circulating melanoma cells and metastases have elevated ROS compared to primary tumors (Piskounova

et al., 2015). Highly metastatic tumors undergo reversible metabolic changes allowing them to increase mitochondrial NADPH and combat ROS stress. Inhibiting this response reduces metastasis, whereas systemic treatment with antioxidants enhances metastasis. Exacerbating oxidative stress potentiates some chemotherapeutic responses (Harris et al., 2015; Raj et al., 2011), and enhances response to radiation therapy (Robbins and Zhao, 2004). Altogether, these studies underscore the importance of managing ROS during tumor progression, and suggest that this might be exploited therapeutically.

Metabolism and therapy resistance

Therapy-resistant tumors have altered metabolic phenotypes relative to treatment-naïve tumors, with enhanced reliance on mitochondrial metabolism in the resistant cancers. Genetic inactivation of oncogenic $KRAS^{G12D}$ in pancreatic cancer leads to tumor regression; however, a small number of cancer cells survive in a dormant state and regenerate tumors if $KRAS^{G12D}$ is reactivated (Viale et al., 2014). Compared to cells with constitutive $KRAS^{G12D}$ expression, the surviving cells have enhanced respiration, reduced glycolysis, and an impaired ability to increase glycolysis when respiration is inhibited. This renders surviving cells susceptible to respiration inhibitors, and treating mice with an ATP synthase inhibitor during tumor regression delayed relapse after $KRAS^{G12D}$ reactivation.

Mitochondria also contribute to melanoma therapy resistance. Higher PGC1α expression portends poor outcome in human melanoma (Vazquez et al., 2013). In melanoma cells, PGC1α expression is regulated by the melanocyte-lineage transcription factor MITF and is required to maintain high levels of respiration, low ROS, and resistance to the oxidizing agent piperlongumine. Silencing PGC1α synergizes with piperlongumine to reduce melanoma xenograft growth. In human melanoma with mutant *BRAF*, gene expression patterns associated with mitochondrial biogenesis predict reduced survival and tumors that relapse after MAPK inhibitor treatment have increased mitochondrial biogenesis gene expression (Zhang et al., 2016). Inhibiting mitochondrial biogenesis using a mitochondrial-targeted Hsp90 inhibitor decreases MAPK inhibitor resistance in xenografts.

In autochthonous models of breast and lung cancer, anti-angiogenic kinase inhibitors enhance AMPK signaling and shift metabolism toward a more oxidative phenotype. Treated cells are more sensitive to inhibitors of oxidative metabolism, and the same drugs synergize with anti-angiogenics to suppress tumor growth (Navarro et al., 2016). Mitochondrial inhibition with metformin can kill chemotherapy-resistant breast tumor stem cells (Janzer et al., 2014). Taken together, these studies demonstrate the importance of mitochondrial function in enabling therapeutic resistance and suggest mitochondrial inhibitors may help curtail cancer progression.

CAN CANCER METABOLISM BE EXPLOITED TO IMPROVE THERAPY?

To target metabolism for therapy, limiting metabolic processes must be identified and understood sufficiently to target the process safely and select responsive patients. Using the classifications described above, transforming and/or enabling activities must be identified with an adequate therapeutic index. Clinical experience with cytotoxic chemotherapy highlights the challenges that will likely confront new metabolic therapies. Many

chemotherapies inhibit nucleotide metabolism (Table 1). These drugs are highly effective in some tumors, but efficacy is not solely determined by proliferative index. Tumor cells acquire mutations in cell cycle checkpoint genes that contribute to therapeutic window, but the differential sensitivity of different cancers to these drugs is incompletely understood. Evidence suggests that tumors use diverse mechanisms to maintain nucleotide pools, and this may contribute to efficacy. However, a better understanding of differential sensitivity to metabolism-targeted chemotherapy may help use these drugs more effectively and suggest new targets.

Recent challenges associated with targeting cancer metabolism

Whether studies of cell-autonomous metabolic reprogramming will identify the best therapeutic targets is unproven. Success targeting glycolysis has been limited. Exposing patients to high levels of 2-deoxyglucose generated tumor responses but caused hypoglycemia symptoms, and more tolerable doses in modern trials have been disappointing (Vander Heiden, 2011). Attempts to target the Warburg effect directly have also been met with limited success. Dependence on the enzyme lactate dehydrogenase (LDH) was demonstrated both genetically and pharmacologically (Fantin et al., 2006; Le et al., 2010; Shim et al., 1997), leading to development of LDHA inhibitors (Boudreau et al., 2016), but none progressed to clinical trials, suggesting either unacceptable toxicity, insufficient drug exposure or a lack of LDHA dependence in human tumors. Lactate transport inhibition is currently being tested as an alternative approach. Activating pyruvate dehydrogenase (PDH) by targeting its inhibitory kinase (PDHK) has been proposed as a therapeutic strategy. The PDHK inhibitor dichloroacetate (DCA) elicits metabolic effects in human tumors (Michelakis et al., 2010), but minimal efficacy data has been reported. Recent data indicate that PDH is active and required by some tumors (Davidson et al., 2016b; Hensley et al., 2016), tempering hope that further activating the enzyme will be therapeutically useful.

One success in targeting cancer metabolism is the reversal of 2HG-mediated reprogramming in IDH mutant tumors (Losman and Kaelin, 2013). Drugs targeting mutant IDH can elicit responses in patients with hematological malignancies, but have been less effective in glioma models (Tateishi et al., 2015). The mechanism of 2HG-mediated transformation may differ in different cancers; however, liabilities caused by high 2HG might be exploited as an alternative approach to treat these cancers.

Identifying tumors susceptible to metabolic therapy

Transforming mutations in metabolic enzymes present clinical opportunities where patients can be selected based on tumor genetics. However, most metabolic changes are not driven by metabolic enzyme mutations, and even in the case of IDH mutations, a durable state of mutant enzyme dependence may not always be present (Tateishi et al., 2015). Thus, how to select patients for drugs targeting metabolic enzymes remains a critical therapeutic question.

Based on successes developing protein kinase inhibitors, one approach has been to screen cell line panels to identify genetically susceptible cancers, and then to validate these hypotheses in animal models. However, differential nutrient use in culture and in tumors suggests that the use of cell lines to identify sensitive cancers could identify activities that

are neutral in vivo. Conversely, enabling pathways in vivo may be less important in culture. A requirement for glutamine metabolism has been observed in many cancer types (Altman et al., 2016), but both tissue of origin and genetics contribute to this phenotype (Yuneva et al., 2012). The auxotrophy of some cancers for individual amino acids is also influenced by a combination of genetic and non-genetic factors. Auxotrophy for arginine or asparagine can be explained in some cases by decreased expression of synthesis enzymes; however, treatment of ALL with asparaginase is effective even when asparagine synthase is expressed, suggesting that additional factors underlie the need for exogenous asparagine (Krall et al., 2016; Stams et al., 2003). Increased biguanide sensitivity has been attributed to various mutations (Buzzai et al., 2007; Shackelford et al., 2013), but tissue environment also affects response to these drugs (Gui et al., 2016). Selecting patients for chemotherapy based on tumor type argues cell lineage can be an effective tool to stratify patients and argues that in addition to genetics, tumor type and location should be considered when developing metabolism-targeted drugs.

Genetically defined metabolic targets

Sensitivity to some enabling metabolic targets is determined by genetics, including passenger deletion of enzymes that prevent metabolic compensation in tumors. For example, most glioblastoma cells express two isoforms of the glycolytic enzyme enolase encoded by the genes *ENO1* and *ENO2. ENO1* resides on chromosome 1p36 at a tumor suppressor locus that is homozygously deleted in 1–5% of glioblastomas (Muller et al., 2012). This reduces metabolic redundancy and creates a therapeutic opportunity to target ENO2. The gene encoding the enzyme methylthioadenosine phosphorylase (MTAP) can be deleted with the *p16/CDKN2A* tumor suppressor gene. The resulting accumulation of MTA reduces PRMT5 methyltransferase activity, creating another therapeutic opportunity (Kryukov et al., 2016; Marjon et al., 2016; Mavrakis et al., 2016). Gene expression changes that create auxotrophies for specific amino acids can also be targeted, with L-asparaginase providing an example of success. Drugs that deplete arginine are being tested in patients with *ASS1*-deficient tumors (Phillips et al., 2013). Limiting serine in the diet can be efficacious in some p53 mutant cancers (Maddocks et al., 2013).

Non-cell autonomous targeting of tumor metabolism

Understanding the interactions between cancer cell and immune cell metabolism will be critical for combining metabolism targeted therapies with immunotherapies. Nutrient availability and metabolism affect T cell and macrophage differentiation, raising the possibility that targeting tumor cell metabolism may either promote or prevent anti-cancer immune responses.

Cancer cells compete with T cells for glucose in tumors, and restricting T cell glucose metabolism causes lymphocyte exhaustion (Chang et al., 2015; Ho et al., 2015). Thus, therapies that decrease glucose use by cancer cells could make glucose available for T cells and enhance immune effector functions to further limit tumor growth. However, if the same therapies inhibit T cell glucose metabolism, they may limit anti-tumor immunity. Other nutrient levels can affect both cancer and immune cells. High arginine levels promote enhanced T cell survival and anti-tumor activity (Geiger et al., 2016), and therapies that

deplete tumor arginine promote immune suppressor cell accumulation (Fletcher et al., 2015). Lactate can blunt T and NK cell function (Brand et al., 2016). Kynurenine, a breakdown product of tryptophan, can modulate both the innate and adaptive immune system and has been implicated in cancer-associated immunosuppression (Platten et al., 2014) and indoleamine-2,3-dioxygenase (IDO) inhibitors that decrease tryptophan metabolism can help break immune tolerance and potentiate chemotherapy (Muller et al., 2005). Increased MTA levels in MTAP-null tumors can also suppress T cell activation (Henrich et al., 2016) and suggests some metabolic interventions might enhance anti-cancer immune responses.

The relationship between tumors and other organ systems is not limited to the immune system. Endothelial cells also undergo factor-induced metabolic reprogramming, and metabolic therapies can limit endothelial cell proliferation and angiogenesis (De Bock et al., 2013). Cancer also causes alterations in whole body metabolism that may influence tumor nutrient availability. Modulating the amino acid composition of the diet can slow cancer growth (Maddocks et al., 2013) and investigations into how diet affects tumor growth remains an underexplored area.

Clinical utility of neutral metabolic activities

By definition, neutral metabolic activities are not therapeutic targets, but some may still present useful opportunities in clinical oncology, particularly as predictive biomarkers or for tumor imaging. PKM2 expression in tumors is the basis for a positron emission tomography (PET) imaging agent. N,N-diarylsulfonamide (DASA) compounds bind to PKM2, and an ^{11}C-labeled analog of DASA-23 is taken up by PKM2-expressing orthotopic gliomas in mice, providing imaging contrast with the normal brain (Witney et al., 2015). Other investigational PET agents exploit the ability of some tumors to take up and retain glutamine (Venneti et al., 2015). Conversion of ^{13}C-labeled pyruvate to lactate can be imaged in patients by hyperpolarized MRI (Nelson et al., 2013). Some targetable activities are also the basis of new imaging techniques, with the detection of 2HG by magnetic resonance spectroscopy a prominent recent example (Andronesi et al., 2012; Choi et al., 2012). Finally, the heterogeneity of metabolic phenotypes among human cancer patients may provide biomarkers that correlate with disease progression (Hakimi et al., 2016).

FUTURE PERSPECTIVES

Analysis of cell-intrinsic metabolic preferences imposed by the oncogenotype has been informative to uncover new paradigms in proliferating cell metabolic regulation. However, the next phase of cancer metabolism research will need to address increasingly complex questions about how intrinsic and extrinsic influences integrate to create exploitable metabolic phenotypes in cancer. This will require consideration of the metabolic preferences hard-wired into cancer cells by tissue-of-origin, interactions between benign and malignant cells within the microenvironment, and influences of the diet and microbiome on the host. Cell culture systems must be improved to better reflect the metabolic limitations in tumors, and these studies will be propelled by improvements in quantitative assessment of metabolic fluxes in different contexts. Ultimately this will enable matching of the right therapies with the right patients to exploit altered metabolism and improve cancer outcomes.

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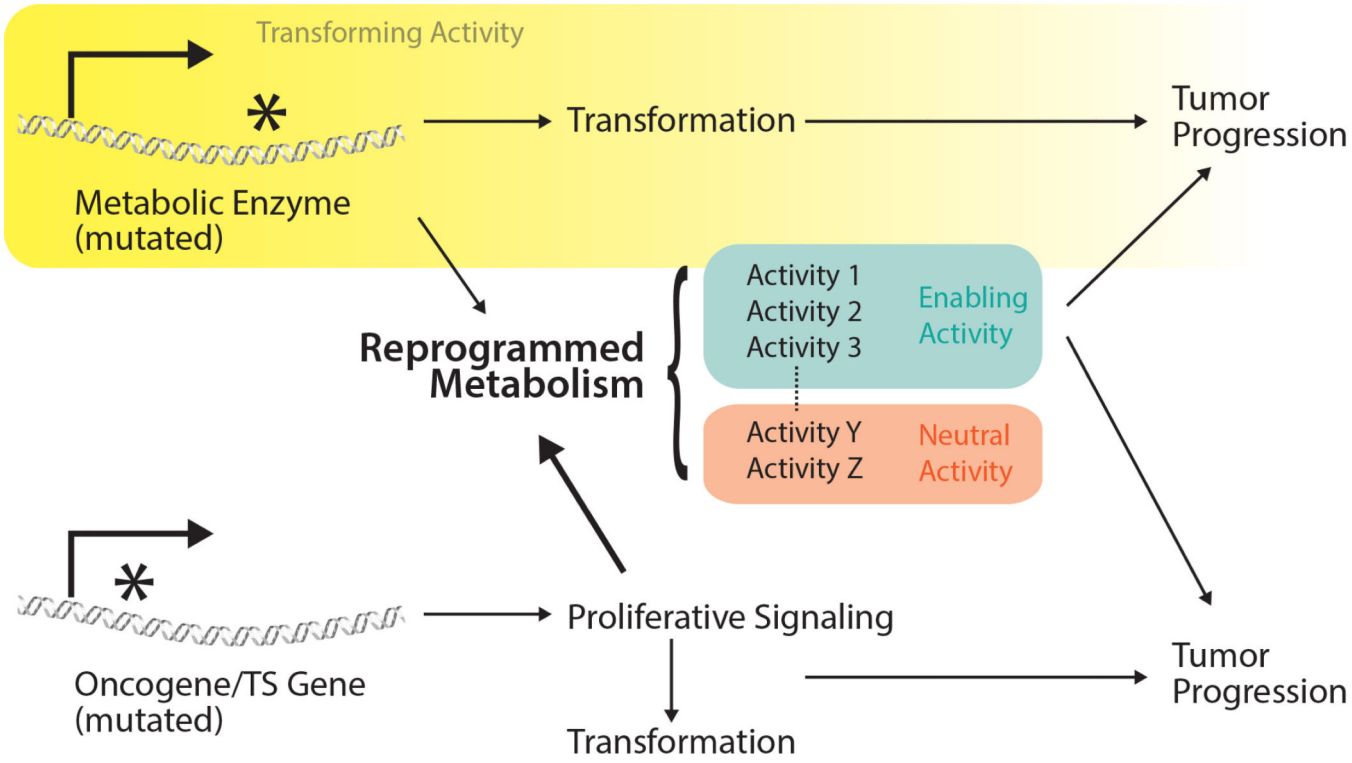

Figure 1. Classification of reprogrammed metabolic activities

Some enzyme mutations result in perturbed metabolic activities or metabolite levels that contribute to cancer initiation (transforming activities). Mutations in oncogenes and tumor suppressor genes transform cells, in part, by activating proliferative signaling and/or by inducing broad changes in gene expression that favor cell proliferation, both of which induce metabolic reprogramming. Some metabolic alterations enable cancer progression while others are neutral and not required for cancer cell proliferation or survival. Enzyme mutations resulting in transforming activities may also induce metabolic network changes that are enabling or neutral for tumor progression.

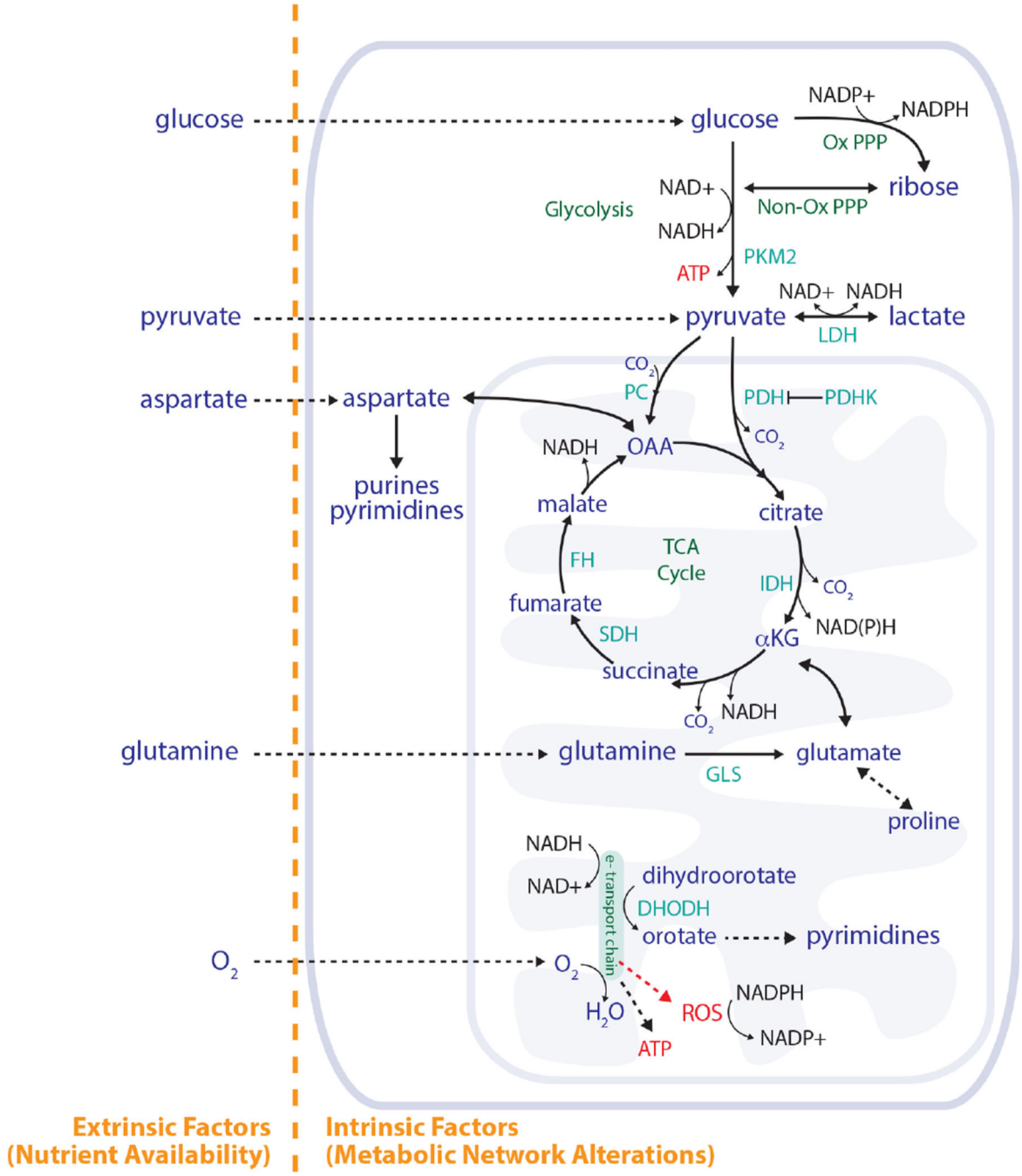

Figure 2. Nutrient availability and the metabolic network both influence metabolic phenotypes

Both nutrient availability and metabolic network configuration affect how cells use metabolism to produce ATP, generate macromolecules, and regulate redox state. Key reactions in central carbon metabolism are shown, including how the TCA cycle and the electron transport chain are involved in purine and pyrimidine synthesis. Some of the reactions catalyzed by enzymes and metabolites discussed in this review are also shown for reference. PKM2, pyruvate kinase M2; LDH, lactate dehydrogenase; PDH, pyruvate dehydrogenase; PDHK, pyruvate dehydrogenase kinase; PC, pyruvate carboxylase; IDH,

isocitrate dehydrogenase; SDH, succinate dehydrogenase; FH, fumarate hydratase; GLS, glutaminase; DHODH, dihydroorotate dehydrogenase; Ox PPP, oxidative pentose phosphate pathway; Non-Ox PPP, non-oxidative pentose phosphate pathway; αKG, α-ketoglutarate; OAA, oxaloacetate; ROS, reactive oxygen species.

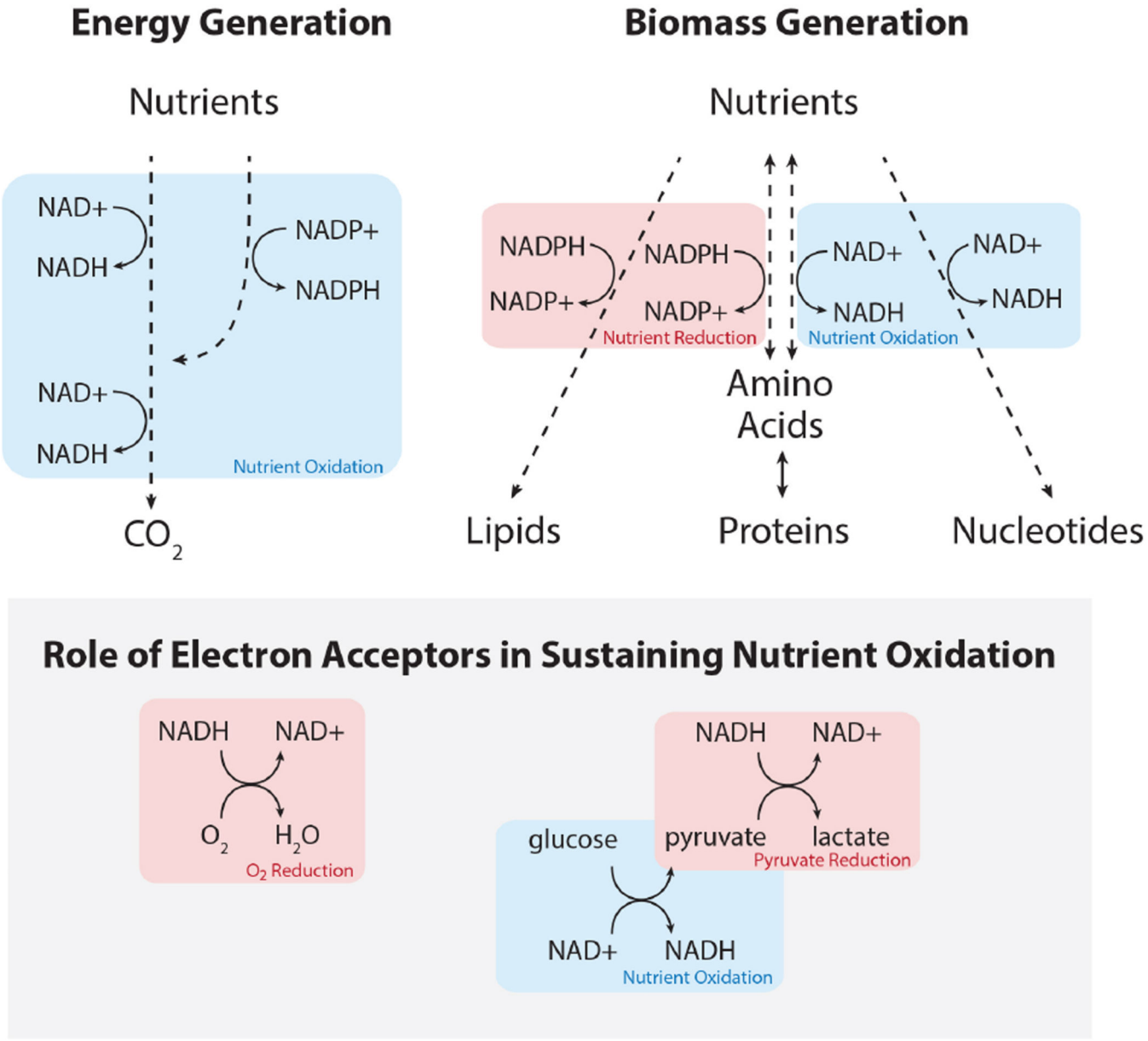

Figure 3. Role of redox cofactors in energy generation and biosynthesis

Cells rely on nutrient oxidation to generate ATP (energy), either through glycolysis or via NADH generation to fuel oxidative phosphorylation. Generating biomass can involve either nutrient reduction or nutrient oxidation. Continued nutrient oxidation requires cycling of NADH back to NAD+, which necessitates transfer of electrons to an electron acceptor such as oxygen.

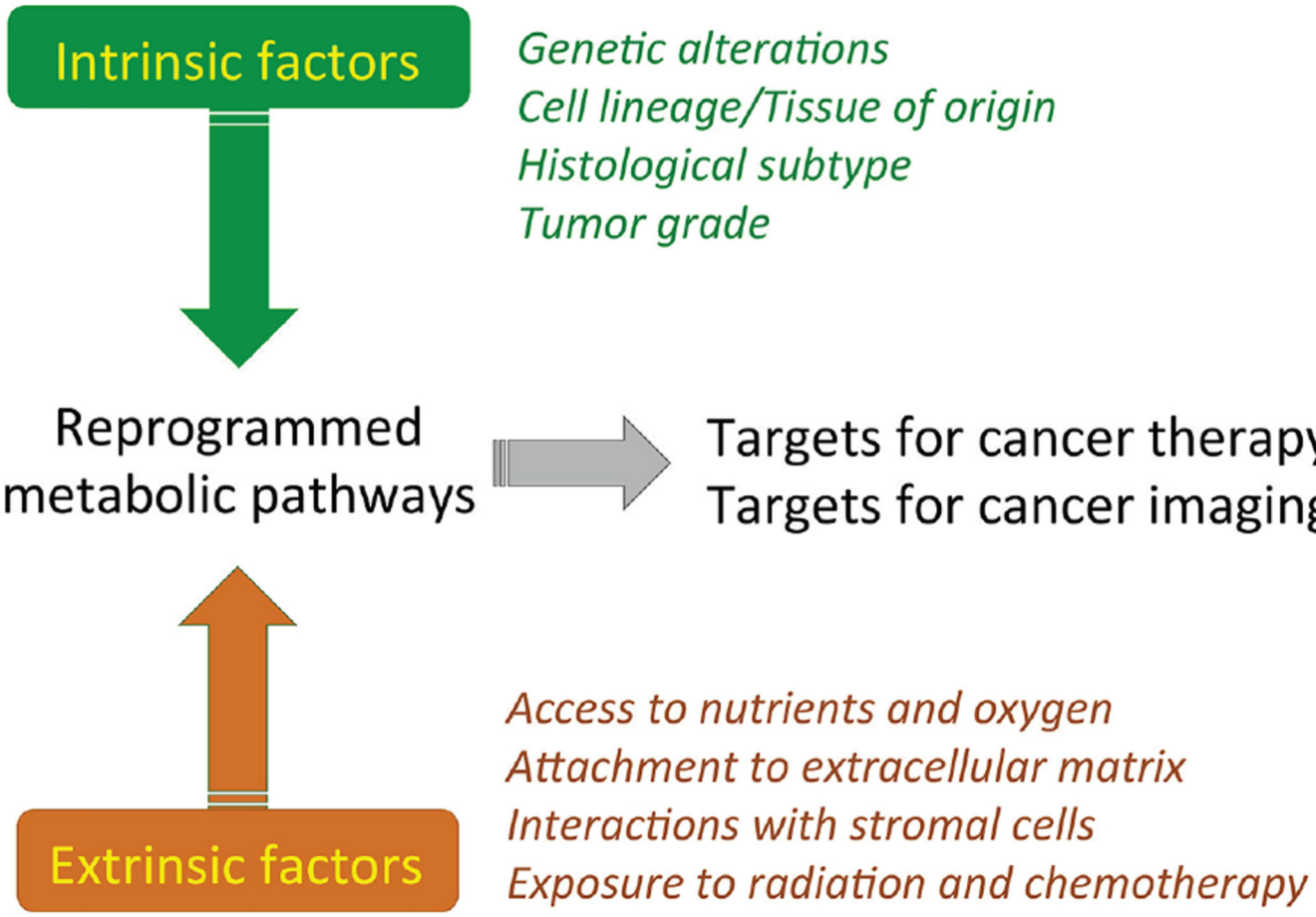

Figure 4. Intrinsic and extrinsic influences on cancer cell metabolic reprogramming

Reprogrammed metabolic pathways, including pathways involved in bioenergetics, anabolism, and redox homeostasis are common features of tumor tissue. The metabolic phenotype of cancer cells is the cumulative result of a variety of processes both intrinsic and extrinsic to the malignant cell. An integrated understanding of the relative contributions of all processes, in the context of intact tumors, will be necessary to exploit metabolic reprogramming in the clinic. Both intrinsically and extrinsically regulated pathways provide opportunities for clinical translation, including new targets for therapy and for non-invasive imaging to detect and monitor cancer.

Table 1

Drugs targeting metabolic enzymes to treat malignancies or suppress immune cell proliferation.

DRUG	TARGET(S)	EXAMPLE INDICATIONS
Nucleotide Metabolism		
Methotrexate	Dihydrofolate Reductase (DHFR)	Lymphoma Breast Cancer Choriocarcinoma Osteosarcoma
Pemetrexed	DHFR Glycinamide ribonucleotide formyl-transferase (GARFT) Thymidylate synthase	Lung cancer Mesothelioma
5-Fluorouracil	Thymidylate synthase	Colon cancer Pancreatic Cancer Breast Cancer
Gemcitabine Cytarabine Fludarabine	Ribonucleotide reductase DNA synthesis	Pancreatic, lung cancer Leukemia Lymphoma
Hydroxyurea	Ribonucleotide reductase	AML
Leflunomide	DHODH	Rheumatoid arthritis psoriatic arthritis
Azathioprine	DNA synthesis	Immunosuppression for transplant
Amino Acid Metabolism		
L-asparginase	Asparagine depletion	ALL
Select Drugs in Trials		
AG120, AG221, AG881, IDH305, BAY1436032, FT-2102	IDH1 and/or IDH2	Clinical trials for AML, MDS, and solid tumors with mutant IDH1 or IDH2
Epacadostat	Indoleamine 2,3-dioxygenase-1 (IDO1)	Clinical trials for CLL, ovarian cancer, melanoma, other cancers
CB-839	Glutaminase	Clinical trials for AML, ALL, solid tumors
TVB-2640	Fatty acid synthase	Clinical trials for solid tumors
PEG-BCT-100 (ADI-PEG20) AEB-1102	Arginine depletion	Clinical trials for hepatocellular carcinoma and other hematological and solid tumors including those with ASS1 deficiency

The cell target(s) for several drugs as well as some approved indications are shown. Some drugs targeting metabolism in clinical trials are also shown.