HHS Public Access

Author manuscript

Cell Chem Biol. Author manuscript; available in PMC 2018 September 21.

Published in final edited form as:

Cell Chem Biol. 2017 September 21; 24(9): 1161–1180. doi:10.1016/j.chembiol.2017.08.028.

Targeting Metabolism for Cancer Therapy

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Abstract

Metabolic reprogramming contributes to tumor development and introduces metabolic liabilities that can be exploited to treat cancer. Chemotherapies targeting metabolism have been effective cancer treatments for decades, and the success of these therapies demonstrates that a therapeutic window exists to target malignant metabolism. New insights into the differential metabolic dependencies of tumors have provided novel therapeutic strategies to exploit altered metabolism, some of which are being evaluated in pre-clinical models or clinical trials. Here, we review our current understanding of cancer metabolism and discuss how this might guide treatments targeting the metabolic requirements of tumor cells.

Introduction

In 1947, Sidney Farber, one of the pioneers of modern chemotherapy, discovered that aminopterin could cause disease remission in children with acute lymphoblastic leukemia (Dayton et al., 2016; Farber and Diamond, 1948). Aminopterin is the precursor of the currently used drugs methotrexate and pemetrexed, both of which are folate analogues that inhibit one-carbon transfer reactions required for de novo nucleotide synthesis (Figure 1, Figure 2a)(Walling, 2006). The early clinical success of antifolates led to the development of an entire class of drugs known as ‘antimetabolites.’ Antimetabolites are small molecules that resemble nucleotide metabolites and inhibit the activity of enzymes involved in nucleotide base synthesis (Table 1). Notable examples include the purine analogues 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG), which inhibit 5-phosphoribosyl-1-pyrophosphatase (PRPP) amidotransferase, the first enzyme in de novo purine biosynthesis (Figure 1a, Figure 2b). 6-MP and 6-TG have been successful in treating many cancers including childhood leukemia (Elion, 1989). The pyrimidine analogue 5-fluorouracil (5-FU) is a synthetic analogue of uracil that inhibits thymidylate synthase, limiting the availability of thymidine

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Disclosures

M.G.V.H. is a consultant and Scientific Advisory Board member for Agios Pharmaceuticals and Aeglea Biotherapeutics.

nucleotides for DNA synthesis (Figure 1b, Figure 2c). 5-FU and the related 5-FU-prodrug capecitabine remain widely used chemotherapies today and are an important treatment for gastrointestinal cancers (Heidelberger et al., 1957; Wagner et al., 2006). Other antimetabolite nucleoside analogues, such as gemcitabine and cytarabine, are incorporated into DNA, resulting in inhibition of DNA polymerases, and are commonly used to treat select cancers (Parker, 2009).

The clinical success of antimetabolites for treating cancer is attributed to the increased metabolic demand of neoplastic cells for nucleotide biosynthesis and DNA replication. However, nucleotide metabolism is only one of many metabolic dependencies altered to support cancer cell proliferation. Proliferating cells have different metabolic requirements from non-proliferating cells (Hsu and Sabatini, 2008; Lunt and Vander Heiden, 2011; Pavlova and Thompson, 2016). While non-proliferating cells have primarily catabolic demands, proliferating cells must balance the divergent catabolic and anabolic requirements of sustaining cellular homeostasis while duplicating cell mass, and thus engage in a metabolic program distinct from that of the normal tissue from which they arose. From a therapeutic perspective, the aberrant metabolism of proliferating cancer cells presents potential opportunities, and there has been a growing interest in studying how best to target cancer metabolism (Bobrovnikova-Marjon and Hurov, 2014; Galluzzi et al., 2013; Martinez-Outschoorn et al., 2017; Vander Heiden, 2011).

Targeting general proliferative metabolism may not offer an adequate therapeutic window since many non-malignant cells, including those in bone marrow, intestinal crypts, and hair follicles, are rapidly proliferating. Furthermore, the proliferation rates of normal cells are often greater than those of cancer cells (Vander Heiden and DeBerardinis, 2017), and prominent side effects of antimetabolite chemotherapy are caused by the destruction of normal rapidly proliferating cells. Myeloid suppression or gastrointestinal toxicity are often dose-limiting toxicities for these drugs.

In spite of toxicity, antimetabolites are standard in many modern chemotherapy regimens that increase patient survival and, in some cases, help cure disease. Factors other than proliferation rate may account for the efficacy of these drugs. Inducing DNA damage with the use of genotoxic chemotherapies can sensitize cells to inhibitors of nucleotide biosynthesis (Brown et al., 2017; Peters et al., 2000), suggesting that oncogenic mutations that reduce the DNA damage response is one explanation for why a therapeutic window exists for antimetabolite compounds. However, antimetabolite drugs are only effective against a subset of cancer types. Many resistant cancers have the same mutational spectrum as sensitive cancers, and defining genetic predictors of chemotherapy response for most malignancies has been difficult. Nevertheless, the fact that antimetabolite chemotherapies are clinically effective suggests that a metabolic therapeutic window exists beyond proliferation rate and response to DNA damage. While the precise mechanisms underlying the differential efficacies of existing antimetabolite therapies are unknown, a better understanding of these and other metabolic therapeutic windows may lead to the development of more effective and selective cancer treatments. Here, we discuss recent advances in cancer metabolism research that have identified metabolic targets and highlight features that might be exploited for improved cancer therapy.

Altered glucose metabolism

More than thirty years preceding Farber's work on antifolates, Otto Warburg reported that cancer cells consume tremendous amounts of glucose and metabolize the majority of the glucose into lactate, even in the presence of oxygen (Warburg, 1924). This phenomenon is now referred to as aerobic glycolysis, or the Warburg effect, and represents a striking metabolic difference between cancer and most normal tissues. Substantial work has sought to target increased glycolysis including efforts to inhibit lactate production and excretion (Doherty and Cleveland, 2013; Hamanaka and Chandel, 2012; Hay, 2016; Pelicano et al., 2006; Zhao et al., 2013). One compound known to block glucose metabolism is 2-deoxyglucose (2-DG) (Wick et al., 1957). 2-DG is phosphorylated by hexokinase to produce 2-deoxyglucose-6-phosphate, which cannot be further metabolized by cells. It therefore accumulates intracellularly and competitively inhibits hexokinase to slow glucose uptake (Figure 3). Numerous preclinical studies have demonstrated anti-proliferative effects of 2-DG (Zhang et al., 2014a). Although early clinical testing yielded responses in some patients, the use of this drug was limited by toxicity associated with hypoglycemia symptoms (Landau et al., 1958). Recent clinical trials have revisited use of 2-DG at lower doses, but these doses are insufficient to inhibit disease progression (Raez et al., 2013; Stein et al., 2010). The relative lack of 2-DG clinical efficacy at tolerable doses has been echoed by most other attempts to directly target aerobic glycolysis. Though efforts to target glucose uptake or lactate production have found some success in preclinical models (Hay, 2016; Shim et al., 1997), clinical success has been limited (Vander Heiden and DeBerardinis, 2017).

Regulation of pyruvate kinase activity can influence aerobic glycolysis (Dayton et al., 2016). Paradoxically, decreased pyruvate kinase activity is associated with increased aerobic glycolysis, suggesting the activation of pyruvate kinase activity might be a way to target cancer (Christofk et al., 2008). Indeed, activation of pyruvate kinase can inhibit cancer cell proliferation and tumor growth in some settings (Anastasiou et al., 2012; Kung et al., 2012; Walsh et al., 2010), but because pyruvate kinase expression is dispensable for the growth of some tumors (Cortes-Cros et al., 2013; Israelsen et al., 2013), whether pyruvate kinase activation will lead to durable responses remains an area of active study (Israelsen et al., 2013; Israelsen and Vander Heiden, 2015)

Despite challenges associated with targeting glucose metabolism directly, glucose uptake by cancer cells has been successfully exploited in patients through the use of the fluoro-deoxyglucose positron-emission-tomography (FDG-PET) imaging to stage cancers and assess response to therapy (d'Amico, 2015; Farwell et al., 2014; Zhu et al., 2011). Notably, many noncancerous tissues, including the brain, are FDG-PET avid (Berti et al., 2014; Cohade, 2010), illustrating that high glucose uptake is not a unique feature of tumors and offering a potential explanation for the relative lack of success in directly targeting glucose metabolism for cancer treatment. Doses of 2-DG that inhibit glycolysis enough to limit cancer growth may not be tolerated due to similar effects in normal tissues that also rely on glucose metabolism.

Altered Metabolic Enzyme Expression

The expression of metabolic genes is frequently altered in cancer. Some changes in metabolic enzyme expression result from gene amplification or deletion, while others are downstream of growth signaling pathways or are the consequences of epigenetic changes. The activity of metabolic enzymes can also be affected by mutations in the genes encoding these enzymes. Regardless of the underlying mechanism, alterations in basal enzymatic activity of a given reaction present potential vulnerabilities that might be targeted for cancer therapy.

Oncogenic isocitrate dehydrogenase mutations

Recurrent somatic point mutations in the genes coding for isocitrate dehydrogenase 1 and 2 (IDH1, IDH2) are found in a wide variety of cancers, including glioblastoma multiforme (GBM) (Yan et al., 2009) and acute myeloid leukemia (AML) (Dang et al., 2016; Mardis et al., 2009). Cancers expressing mutant IDH represent a unique case in which a metabolic enzyme can act as an oncogene and contribute to tumor development. Wild-type IDH1 and IDH2 catalyze the reversible oxidative decarboxylation of isocitrate to alpha-ketoglutarate (αKG) and CO_2 (Figure 4a). Cancer associated mutations in IDH1 and IDH2 eliminate this function and confer a neomorphic activity to the enzyme, generating D-2-hydroxyglutarate (D-2HG) via the reduction of αKG (Figure 4b)(Dang et al., 2009; Ward et al., 2010). Though it is found at low levels in normal cells, D-2HG can accumulate to millimolar levels in cancer cells expressing mutant IDH. At these high concentrations, D-2HG can inhibit αKG-dependent dioxygenases, including enzymes involved in histone and DNA demethylation (Chowdhury et al., 2011; Janke et al., 2017; Koivunen et al., 2012; Xu et al., 2011). As a result, D-2HG accumulation in cancer cells expressing mutant IDH results in hypermethylation of histones and CpG islands in DNA (Figueroa et al., 2010; Lu et al., 2012; Turcan et al., 2012). These epigenetic changes caused by D-2HG contribute to cancer phenotypes (Losman et al., 2013; Rohle et al., 2013; Saha et al., 2014; Wang et al., 2013), and have been proposed to promote oncogenesis by preventing normal cellular differentiation (Losman and Kaelin, 2013).

Pharmacological agents that inhibit mutant IDH1 and IDH2 enzyme activity are being developed and assessed for antitumor efficacy (Figure 4c)(Dang et al., 2016). One of the first compounds reported was AGI-5198, which targets mutant IDH1. AGI-5198 reduces intratumoral D-2HG levels, induces expression of genes involved in glial cell differentiation, and suppresses growth of IDH1-mutant human glioma cells in a xenograft model (Rohle et al., 2013). A specific inhibitor of mutant IDH2, AG-221 (enasidenib) confers survival benefit in a mouse model of IDH2-mutant AML (Quivoron et al., 2014; Yen et al., 2017) and became the first compound targeting mutant IDH to enter clinical trials in 2014. Early results in IDH2-mutant AML patients have suggested enasidenib can provide clinical benefit (DiNardo et al., 2015; Stein et al., 2014), and this drug is also being evaluated in solid tumors. Mutant IDH1 inhibitors including AG-120 (ivosidenib) and IDH305, as well as the pan-mutant IDH inhibitor AG-881 (Table 1), are also in clinical trials to treat both hematologic malignancies and solid tumors, and will further inform whether targeting mutant IDH can control disease where IDH mutations are prevalent.

Despite success in some preclinical models and patients with AML, mutant IDH inhibitors may not be effective in all IDH-mutant cancers. For example, these drugs are unable to reverse epigenetic changes or inhibit tumor proliferation in many models of IDH mutant glioma, despite a robust ability to lower 2-HG in cells and tumors (Tateishi et al., 2015; Turcan et al., 2013). IDH1 mutations are early events in the development of glial cancer (Watanabe et al., 2009), raising the possibility that IDH mutations are important for tumor initiation, but accumulation of additional oncogenic mutations renders GBM tumors less dependent on constitutive expression of mutant IDH for tumor proliferation and progression (Johnson et al., 2014; Wakimoto et al., 2014). Nevertheless, the presence of an IDH mutation and high levels of 2-HG might still drive dependencies on some pathways and introduce therapeutic vulnerability. For example, tumors harboring an IDH mutation have increased sensitivity to hypomethylating agents (Turcan et al., 2013), electron transport chain inhibitors (Grassian et al., 2014), depletion of the coenzyme NAD+ (Tateishi et al., 2015) and chemoradiotherapy (Cairncross et al., 2014). However, some evidence suggests that inhibiting mutant IDH could confer resistance to some therapies, as inhibitors targeting mutant IDH1 can antagonize the effects of radiation therapy in glioma (Molenaar et al., 2015). Thus, testing whether combination therapies are synergistic or antagonistic with inhibition of mutant enzyme function is needed to guide treatment.

Upregulated glutaminolysis

Glutamine is a non-essential amino acid, and yet cancer cells proliferating in vitro consume glutamine far in excess of any other amino acid and are often dependent on extracellular glutamine for survival (DeBerardinis and Cheng, 2010; Eagle, 1955; Jain et al., 2012). Glutamine is an important nitrogen donor for amino acids and nucleotides (Hosios et al., 2016), but glutamine uptake can exceed the nitrogen requirement of some cancer cells (DeBerardinis et al., 2007). Glutamine carbon has been found to contribute to aspartate, glutamate and tricarboxylic acid (TCA) cycle metabolites via glutaminolysis (Figure 5) (Altman et al., 2016). High rates of glutaminolysis has been proposed to support rapid proliferation by supplying precursors to low-flux biosynthetic pathways (Newsholme et al., 1985). Providing cells with αKG, oxaloacetate, or pyruvate is sufficient to rescue cancer cell proliferation in conditions of glutamine starvation, confirming that glutamine supports proliferation by replenishing depleted TCA cycle intermediates, a process termed anaplerosis (Altman et al., 2016; Weinberg et al., 2010; Yuneva et al., 2007).

Glutamine metabolism is upregulated by various oncogenic signaling pathways (Altman et al., 2016). In certain contexts, MYC-transformed cancers become glutamine dependent and undergo apoptosis in the absence of glutamine (Yuneva et al., 2007). MYC has been found to increase mRNA and protein levels of glutamine transporters as well as expression of the enzyme glutaminase, which catalyzes the first step in glutaminolysis (Gao et al., 2009; Wise et al., 2008; Yuneva et al., 2012). Importantly, inhibiting glutamine entry into the TCA cycle can blunt tumor progression in a MYC-driven cancer model of liver cancer (Xiang et al., 2015; Yuneva et al., 2012) and a MYC-inducible Burkitt lymphoma model (Le et al., 2012; Xiang et al., 2015).

The dependence of cancer cells on glutamine has made glutaminolysis an attractive cancer therapy target (Altman et al., 2016; Daye and Wellen, 2012; DeBerardinis and Cheng, 2010; Vander Heiden, 2011). Clinical trials using glutamine analogues to treat cancers were initiated decades ago, but these trials were abandoned due to lack of efficacy and/or severe patient toxicity (Livingston et al., 1970; O'Dwyer et al., 1984). The absence of a therapeutic window for these studies can likely be attributed to fact that these drugs were relatively non-specific and a panoply of glutamine utilizing enzymes were likely affected.

Current attempts to target glutaminolysis clinically have largely focused on inhibiting glutaminase. Mammals have two glutaminase genes, GLS and GLS2, and targeting the enzymes encoded by these genes with chemical inhibitors has been found to decrease cancer cell proliferation in both in vitro and in vivo models (Gross et al., 2014; Jacque et al., 2015; Le et al., 2012; Xiang et al., 2015; Yuneva et al., 2012). One potent glutaminase inhibitor, CB-839, is currently being evaluated in cancer trials in patients (Table 1), although the exact disease context where glutaminase inhibition will be most effective remains an area of active investigation. There is also data that GLS2 activity can be tumor suppressive (Hu et al., 2010), underscoring the importance of defining the patient population likely to benefit from glutaminase inhibition.

Increased dependence on serine

Increased activity of de novo serine synthesis enzymes in cancer has been observed for more than 30 years (Snell, 1984; Snell et al., 1988). More recently, it was found that increased expression of the serine synthesis enzyme phosphoglycerate dehydrogenase (PHGDH) in some cancers can result from copy number gain of a region on chromosome 1p (Beroukhim et al., 2010; Locasale et al., 2011; Possemato et al., 2011) or a consequence of oncogenic signaling, including NRF2 and ATF4 signaling (DeNicola et al., 2015), or hypoxia responses (Samanta et al., 2016). The PHGDH gene encodes the enzyme that catalyzes conversion of the glycolytic intermediate 3-phosphoglycerate into 3-phosphohydroxypyruvate, and 3-phosphohydroxypyruvate is converted to serine via two subsequent reactions (Figure 6). Increased PHGDH gene expression leads to greater production of serine from glucose and is associated with specific subsets of breast cancer, lung adenocarcinoma, and melanoma (Locasale et al., 2011; Possemato et al., 2011; Zhang et al., 2017). Serine is present in plasma and can be taken up by cells via amino acid transporters, yet PHGDH expression and increased serine biosynthesis have been shown to be important for supporting cancer cell proliferation and survival in both in vitro and in vivo settings (Locasale et al., 2011; Possemato et al., 2011). However, PHGDH activity may not be a requirement for proliferation for all PHGDH-amplified cancers, as expression has been shown to be dispensable in a breast cancer xenograft model (Chen et al., 2013).

Why some cancers are dependent on increased serine production is unknown, but increased flux through this pathway may serve to maintain adequate intracellular serine levels. Serine is an amino acid, and thus is required for protein synthesis, but serine can also support many other important critical metabolic processes including synthesis of glycine, glutathione, and phospholipids. With respect to proliferating cells such as cancer, serine is the primary carbon donor to the tetrahydrofolate (THF) cycle, which is required for both purine and pyrimidine

nucleotide biosynthesis (Figure 6)(Snell et al., 1987). Serine can also contribute to NADPH production via the folate cycle, which serves to maintain redox homeostasis and support anabolic reactions (Fan et al., 2014; Lewis et al., 2014; Ye et al., 2014). Emerging work suggests that increased serine synthesis may be particularly important for maintaining redox homeostasis during metastasis (Piskounova et al., 2015).

Given the cancer cell requirement for serine, de novo serine synthesis is a potential target for cancer therapy. Functional PHGDH loss is toxic to tumor cells with PHGDH amplification or high serine biosynthetic flux (Locasale et al., 2011; Mattaini et al., 2015; Possemato et al., 2011; Zhang et al., 2017), and small-molecule inhibitors targeting PHGDH have been shown to inhibit serine synthesis and tumor proliferation in vitro and in xenograft cancer models (Mullarky et al., 2016; Pacold et al., 2016; Wang et al., 2017). However, inhibitors of PHGDH might have a limited therapeutic index, as de novo serine synthesis has an important physiological role in the central nervous system (Furuya, 2008) and PHGDH-deficient mice exhibit severe brain morphogenesis defects (Yoshida et al., 2004). Compounds with decreased distribution in the brain may be more effective for cancer therapy.

Certain tumors are dependent on uptake of environmental serine (Jain et al., 2012; Maddocks et al., 2013; Maddocks et al., 2017), and limiting plasma serine availability can be beneficial for patients with these cancers. Removing serine from culture media limits incorporation of one-carbon units into nucleotides and impairs proliferation (Labuschagne et al., 2014). Additionally, serine deprivation by dietary restriction is sufficient to slow growth of both xenograft (Gravel et al., 2014; Maddocks et al., 2013) and autochthonous cancer models, although efficacy of serine deprivation appears to be influenced by both the oncogenic driver mutation and tissue context (Maddocks et al., 2017). Combining serine restriction with other drugs may also potentiate antitumor responses (Gravel et al., 2014; Maddocks et al., 2013; Maddocks et al., 2017). Further understanding the roles of de novo serine synthesis and serine uptake in different tumor contexts can yield important insights into how to target serine metabolism.

FH and SDH loss in heritable cancer syndromes

In addition to genetic events that increase metabolic enzyme expression, some cancers select for deletion of metabolic enzymes. Familial cancer syndromes caused by fumarate hydratase (FH) or succinate dehydrogenase (SDH) deletion suggest that these TCA enzymes can behave as classical tumor suppressors. Affected families inherit one defective copy of either FH or SDH, and develop an aggressive form of cancer upon loss of heterozygosity (Baysal et al., 2000; Tomlinson et al., 2002). Loss of FH activity or SDH activity results in disruption of the TCA cycle and accumulation of fumarate or succinate, respectively. Like D-2HG, fumarate and succinate accumulation can inhibit some αKG-dependent dioxygenases, resulting in hypermethylation of DNA and histones in tumors exhibiting loss of FH or SDH (Hoekstra et al., 2015; Letouze et al., 2013; Xiao et al., 2012). Additionally, succinate and fumarate inhibit the prolyl hydroxylase domain-containing (PHD) enzymes that regulate stability of hypoxia-inducible factors (HIFs), such that FH and SDH deficient cancers activate the hypoxic gene expression program even under normoxic conditions

(Hewitson et al., 2007; Pollard et al., 2005; Selak et al., 2005). Both epigenetic changes and aberrant HIF activation can contribute to tumor initiation and progression in these cancers.

Loss of FH or SDH introduces vulnerabilities that may be amenable to therapeutic targeting. In silico modeling of metabolic networks suggests that FH-null cells can upregulate heme metabolism to enable their survival (Frezza et al., 2011). The heme biosynthesis pathway uses succinyl-CoA to generate heme (Figure 5), which can be degraded to bilirubin and excreted from cells, allowing cells to dispose of excess TCA cycle carbon. Thus, FH-null cells may increase flux through this pathway as a means to allow partial TCA cycle activity. Consequently, FH deletion renders mouse and human cells more sensitive to genetic and pharmacological inhibition of heme oxygenase 1 (Hmox1), an enzyme involved in heme degradation.

Another potentially targetable metabolic liability of renal cell cancers that have lost FH expression is a dependence on exogenous arginine. The high levels of fumarate resulting from FH deficiency drives argininosuccinate lyase (ASL) and argininosuccinate synthase (ASS1) in a direction that consumes arginine (Figure 7). Depletion of intracellular arginine causes these cells to become arginine auxotrophs (Adam et al., 2013; Zheng et al., 2013), and therapies that deplete exogenous arginine (Table 1) may be effective in treating malignancies where FH is lost (Phillips et al., 2013).

Loss of SDH also results in TCA cycle dysfunction, leading to the accumulation of succinate and depletion of aspartate, fumarate, citrate, and malate. In this context, aspartate cannot be synthesized from glutamine or other sources of αKG, and aspartate production is dependent on pyruvate carboxylase (PC) activity. PC catalyzes carboxylation of pyruvate to oxaloacetate (Figure 5), which can then undergo transamination to form aspartate (Figure 7). To cope with TCA cycle truncation and still produce aspartate, SDH defective cells upregulate PC protein expression in culture and in tumors to synthesize aspartate from glucose (Cardaci et al., 2015; Lussey-Lepoutre et al., 2015). PC ablation impairs SDH-deficient cell proliferation and tumor formation, and thus targeting PC might be exploited to treat these types of cancers.

Loss of argininosuccinate synthase 1 expression

Somatic loss of metabolic enzyme expression may be selected for in other tumor types. For example, some melanoma, lymphoma, glioma, and prostate cancers reduce or lose the expression of the urea cycle enzyme argininosuccinate synthase 1 (ASS1) (Delage et al., 2010). As noted above, ASS1 is involved in arginine synthesis, catalyzing the conversion of citrulline and aspartate to the arginine precursor argininosuccinate (Figure 7). Genetic or epigenetic silencing of ASS1 expression provides an advantage to tumor cells by allowing them to preserve cellular aspartate (Rabinovich et al., 2015), a poorly transported nutrient that can be a critical output of the TCA cycle to support de novo nucleotide synthesis and cell proliferation (Birsoy et al., 2015; Sullivan et al., 2015).

A potential liability of ASS1 deficient cancers is that, like FH null cancers, they are unable to synthesize arginine de novo. As functional arginine auxotrophs, these cells are reliant on exogenous arginine for proliferation and survival and may be sensitive to therapies that

lower arginine availability (Table 1). Arginine deiminase (ADI) is a microbial enzyme that catabolizes arginine and can be used to deplete extracellular arginine levels. Recombinant pegylated arginine deiminase (ADI-PEG20) has been tested in clinical trials to treat melanoma and hepatocellular carcinoma with some therapeutic benefit (Ascierto et al., 2005; Izzo et al., 2004; Ott et al., 2013; Szlosarek et al., 2013; Yang et al., 2010). However, the use of arginine-catabolizing enzymes may not be an effective therapeutic strategy for all ASS1-deficient cancers, as some ADI-treated tumors have been found to re-express ASS1 (Feun et al., 2012; Long et al., 2013; Shen et al., 2003). Whether some tumors are more dependent on loss of ASS1 expression to proliferate is an area of active investigation, as these may be more responsive to arginine depleting drugs. The combination of arginine depletion with other therapies might also limit resistance, and the identification of synthetic lethal targets with ASS1-loss is another approach being evaluated to increase the clinical efficacy of therapies that deplete circulating arginine (Bean et al., 2016; Kremer et al., 2017; Locke et al., 2016).

Metabolic collateral lethality

Loss of metabolic enzyme expression can also occur as a passenger event. For example, genomic deletions leading to loss of tumor suppressor genes can also lead to loss of adjacent non-essential metabolic genes. Because cells often exhibit redundancy in essential pathways, this phenomenon can introduce a therapeutic opportunity to target cancer cells that has been termed collateral lethality (Muller et al., 2015). Pancreatic ductal adenocarcinoma (PDAC) cells exhibiting homozygous deletion of the tumor suppressor SMAD4 often lose malic enzyme 2 (ME2) expression due to the chromosomal proximity of the two genes. Targeting the malic enzyme 3 (ME3) isoform was found to impair tumor proliferation of PDAC xenografts lacking ME2 expression, but had no effect on tumors with intact ME2 (Dey et al., 2017). Similarly, the gene encoding enolase 1 (ENO1) is on the tumor-suppressor locus 1p36, and undergoes homozygous deletion in 1–5% of GBM cancers. Knockdown of enolase 2 (ENO2) in ENO1-null GBM cells resulted in significant inhibition of proliferation and intracranial tumorigenesis, whereas ENO1 expressing cancer cells were insensitive to ENO2 ablation. Furthermore, ENO1 loss results in extreme sensitivity to the pan-enolase inhibitor phosphonoacetohydroxamate (PHAH) and SF2312 (Leonard et al., 2016; Muller et al., 2012). In both examples, decreased metabolic enzyme redundancy rendered the cells dependent on a specific isoform of an enzyme that could be selectively targeted. It also decreases total cellular levels of enzymatic activity for a given reaction, thereby lowering the threshold for toxicity for targeting the corresponding enzyme.

Passenger deletion of metabolic genes can introduce vulnerabilities involving other pathways as well. Deletion of the tumor suppressor CDKN2A results in concomitant deletion of the methionine salvage pathway enzyme methylthioadenosine phosphorylase (MTAP) in many cancers, including 53% of glioblastomas and 26% of pancreatic cancers (Mavrakis et al., 2016). MTAP cleaves methylthioadenosine (MTA), a product of polyamine biosynthesis, into 5-methylthioribose-1-phosphate (MTR) and adenine, which are further metabolized to methionine and adenosine monophosphate (AMP), respectively (Figure 8). MTAP deficient cells are more reliant on de novo purine synthesis to generate AMP, since they are unable to cleave MTA to salvage adenine, and thus MTAP loss makes cells more

susceptible to inhibitors of purine biosynthesis as well as to methionine depletion (Hori et al., 1996). Co-administration of MTA with toxic adenosine analogues has been shown to be selectively lethal to MTAP deficient cancer cells, since MTAP-expressing normal tissues are able to convert MTA to adenine to competitively inhibit the effects of the analogues (Lubin and Lubin, 2009). L-alanosine inhibits conversion of inosine monophosphate (IMP) to AMP, and shows selective toxicity towards MTAP-null cancer cells (Batova et al., 1999; Efferth et al., 2003; Harasawa et al., 2002), but was found to be clinically ineffective in patients with advanced MTAP-deficient tumors in a Phase II trial (Kindler et al., 2009). Pharmacokinetic analyses confirming successful purine biosynthesis inhibition by doses of L-alanosine used in the study were not reported, so further exploration of why this approach failed may yield insight into how best to exploit MTAP deficiency.

Loss of MTAP expression can result in another vulnerability for cancer cells because the MTA that accumulates following MTAP loss can act as a potent inhibitor of the enzyme arginine methyltransferase 5 (PRMT5). MTAP loss results in reduced PRMT5 activity and renders MTAP-null cancer cell more sensitive to PRMT5 depletion than isogenic counterparts that express MTAP (Kryukov et al., 2016; Marjon et al., 2016; Mavrakis et al., 2016). Additionally, ablation of methionine adenosyltransferase II alpha (MAT2A), the enzyme that produces the canonical and high-affinity PRMT5 substrate, S-adenosylmethionine (SAM), also reduces PRMT5-dependent methylation and proliferation in MTAP-deleted cancer cells (Marjon et al., 2016). However, PRMT5 inhibitors in current clinical trials may not be effective in MTAP null cancers, in part because the high levels of MTA in these cells compete for binding of the inhibitors to the enzyme. Future studies will better define whether reducing PRMT5 activity using drugs that act via a different mechanism could be used as effective treatments in tumors where MTAP is co-deleted with CDKN2A.

Emerging Metabolic Targets

Numerous metabolic differences between cancer cells and normal cells have been described. Some recent examples to illustrate how these differences might be exploited for therapy are highlighted, but many other targets have been proposed and are discussed in detail elsewhere (Bobrovnikova-Marjon and Hurov, 2014; Galluzzi et al., 2013; Martinez-Outschoorn et al., 2017).

Targeting de novo lipid synthesis

Several lines of evidence suggest that targeting de novo fatty acid synthesis might be effective in the treatment of some cancers. Fatty acids are a key component of cell membranes and can also act as signaling molecules or store energy. It was first discovered in the 1950s that tumors are able to synthesize lipids, and a subsequent study determined that the large majority of lipids in tumors cells are synthesized de novo, rather being consumed from exogenous sources (Medes et al., 1953; Ookhtens et al., 1984). Since then, numerous studies have identified de novo fatty acid biosynthesis as a key metabolic requirement for some cancers, and it has been dubbed by some as a distinct metabolic “hallmark of the transformed phenotype” (Kuhajda et al., 1994; Menendez and Lupu, 2006; Rohrig and

Schulze, 2016). With the exception of liver, adipose tissue, and lactating breast, adult tissues do not synthesize fatty acids de novo under normal physiological conditions (Menendez and Lupu, 2006), so inhibition of de novo fatty acid synthesis might have an adequate therapeutic window.

Fatty acid synthesis is a multi-step process that primarily occurs in the cytosol of cells. First, acetyl-CoA groups are converted to malonyl-CoA via the enzyme acetyl-CoA carboxylase (ACC). Next, the multidomain enzyme fatty acid synthase (FASN) assembles fatty acid chain palmitate from malonyl-CoA. Although fatty acid synthesis occurs in the cytosol, cytosolic acetyl-CoA is produced from mitochondrial citrate, which is exported from mitochondria and cleaved by cytosolic ATP-citrate lyase (ACLY) (Figure 9). Cancer cells are also able to generate acetyl-CoA from cytosolic acetate (Comerford et al., 2014; Gao et al., 2016; Kamphorst et al., 2014; Mashimo et al., 2014). However, acetate is not always abundant in blood and is not the predominate source of acetyl-CoA used for fatty acid synthesis in some cells (Hosios and Vander Heiden, 2014). Some cancers are nevertheless dependent on expression of acetyl-CoA synthetase 2 (ACSS2), the cytosolic enzyme that allows cells to synthesize acetyl-CoA from acetate, making this represents a potential therapeutic target (Comerford et al., 2014; Schug et al., 2015).

Numerous inhibitors have been developed to target fatty acid synthesis, with attempts to limit cytosolic acetyl-CoA availability via ACLY inhibition as well as direct targeting of the enzymes ACC and FASN (Figure 9). ACLY activity is elevated in cancers (Migita et al., 2008), and targeting ACLY genetically or chemically prevents xenograft tumor formation and proliferation (Adam et al., 2013; Bauer et al., 2005; Hatzivassiliou et al., 2005; Migita et al., 2008). Genetic knockdown of ACC induces apoptosis in cancer cell lines (Brusselmans et al., 2005; Chajes et al., 2006), and an allosteric inhibitor of ACC, ND-646, has shown antitumor efficacy in autochthonous mouse lung tumor models (Svensson et al., 2016). Targeting FASN has been found to reduce palmitoylation of tubulin and disrupt microtubule organization, inhibiting tumor cell growth (Heuer et al., 2017). The compound TVB-2640 is the first compound targeting FASN to enter clinical trials (Table 1), and when combined with paclitaxel, can cause partial responses or prolonged stable disease (Brenner et al., 2017).

Differential requirements for NAD+/NADH homeostasis

Warburg’s observation that cancer cells have dramatically increased glucose consumption and lactate production, even in the presence of oxygen, led to the hypothesis that cancer cells have diminished mitochondrial function (Warburg, 1956). However, subsequent work determined that despite engaging in aerobic glycolysis, cancer cells consume oxygen at levels comparable to normal tissue (Weinhouse, 1956; Zu and Guppy, 2004). Moreover, inhibitors of cellular respiration block proliferation, suggesting that most cancer cells require respiration in order to proliferate (Harris, 1980; Howell and Sager, 1979; Kroll et al., 1983; Loffer and Schneider, 1982; Zhang et al., 2014b). Respiration is also needed for tumor initiation, as tumor cells with impaired oxidative phosphorylation due to depletion of mitochondrial DNA (mtDNA) exhibit increased tumor latency upon subcutaneous transplantation. In fact, cells derived from these tumors acquire host mtDNA to regain the

ability to do respiration, providing compelling evidence that respiration is required and selected for in tumorigenesis (Tan et al., 2015a).

Most cells in the body generate ATP via respiration, so targeting respiration might be expected to be toxic with a limited therapeutic window. However, metformin, one of the commonly prescribed drugs for treating type II diabetes, is safe despite acting as a mitochondrial complex I inhibitor that impairs respiration (Bridges et al., 2014; El-Mir et al., 2000; Owen et al., 2000; Wheaton et al., 2014). Furthermore, retrospective clinical studies have found that metformin use is associated with improved cancer outcomes, reductions in cancer incidence, and decreased cancer mortality (Evans et al., 2005; Franciosi et al., 2013; Gandini et al., 2014; Lee et al., 2012; Noto et al., 2012). Metformin has also been found to cooperate with neo-adjuvant chemotherapy to result in complete tumor regression in some breast cancer patients (Jiralerspong et al., 2009).

The anti-tumorigenic properties of metformin and other biguanides have been modeled in various mouse cancer models (Buzzai et al., 2007; Huang et al., 2008; Shackelford et al., 2013; Wheaton et al., 2014). Although the precise mechanism of metformin action remains controversial (Luengo et al., 2014), recent work has shown that the anti-tumorigenic effect of metformin can at least be partially accounted for by direct mitochondrial complex I inhibition in tumors (Gui et al., 2016; Wheaton et al., 2014). Consistent with this notion, other complex I inhibitors have shown efficacy as anti-tumor agents (Appleyard et al., 2012; Schockel et al., 2015) and may show selective toxicity against oncogene-ablation resistant cells (Viale et al., 2014) and cancer stem cells (Sancho et al., 2015). Additional complex I inhibitors are under development (Bastian et al., 2017), and other inhibitors of respiration or mitochondrial metabolism, including the lipoic acid derivative CPI-613 (Table 1), are currently being assessed in clinical trials (Lycan et al., 2016; Pardee et al., 2014).

Recent work has shed some light on the potential therapeutic window for treating tumors with respiration inhibitors. Mitochondria are viewed as the powerhouse of the cell, with respiration considered primarily as an ATP-producing catabolic process. However, mitochondrial ATP production appears dispensable for many proliferating cells (Birsoy et al., 2015; Sullivan et al., 2015; Titov et al., 2016). Instead, respiration serves an alternative anabolic role for proliferating cells by regenerating the oxidized form of nicotinamide adenine dinucleotide (NAD+) from the reduced form (NADH) (Birsoy et al., 2015; Sullivan et al., 2015; Titov et al., 2016). Maintenance of intracellular NAD+ is required for many cellular processes, including protein deacetylation, ADP-ribosylation and calcium signaling (Chiarugi et al., 2012). Additionally, NAD+ serves as a critical redox cofactor required to generate oxidized molecules, such as amino acids and nucleotides necessary for biomass accumulation (Birsoy et al., 2015; Sullivan et al., 2015; Titov et al., 2016). Proliferating cells often require a high NAD+/NADH ratio to support anabolic reactions, and in some contexts the NAD+/NADH ratio directly correlates with proliferation rate (Gui et al., 2016). Higher NAD+/NADH ratios appear important for proliferation while lower ratios favor mitochondrial ATP production. Thus, one possible explanation for the potential therapeutic window of respiration inhibitors is that the NAD+/NADH ratio regime required for proliferation of tumor cells is distinct from that which is required to maintain ATP production in normal cells.

Targeting NAD+ synthesis could be another mechanism to limit NAD+ pools and target proliferative metabolism. NAD+ is produced via multiple synthesis and salvage pathways, but a major source of NAD+ in proliferating cells is salvage from nicotinamide. The rate-limiting enzyme in this pathway is nicotinamide phosphoribosyltransferase (NAMPT), which is highly expressed in tumors arising from diverse tissues. Small-molecules targeting NAMPT can be effective anti-tumor agents in vitro and in xenograft cancer models (Nahimana et al., 2009; Tan et al., 2015b; Watson et al., 2009). In clinical trials, use of these inhibitors as single agents has not caused tumor remission (von Heideman et al., 2010), but additional studies may uncover how best to safely use these drugs for patient benefit. For example, NAMPT inhibitors may be more effective in contexts of MYC-amplified glioblastoma (Tateishi et al., 2016) or when used in combination with other drugs known to deplete NAD+ pools (Bajrami et al., 2012; Chan et al., 2014).

Targeting nucleotide acquisition and synthesis

Acquiring nucleotides is critical for cell proliferation. Nucleic acids can be synthesized de novo or scavenged from the environment. Though nucleotide salvage pathways can support tumor cell proliferation in certain contexts (Tabata et al., 2017), concentrations of circulating nucleotides are likely too low for many tumors to satisfy their nucleotides demand via salvage alone (Traut, 1994). Nevertheless, the ability of some tumor cells to scavenge nucleotides is exploited for cancer therapy. While most cells are able to scavenge the epigenetically modified cytosine bases 5-hydroxymethyl-2′deoxycytidine (5hmdC) and 5-formy-2′deoxycytidine (5fdC) and incorporate these bases into the DNA without compromising genome integrity, cancer cell lines overexpressing cytidine deaminase (CDA) convert these bases to the corresponding modified uracil analogues, which induce cytotoxicity when incorporated into DNA (Zauri et al., 2015). Thus, administering 5hmdC and 5fdC may selectively target tumors overexpressing CDA.

The clinical success of some antimetabolites argues select tumors are reliant on de novo nucleotide synthesis. Nucleotide biosynthesis interfaces with other metabolic pathways; ribose is synthesized from glucose via the pentose phosphate pathway and nucleotide bases require carbon atoms from amino acids and the one-carbon pool as well as nitrogen atoms from aspartate and glutamine. Consequently, targeting amino acid and folate metabolism can affect nucleotide production. For example, eliminating environmental serine, limiting aspartate synthesis via mitochondrial inhibition, and ablating the mitochondrial folate pathway impairs purine biosynthesis (Ducker et al., 2016; Labuschagne et al., 2014; Sullivan et al., 2015). This raises the possibility that these interventions can widen the therapeutic window of established antimetabolites, and future studies will determine whether targeting these pathways is synergistic with existing antimetabolite therapies in certain contexts.

Nucleotide production is downstream of some oncogenic signaling pathways. Activation of mTOR can increase ribose synthesis via the oxidative pentose phosphate pathway (Duvel et al., 2010) and enhance flux through the pyrimidine and purine synthesis pathways (Ben-Sahra et al., 2013; Ben-Sahra et al., 2016; Robitaille et al., 2013), suggesting that targeting nucleotide metabolism in tumor contexts with mTOR hyperactivation may be more effective. PTEN-deficient cells, which have active mTOR signaling, are more sensitive to inhibition of

DHODH by brequinar and leflunomide (Mathur et al., 2017). Conversely, inhibiting oncogenic signaling using PI3K inhibitors, has been found to deplete DNA nucleotides, decrease DNA synthesis, and cause DNA damage (Juvekar et al., 2016). KRAS/LKB1-null lung cancer cells are more reliant on the urea cycle enzyme carbamoyl phosphate synthetase-1 (CPS1) for pyrimidine biosynthesis, although this dependency is independent of mTOR signaling (Kim et al., 2017).

Increased requirement for detoxification of reactive metabolites

Cancer cells generally have increased levels of reactive metabolites (DeBerardinis and Chandel, 2016; Sullivan et al., 2016). These metabolites can be formed as error products of metabolic enzymes or can be formed non-enzymatically due to the intrinsic reactivity of certain metabolic intermediates. Some of these byproducts, including reactive oxygen species (ROS) and methylglyoxal, are themselves chemically unstable and, thus, can covalently modify both amino acids and nucleic acids. While elevation of reactive metabolites can support oncogenesis in some contexts (Arnold et al., 2001; Irani et al., 1997; Suh et al., 1999; Weinberg et al., 2010), at high levels reactive metabolites become toxic and kill cells due to the resulting damage to the proteome and genome (Karisch et al., 2011; Rabbani and Thornalley, 2014). Cancer cells rely on several pathways to prevent reactive metabolite accumulation. For example, the transcription factor Nrf2, which mediates an antioxidant response program to detoxify ROS, is downstream of several oncogenic drivers, and loss of Nrf2 in this context can impair tumor proliferation (Chio et al., 2016; DeNicola et al., 2011). Disruption of this and other detoxification pathways is predicted to have a more deleterious effect on cancer cells than normal cells, and thus serves as a potential targetable metabolic liability.

An alternative strategy for exploiting the increased production of reactive metabolites observed in cancer cells is to target the synthesis or utilization of antioxidants such as glutathione. Glutathione is a cysteine-containing tripeptide that plays a crucial role in many detoxification pathways. It is one of the most abundant metabolites in the cell and serves to reduce the levels of reactive metabolites by serving as a substrate for electrophilic attack. Several screens for small-molecules that selectively kill transformed cells have identified compounds that reduce glutathione levels (Dolma et al., 2003; Raj et al., 2011; Trachootham et al., 2006), and genetic or pharmacological inhibition of glutathione synthesis results in ROS accumulation and impedes cancer initiation and cell proliferation (Harris et al., 2015; Lien et al., 2016). Therapeutic interventions that decrease intracellular glutathione levels, such as administration of the oxidized form of vitamin C, dehydroascorbate (DHA), can result in cancer cell death and impaired tumor progression (Yun et al., 2015)

Another way to deplete intracellular glutathione is by limiting availability of the amino acid cysteine, the key reactive residue of glutathione that is required for its synthesis. Many cancer cells are auxotrophic for this amino acid, and lowering whole body cysteine levels with bacterial cysteineases is a potential cancer treatment being evaluated in clinical trials (Graczyk-Jarzynka et al., 2017). Targeting the cystine and glutamate transporter xCT (SLC7A11) is another approach to limit intracellular cysteine availability and prevent cysteine-dependent glutathione synthesis. Inhibitors of this transporter have been found to

deplete intracellular glutathione in cancer cells, resulting in iron-dependent accumulation of ROS and a form of cell death termed ferroptosis (Dixon et al., 2012; Dixon et al., 2014; Yang et al., 2014).

Lineage and Environment Specific Vulnerabilities

Analysis of gene expression across different cancer types has determined that metabolic enzyme expression is heterogeneous across tumors, and there is no universal metabolic transformation common to all cancers. In fact, tumors retain many features that correspond to their parental normal tissue (Gaude and Frezza, 2016; Hu et al., 2013). It is not known whether this effect results from rigid lineage-specific metabolic expression programs or from the similar local microenvironment experienced by the tumor and normal tissue. However, these analyses suggest that metabolic vulnerabilities may not be universal across all cancers and highlight the possibility that some metabolic dependencies of cancer may be modulated by environment or defined by tumor lineage.

Differential utilization of amino acids

Acquisition of amino acids is an important biosynthetic requirement for cancer cells to support proliferation (Hosios et al., 2016). How cells acquire amino acids can vary according to cell type and environment, and therefore targeting amino acid metabolism could offer a therapeutic window for cancer treatment (Yuneva et al., 2012). Recently, it has been determined that mouse lung and pancreatic tumors exhibit differences in amino acid metabolism, even when harboring the same genetic lesion. Lung tumors support their nitrogen requirement by catabolizing free branched chain amino acids (BCAA), whereas pancreatic tumors expressing the same driver mutation do not. Targeting BCAA transaminases inhibits lung tumor formation better than pancreatic tumor formation, suggesting that dependence on branched chain amino acid catabolism is determined by cell lineage rather than tumor site (Mayers et al., 2016). Tumors of other lineages are also dependent on BCAA transaminases, including some glioblastomas and blast crisis chronic myeloid leukemia (Hattori et al., 2017; Tonjes et al., 2013). Together, these observations suggest that tissue-of-origin can influence metabolic requirements and vulnerabilities.

Asparagine auxotrophy in acute lymphoblastic leukemia

The non-essential amino acid asparagine is abundant in plasma and can also be synthesized by many cell types, so either source of asparagine is dispensable for most cells. Acute lymphoblastic leukemia (ALL) and related lymphomas, however, are auxotrophic for asparagine (Neuman and McCoy, 1956). Bacterial L-asparaginase deamidates asparagine to aspartic acid, thereby limiting the availability of asparagine for cancer cells. L-asparaginase has been found to be effective in the treatment of ALL and is included in standard chemotherapy regimens for this disease (Table 1)(Egler et al., 2016). Though the mechanism of asparagine auxotrophy in ALL cells was assumed to be genetically defined, studies have shown that clinical response to L-asparaginase treatment is independent of asparagine synthase (ASNS) expression, the enzyme that converts aspartate to asparagine (Figure 7) (Appel et al., 2006; Stams et al., 2003). In fact, genome-wide analysis has shown that there is no consistent gene expression pattern that dictates sensitivity to L-asparaginase (Fine et

al., 2005). The absence of a genetic driver for asparagine auxotrophy, combined with the fact that L-asparaginase has little known clinical utility outside of the context of ALL, suggests that this metabolic vulnerability may be lineage dependent.

Inducing differentiation in myeloid cells

A common feature of acute myeloid leukemia (AML) is that leukemic myeloblasts arrest at an immature stage of differentiation. This differentiation blockade is a hallmark of AML even though there are multiple driver mutations for this disease. Inhibitors of mutant IDH1 or IDH2 have been shown to induce differentiation in AML cells harboring mutant IDH (Okoye-Okafor et al., 2015; Wang et al., 2013). The transcription factor HoxA9 is overexpressed in 70% of AML cases, and overexpression of this transcription factor alone is sufficient to immortalize murine bone marrow derived myeloid cells (Ayton and Cleary, 2003; Golub et al., 1999; Kroon et al., 1998). Recently, a myeloid cell screen involving HoxA9-enforced differentiation arrest found that inhibition of dihydroorotate dehydrogenase (DHODH), an enzyme in the pyrimidine biosynthesis pathway (Figure 1b), can induce differentiation (Sykes et al., 2016). Targeting DHODH depletes uridine and downstream metabolites, and providing uridine is sufficient to maintain myeloid arrest, even in the presence of compounds targeting DHODH. Treatment with brequinar sodium (BRQ), an inhibitor of DHODH that is approved to treat autoimmune disease, is able to overcome myeloid differentiation blockade and reduces leukemic cell burden in patient-derived xenografts and syngeneic mouse AML models of diverse genetic subtypes. BRQ was previously evaluated to treat advanced solid tumors but was not shown to be effective in clinical trials (Arteaga et al., 1989; Noe et al., 1990; Peters et al., 1990). However, the effect of BRQ on patients with hematologic malignancies has not yet been evaluated. Future trials will determine whether targeting DHODH could exploit a cell lineage-dependent liability in hematological malignancies.

Non-tumor cells can influence tumor cell metabolism

Metabolic symbiosis likely exists between tumor cells and the surrounding stroma, and this interaction could also contribute to tumor growth and proliferation. Typically, lactate is excreted at high rates by tumor cells, but lactate has also been described as an oxidative substrate for some cancers. It has been reported that lactate produced by cancer-associated fibroblasts can enter the TCA cycle of cancer cells (Bonuccelli et al., 2014; Witkiewicz et al., 2012), and lactate produced in hypoxic regions of a tumor can fuel respiration in well-oxygenated tumor cells (Kennedy et al., 2013; Sonveaux et al., 2008). Intraoperative isotopically-labeled glucose infusions performed on non-small cell lung cancer patients revealed higher contribution of glucose carbon to TCA intermediates than glycolytic intermediates in tumors, leading the authors to conclude that lactate could serve as an anaplerotic substrate in this context as well (Hensley et al., 2016). Lactate utilization by tumors is dependent on monocarboxylate transporters (MCTs) (Figure 3), which are highly expressed in a variety of tumors (Pinheiro et al., 2012). Compounds targeting MCT1 are currently being evaluated for antitumor efficacy (Table 1)(Marchiq and Pouyssegur, 2016).

Alanine is rarely limiting for proliferation, as cancer cells typically excrete, rather than consume, alanine (DeBerardinis et al., 2007; Hosios et al., 2016; Jain et al., 2012). However,

in some contexts cells may not synthesize alanine in excess of their biosynthetic requirements. Pancreatic ductal adenocarcinoma cells can consume alanine produced by pancreatic stellate cells in vitro, and the secreted alanine appears to help promote tumor cell proliferation and survival under nutrient-limited conditions (Sousa et al., 2016). An improved understanding of the interaction between PDAC tumors and stroma can help determine the metabolic limitations of pancreatic tumor growth, and guide target selection to exploit this symbiotic relationship for therapy.

Metabolic dependencies can be modulated by environment

Differences in nutrient availability may contribute to sensitivity or resistance of cancer cells to some drugs. For example, most cells in culture rely on glutamine metabolism, but targeting glutaminase is not an effective cancer therapy in all contexts. Glutamine tracing studies have demonstrated that in some tumor tissues, glutamine contributes minimally to TCA cycle intermediates, and those cancers can be resistant to glutaminase inhibition (Davidson et al., 2016; Hensley et al., 2016; Marin-Valencia et al., 2012; Sellers et al., 2015; Tardito et al., 2015). Importantly, cell lines derived from resistant lung tumors become sensitive to glutaminase inhibition in vitro, highlighting that environment can be a contributor to glutaminase sensitivity (Davidson et al., 2016). What factors determine the differential use of glutamine in different environments remains an active question. Targeting redox homeostasis with the drug metformin is another example where environment can influence drug efficacy (Gui et al., 2016). Altering culture media conditions is sufficient to change cancer cell sensitivity to metformin, highlighting the importance of environment in modulating metabolic dependencies.

What Dictates Metabolic Dependencies?

One of the biggest hurdles for cancer drug development is identifying the patients most likely to respond to a given therapy. With the recent success of some targeted cancer therapies, patient selection for drugs is often predicated on expression of an oncogene or the increased activity of a downstream signaling pathway. However, this same approach may not identify responders for all metabolic cancer therapies, and indeed, response to chemotherapies that target metabolism has not been well predicted by this approach. The protein targets of methotrexate and 5-FU are present in almost all cancers, but the efficacy of these drugs varies dramatically across malignancies. Many of the emerging metabolic targets discussed in this review are also expressed widely in cancer, but dependency on these metabolic pathways is not always universal. For example, while targeting ACC to limit fatty synthesis can suppress lung tumor progression in some models (Svensson et al., 2016), loss of ACC activity can accelerate tumor growth in other cancer models (Jeon et al., 2012). Similarly, many PHGDH-amplified tumors and cell lines are sensitive to genetic or pharmacological inhibition of the enzyme (Locasale et al., 2011; Mullarky et al., 2016; Pacold et al., 2016; Possemato et al., 2011; Wang et al., 2017; Zhang et al., 2017), but for some tumor models PHGDH expression can be dispensable for growth (Chen et al., 2013). Even among cancers where mutant IDH is an oncogenic driver, sensitivity to mutant IDH inhibitors appears to differ between leukemia and solid tumor models (Tateishi et al., 2015; Turcan et al., 2013).

There is growing evidence that metabolic dependencies in cancer are influenced by tissue environment, cancer lineage, as well as genetic events. Cancer tissue-of-origin has served as a successful way to select patients for chemotherapies targeting metabolism for decades, and environment can also influence the efficacy of drugs targeting DHODH, mitochondrial complex I, and glutaminase (Davidson et al., 2016; Gui et al., 2016; Marin-Valencia et al., 2012; Sellers et al., 2015; Sykes et al., 2016; Tardito et al., 2015). Unraveling the complexity for how lineage, environment and genetics interact to create metabolic dependencies will be challenging, but may provide a path to exploit metabolism in a way that could be transformative for patients. Additionally, immunotherapies are playing an increasing role in cancer therapy, and immune cell fate can also be influenced by metabolism. Determining how immune cell metabolism interacts with tumor metabolism, and how this is modulated by drugs targeting metabolic enzymes, might aid in the design of more effective immunotherapies (Buck et al., 2017; Mockler et al., 2014).

Many drugs targeting metabolism are among the most effective clinical drugs for particular diseases, and many newer metabolic therapies are limited more by toxicities than by their ability to kill cancer cells. A better understanding of the metabolic dependencies in specific tumor tissues holds the key for defining the aspects of metabolism most limiting for tumor growth and finding a therapeutic window to exploit those vulnerabilities for better cancer treatment.

Acknowledgments

The authors thank members of the Vander Heiden laboratory for thoughtful discussions and comments on the manuscript. M.G.V.H. acknowledges support from the Lustgarten Foundation, SU2C, the Ludwig Center at MIT, the NCI, and an HHMI Faculty Scholar's award. A.L. was supported by the Ludwig Center for Molecular Oncology Fund and NSF (GRFP DGE-1122374). D.Y.G received support from NIH (T32 GM007753).

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The success of chemotherapies targeting metabolism illustrate that metabolic liabilities can be exploited to treat cancer. We review new insights into the differential metabolic dependencies of tumors and discuss how understanding cancer metabolism might guide the development of new drugs that target the metabolic requirements of tumor cells.

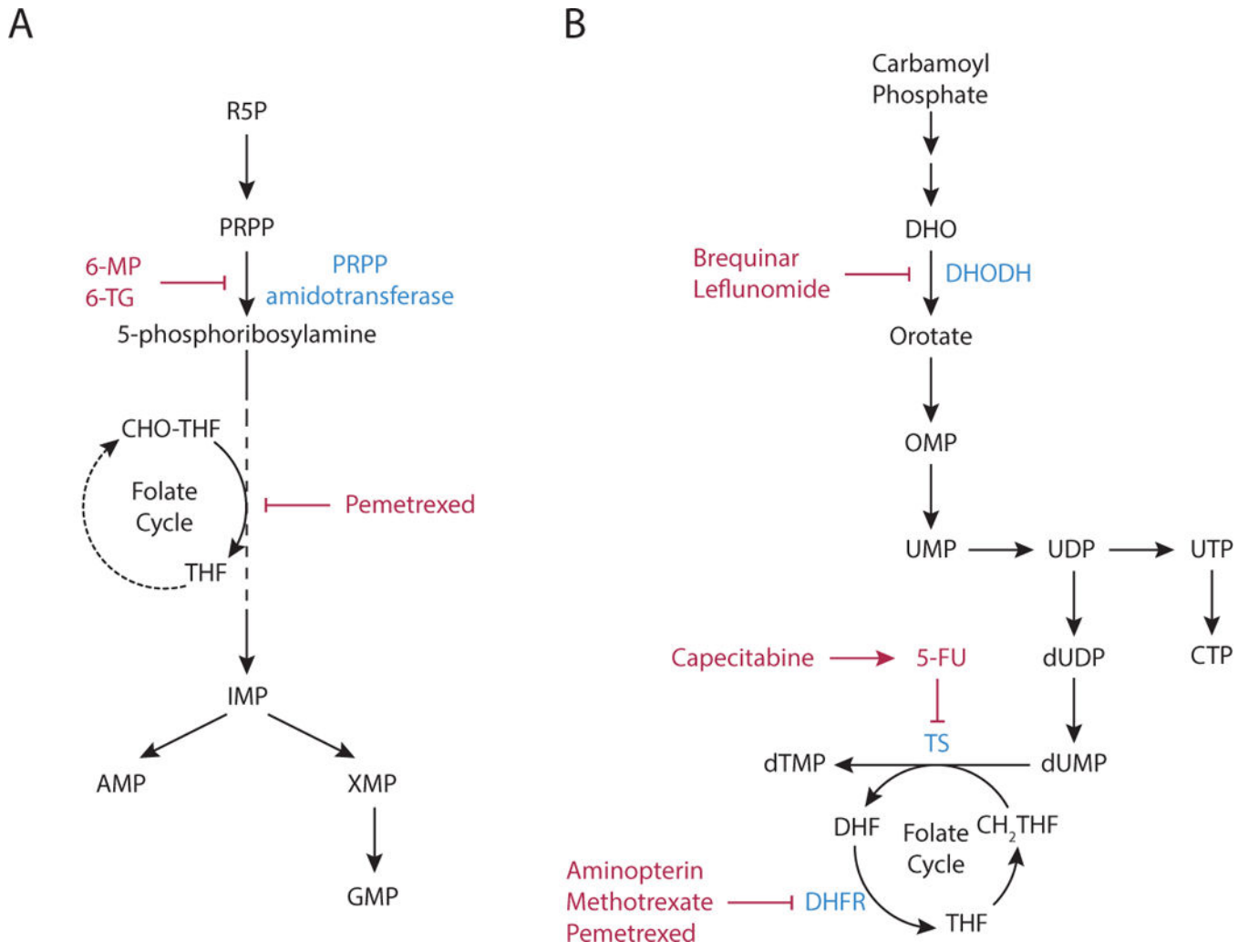

Figure 1. Nucleotide Biosynthesis

(A) Purine nucleotide synthesis. The first reaction in purine production generates 5-phosphoribosyl-1-pyrophosphatae (PRPP) from ribose 5-phosphate (R5P). The second step is catalyzed by PRPP amidotransferase, and commits PRPP to purine synthesis. This step can be inhibited by the antimetabolites, 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG). Subsequent steps in the pathway assemble the purine ring and result in the formation of inosine monophosphate (IMP), which in turn can be converted to either adenosine monophosphate (AMP) or guanosine monophosphate (GMP) by distinct reactions. The synthesis of the purine ring requires N^{10}-formyl-tetrahydrofolate (CHO-THF) via a reaction that can be inhibited by pemetrexed.

(B) Pyrimidine nucleotide synthesis. Pyrimidine nucleotide synthesis begins with the conversion of carbamoyl phosphate to the pyrimidine base orotate. One of the steps in pathway is catalyzed by dihydroorotate dehydrogenase (DHODH), which can be inhibited by brequinar sodium and leflunomide. Next, orotate is combined with PRPP to generate orotate monophosphate (OMP), which is subsequently converted to uridine monophosphate (UMP). UMP can be phosphorylated to form UDP and UTP, and the latter can be further converted to citidine triphosphate (CTP). Uridine nucleotides can also be used for de novo

thymine nucleotide synthesis. UDP is converted to deoxy-UMP (dUMP), and the enzyme thymidylate synthase (TS) generates dTMP by catalyzing the methylation of dUMP using N^5,N^{10}-methylene-tetrahydrofolate (CH_2-THF) as the methyl donor. TS activity is inhibited by the antipyrimidine 5-fluorouracil (5-FU) and the 5-FU pro-drug capecitabine. Thymidine synthesis can also be inhibited by the antifolates aminopterin, methotrexate, and pemetrexed, as these drugs inhibit the enzyme dihydrofolate reductase (DHFR), limiting the availability of CH_2-THF.

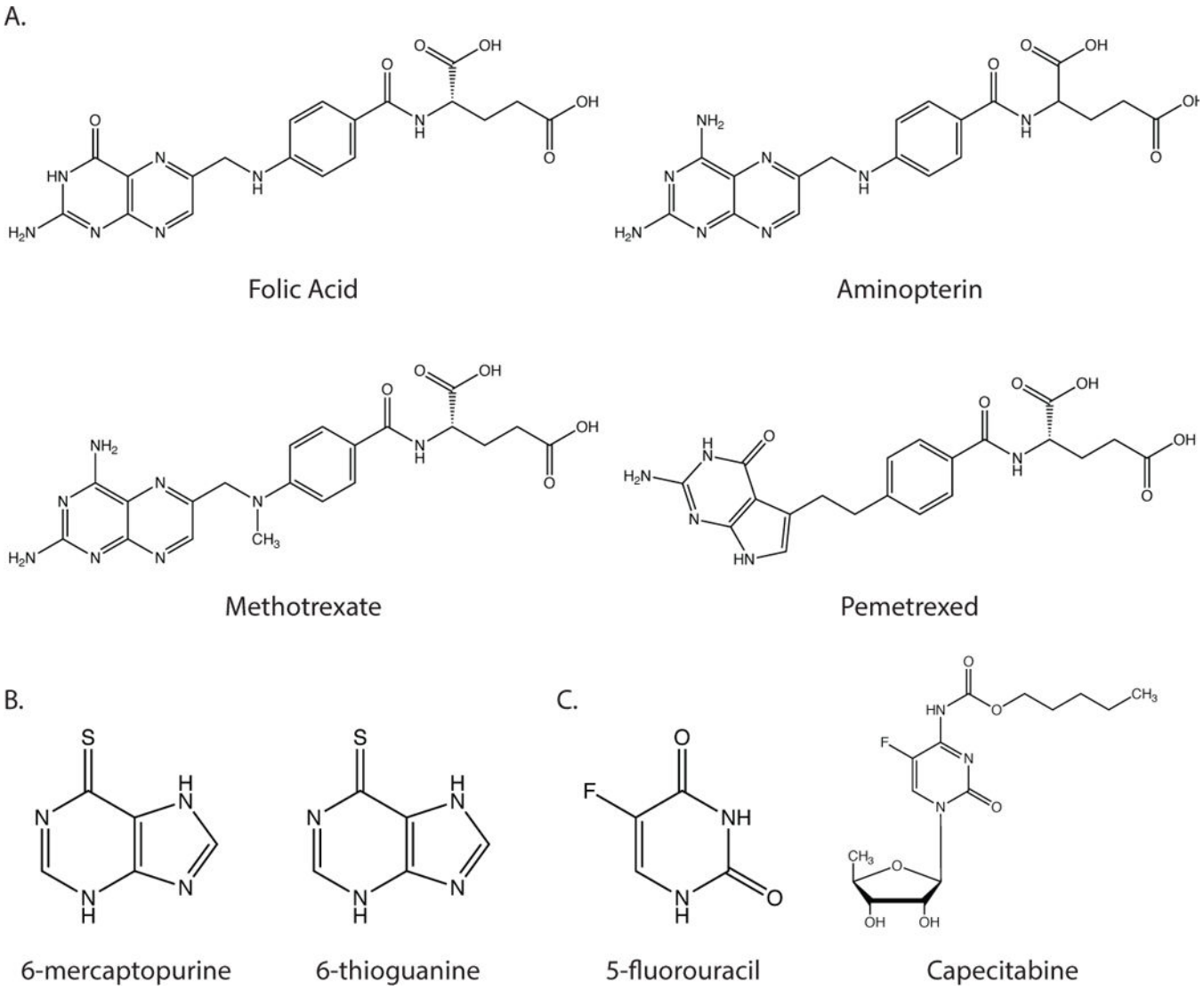

Figure 2. Antimetabolites

(A) Structures of folic acid and the antifolate compounds aminopterin, methotrexate and pemetrexed. (B) Structures f the purine analogues 6-mercaptopurine and 6-thioguanine (C) Structures of pyrimidine analogue 5-fluorouracil and the 5-fluorouracil prodrug capecitabine.

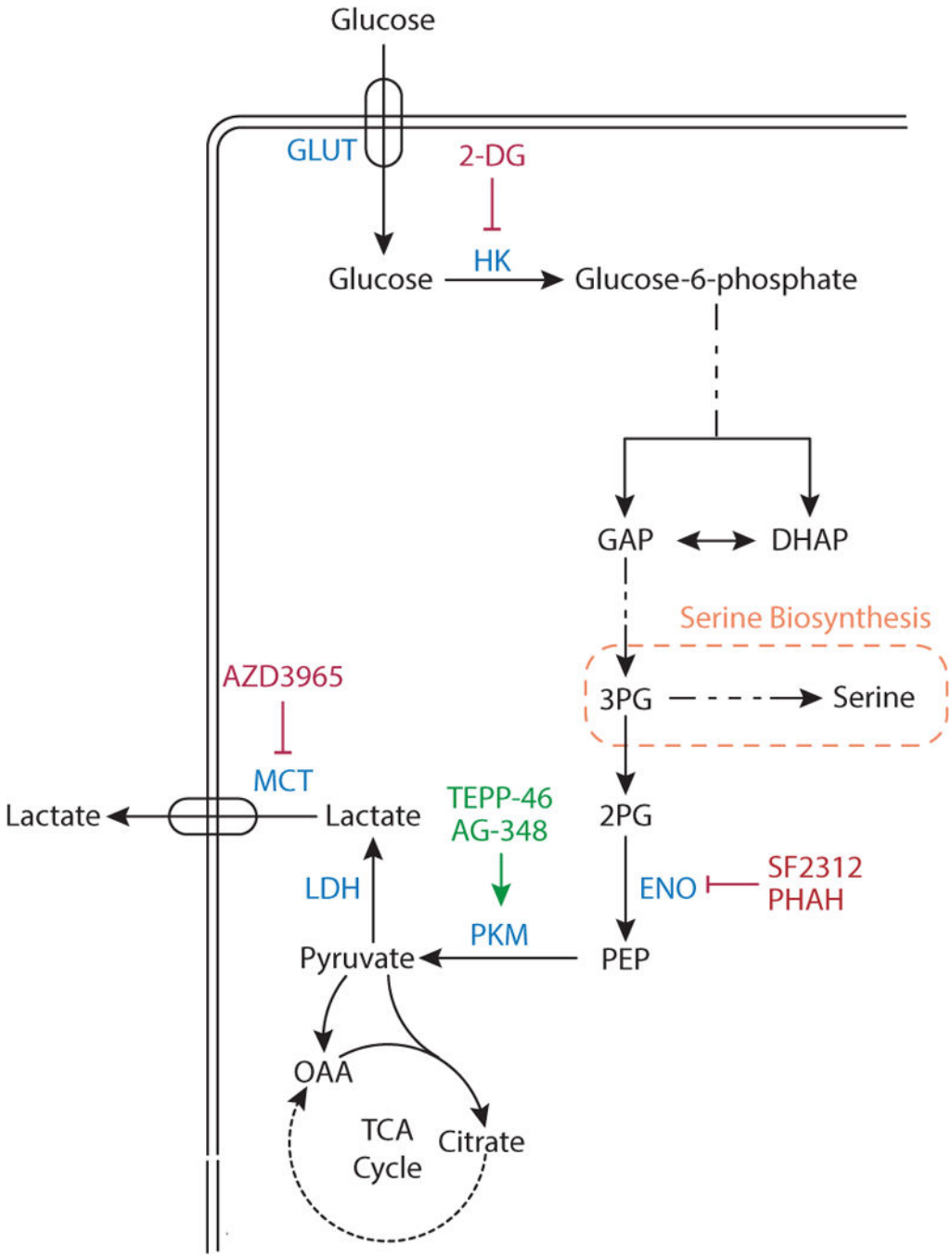

Figure 3. Glycolysis

Glucose is imported in cells by one of several glucose transporters (GLUT). Glucose is phosphorylated by hexokinase (HK), a step that can be competitively inhibited by the compound 2-deoxyglucose (2-DG). In a later step of glycolysis, glucose carbon is cleaved into two interconvertible three-carbon units, dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3-phosphate (GAP). Downstream of GAP, 3-phosphoglycerate (3-PG) is converted to 2-phosphoglycerate (2-PG), and the enzyme enolase (ENO) generates phosphoenolpyruvate (PEP) from 2-PG. ENO activity can be inhibited by the compounds

phosphonoacetohydroxamate (PHAH) and SF-2312. PEP is converted to pyruvate by pyruvate kinase (PKM), which can be activated by the drugs TEPP-46 and AG-348. Pyruvate can be oxidized in the TCA cycle, or it can produce lactate via lactate dehydrogenase (LDH), with lactate excreted by monocarboxylate transporters (MCT). MCT isoform 1 can be inhibited by the compound AZD3965.

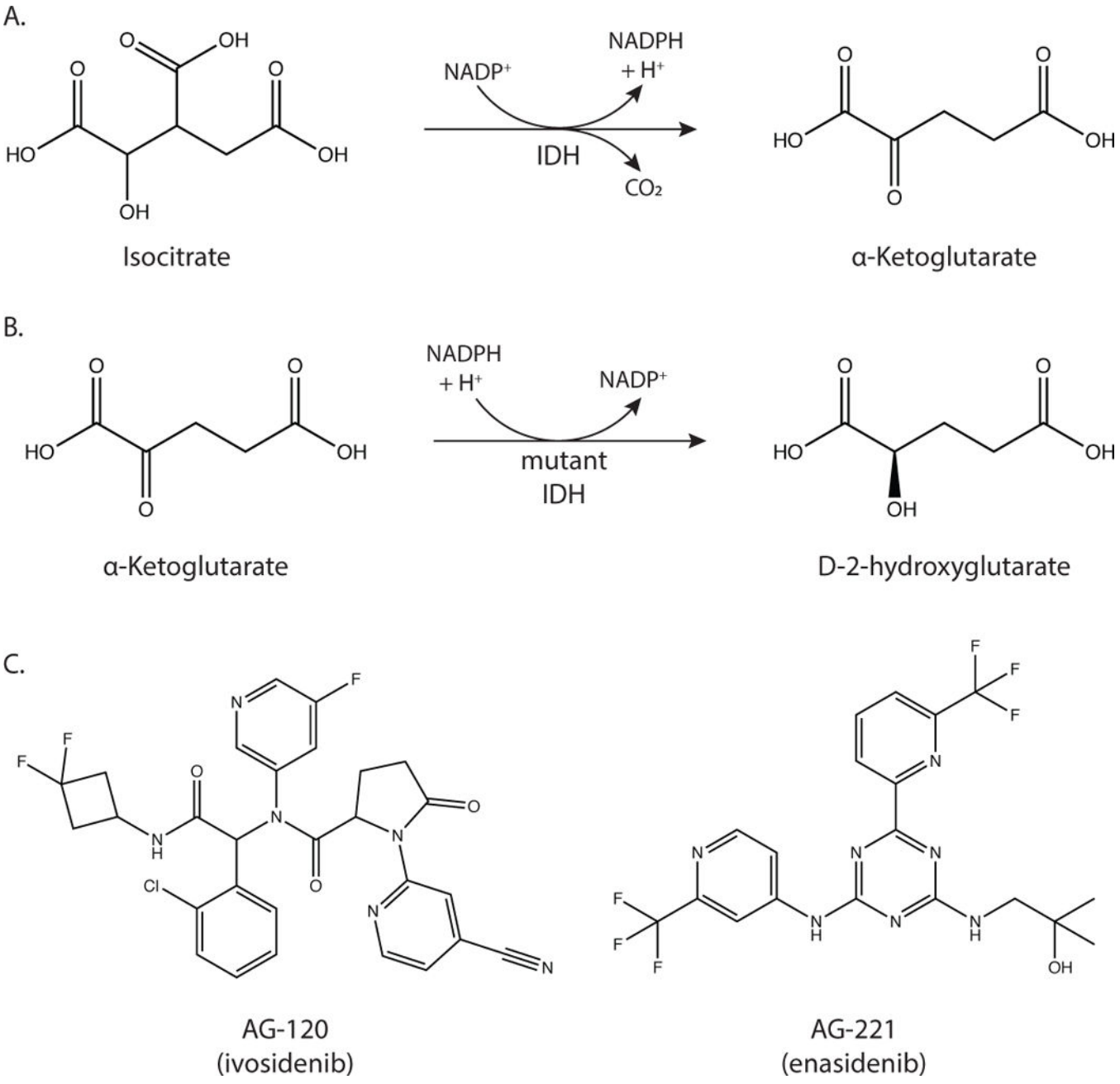

Figure 4. Mutant IDH

(A) The reaction catalyzed by wild-type IDH is the decarboxylation of isocitrate to α-ketoglutarate. (B) The reaction catalyzed by mutant IDH1 and IDH2 is the reduction of α-ketoglutarate to D-2-hydroxyglutarate. (C) Structures of AG-120 (ivosidenib) and AG-221 (enasidenib), which inhibit mutant IDH1 and IDH2 respectively.

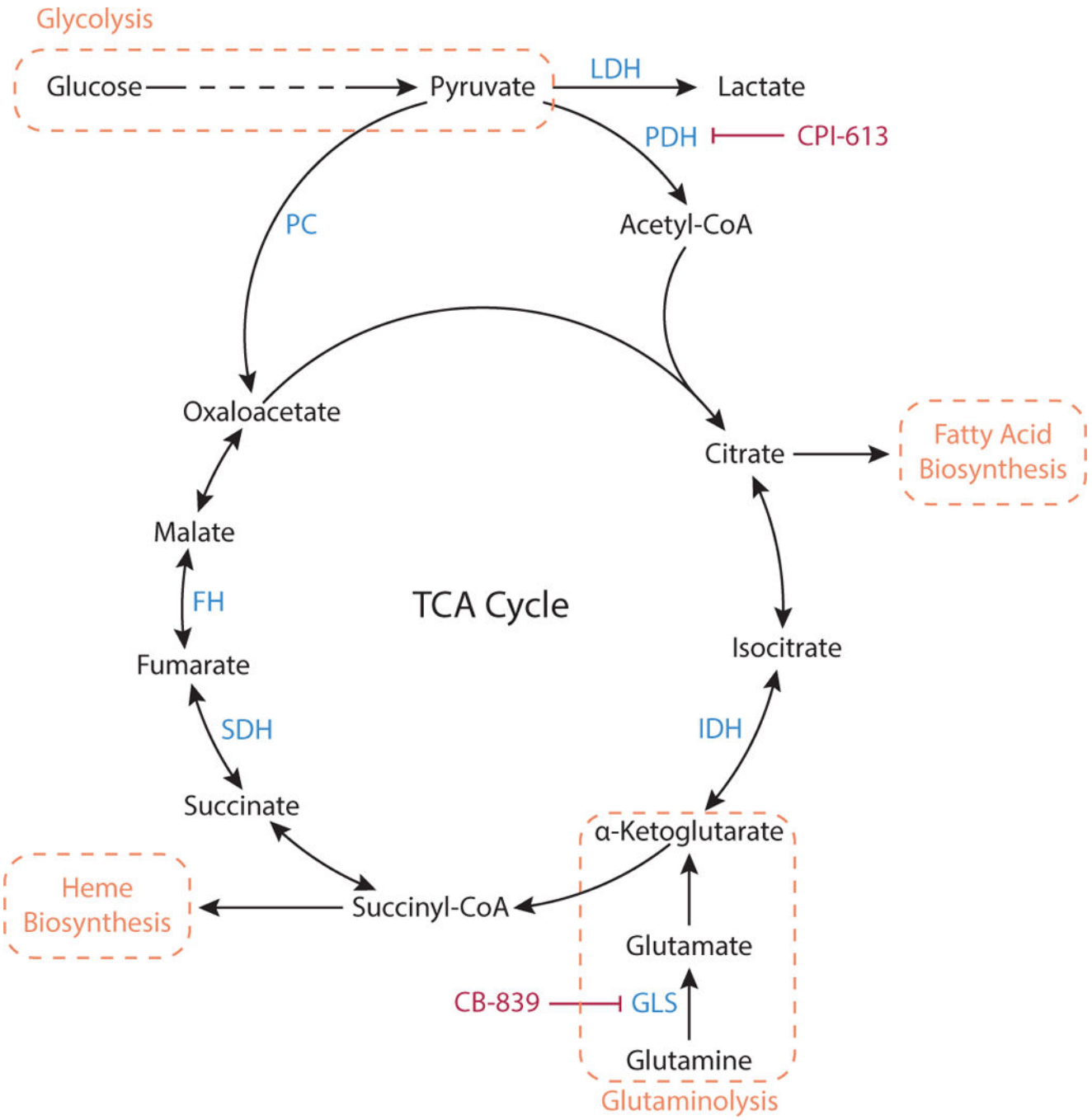

Figure 5. TCA Cycle

Pyruvate produced by glycolysis can be metabolized by the TCA cycle. Pyruvate is oxidized via pyruvate dehydrogenase (PDH) to the two-carbon unit acetyl-CoA, and subsequently combined with the four-carbon oxaloacetate to generate citrate. The cycle regenerates oxaloacetate while generating precursors that are important for biosynthetic processes including heme and fatty acid synthesis. When molecules are removed from the TCA cycle to feed these pathways, TCA intermediates must be replenished in a process termed anaplerosis. Pyruvate can serve as an anaplerotic substrate when converted to oxaloacetate

by the enzyme pyruvate carboxylase (PC). Glutaminolysis, the conversion of glutamine to glutamate via glutaminase (GLS), can also support anaplerosis via production of α-ketoglutarate. PDH activity is inhibited by the lipoic acid derivative CPI-613 and GLS activity is inhibited by CB-839.

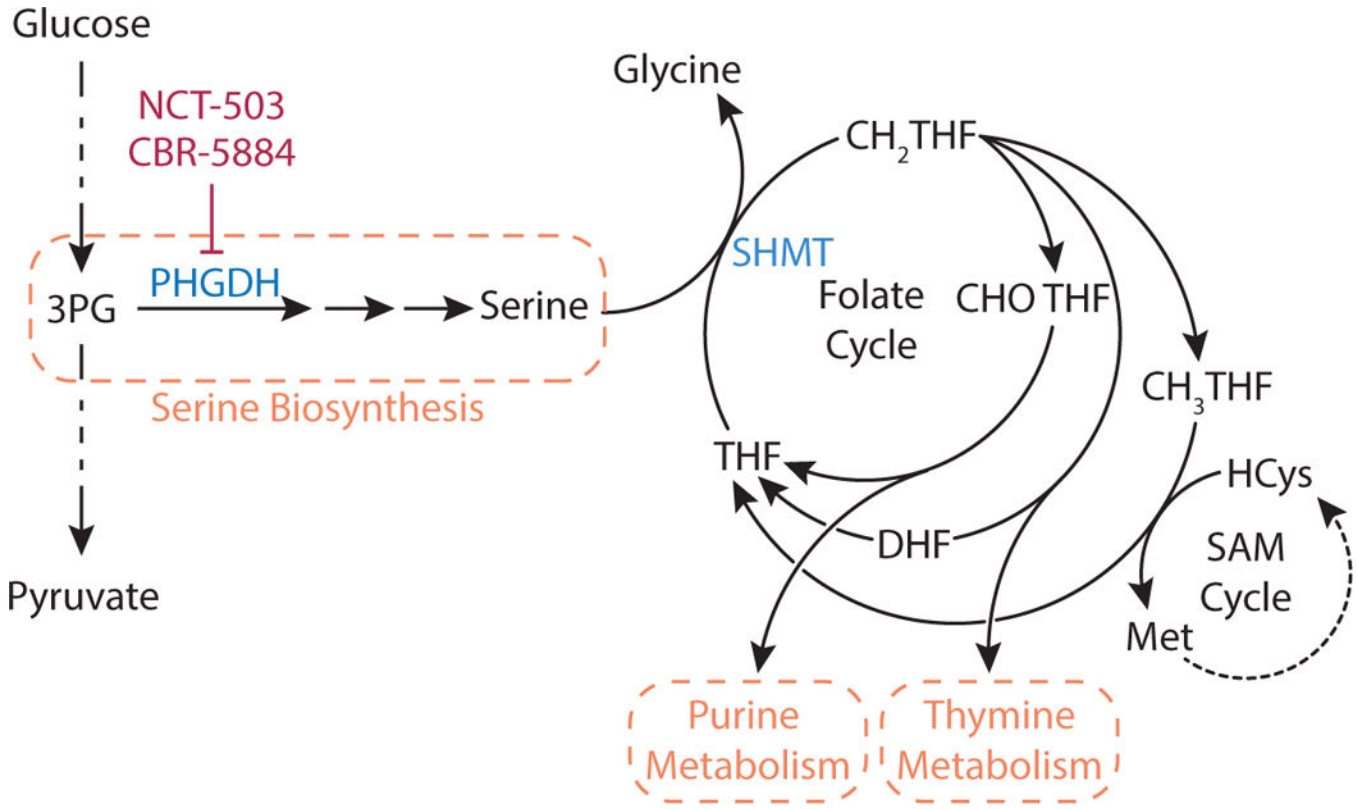

Figure 6. Serine Biosynthesis and Folate Cycle

The glycolytic intermediate 3-phophoglycerate (3-PG) is metabolized to serine in a three-step pathway where the first step is catalyzed by the enzyme phosphoglycerate dehydrogenase (PHGDH), which can be inhibited by NCT-503 and CBR-5884. Serine metabolism to glycine by serine hydroxymethyltransferase (SHMT) transfers a one carbon unit to tetrahydrofolate (THF) to form N^5,N^{10}-methylene-tetrahydrofolate (CH_2-THF). CH_2-THF is the methyl donor for thymidine nucleotides, or it can be converted to N^{10}-formyl-tetrahydrofolate (CHO-THF) for purine biosynthesis or to N^5-methyl-THF (CH_3-THF) to support methionine production and numerous methylation reactions via the S-adenosyl methionine (SAM) cycle.

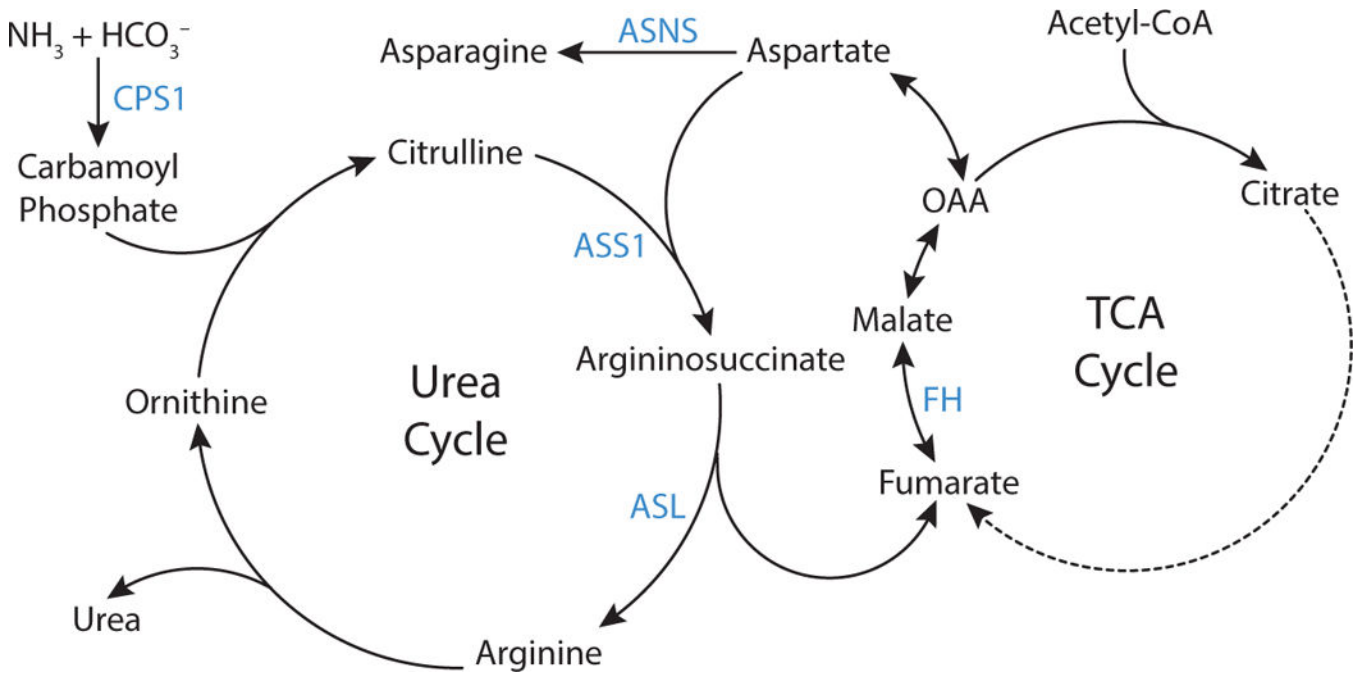

Figure 7. Urea Cycle

The urea cycle permits excretion of excess nitrogen as urea. Carbamoyl phosphate is synthesized from ammonia and bicarbonate by the enzyme carbamoyl phosphate synthetase 1 (CPS1), and subsequently carbamoyl phosphate and ornithine are used to produce citrulline. The enzyme argininosuccinate synthase (ASS1) condenses citrulline with aspartate to form argininosuccinate, which is then cleaved to arginine and fumarate by argininosuccinate lyase (ASL). Arginine is then hydrolyzed to produce urea and regenerate ornithine, completing the cycle. Fumarate produced by the urea cycle can regenerate aspartate via enzymes involved in the tricarboxylic acid (TCA) cycle as shown. Asparagine synthetase (ASNS) catalyzes production of asparagine from aspartate.

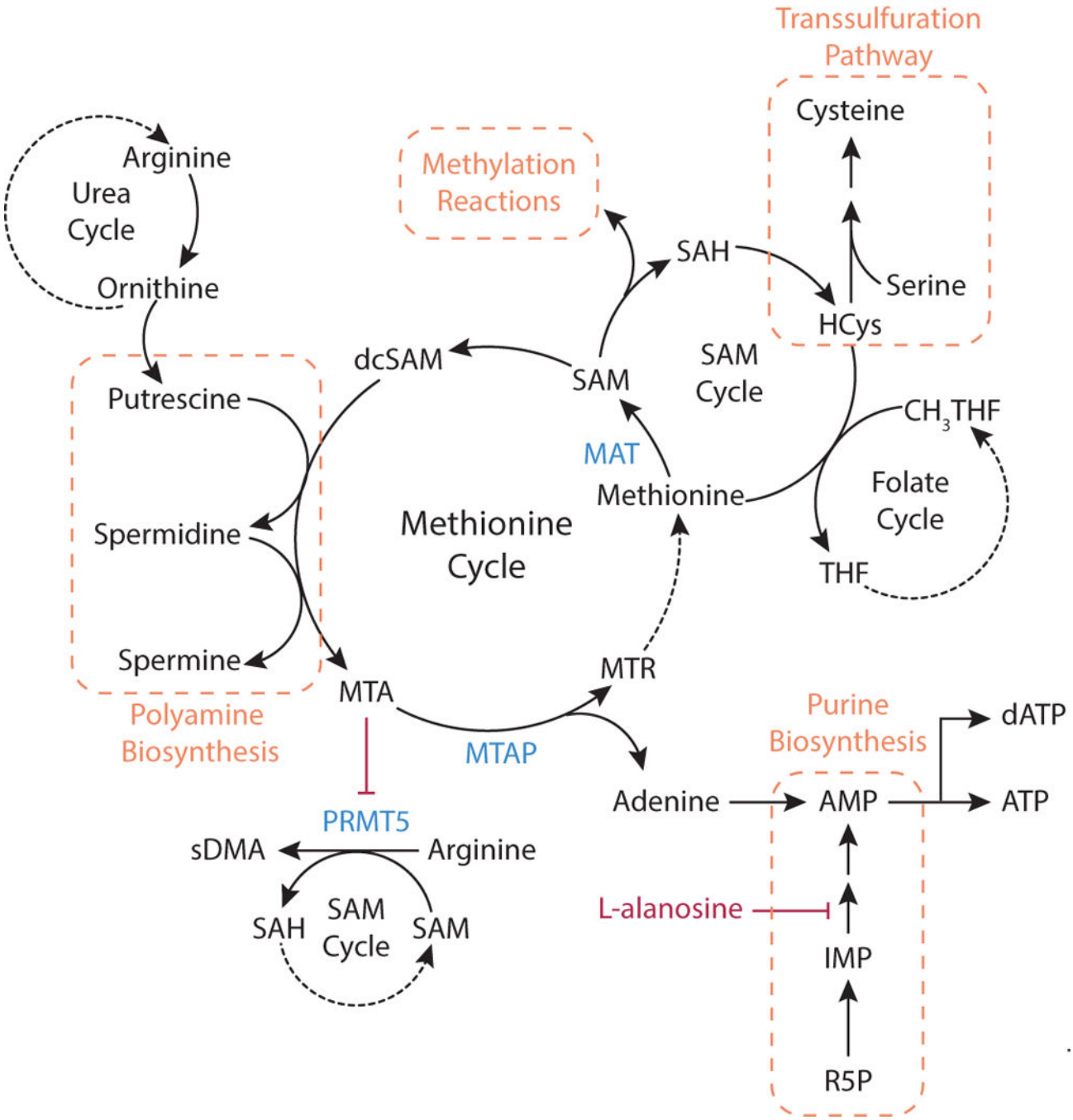

Figure 8. Methionine Cycle

Methionine is an essential amino acid that can be used for methylation reactions, cysteine synthesis, and polyamine generation. Methionine is converted to S-adenosylmethionine (SAM) by methionine adenosyltransferase (MAT). Methyl transferases utilize SAM as the methyl donor for many methylation reactions in cells. Demethylation of SAM generates S-adenosylhomocysteine (SAH), which is hydrolyzed to homocysteine (HCys) and adenosine. Methionine is regenerated from homocysteine by transfer of the methyl group from N^5-methyl-THF (CH_3-THF). Homocysteine is also an intermediate of cysteine synthesis, where

serine and homocysteine condense and form cysteine via the transsulfuration pathway. SAM can also support polyamine synthesis when SAM is decarboxylated to form S-adenosylmethioninamine, also known as decarboxylated S-adenosylmethionine (dcSAM). Together with the urea cycle metabolite ornithine, this compound generates putrescine and subsequently spermine and spermidine. In these reactions, dcSAM is converted to 5′-methylthioadenosine (MTA). Accumulation of MTA inhibits the enzyme protein arginine N-methyltrasferase 5 (PRMT5), which uses SAM as a methyl donor to synthesize symmetrical dimethylarginine (sDMA) from arginine. In the methionine cycle, MTA is cleaved to 5-methylthioribose-1-phosphate (MTR) and adenine by the enzyme methylthioadenosine phosphorylase (MTAP). Adenine can be converted to AMP, and the adenosine analogue L-alanosine can limit AMP production via the purine synthesis pathway. MTR can be converted to methionine, completing the methionine cycle.

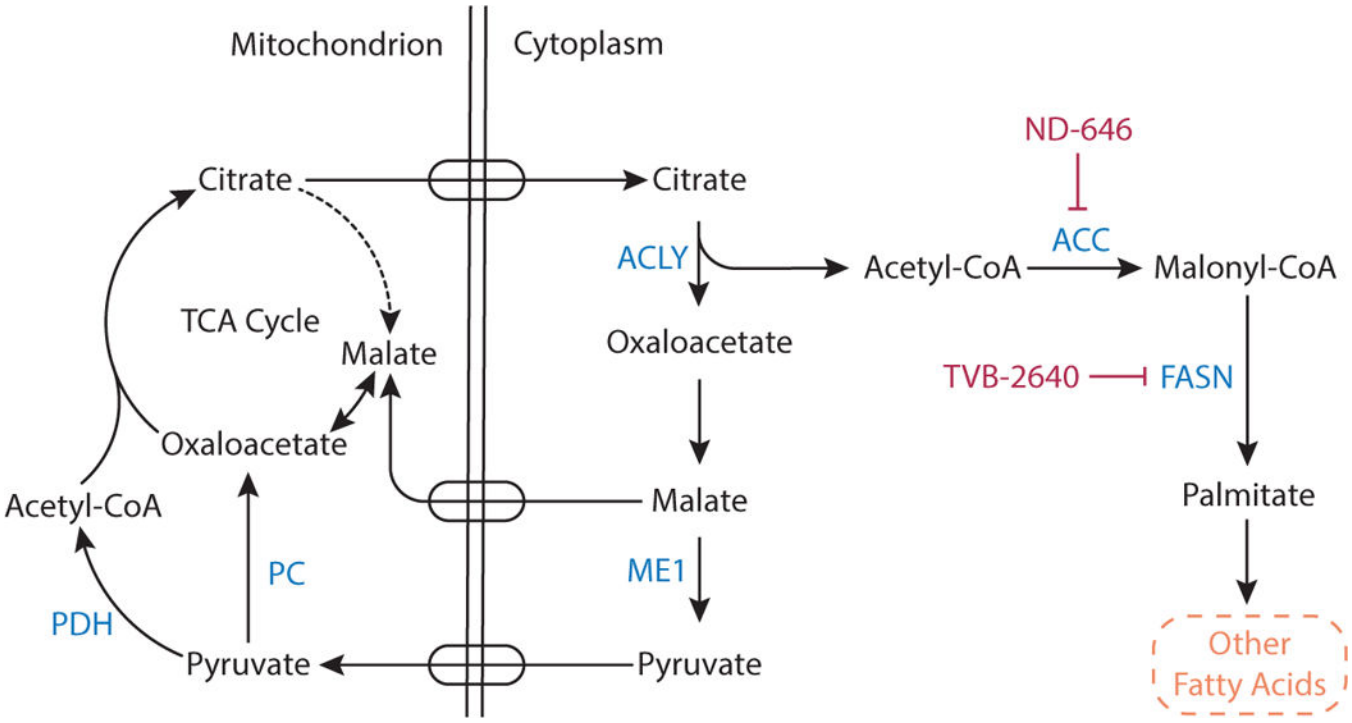

Figure 9. Fatty Acid Synthesis

Citrate is a carrier of acetyl groups from the mitochondria to the cytoplasm to support fatty acid synthesis. Mitochondrial citrate is transported into the cytosol where ATP citrate lyase (ACLY) cleaves citrate to acetyl-CoA and oxaloacetate. Oxaloacetate is converted to malate, and malate can be transported back into the mitochondrial matrix or can be converted into pyruvate in the cytoplasm by malic enzyme 1 (ME1). Cytosolic acetyl-CoA contributes to fatty acid synthesis. First, the enzyme acetyl-CoA carboxylase (ACC) catalyzes carboxylation of acetyl CoA to malonyl CoA. Fatty acid synthase (FASN) then uses malonyl-CoA to sequentially add two carbon units to a growing acyl chain and synthesize the saturated 16-carbon fatty acid palmitate, which serves as a precursor to other fatty acids. The compound ND-464 and TVB-2640 are inhibitors of ACC and FASN, respectively.

Table 1

Select agents targeting metabolism that are approved, or are in trials, for the treatment of cancer, focusing on targets discussed in this review.

Drug	Target Enzyme
Methotrexate	Dihydrofolate reductase (DHFR)
Pemetrexed	DHFR Thymidylate synthase (TS) Glycinamide ribonucleotide formyltransferase (GARFT)
6-Mercaptopurine 6-Thioguanine	PRPP amidotransferase
Capecitabine 5-Fluorouracil	Thymidylate synthase (TS)
Gemcitabine Cytarabine	DNA polymerase/ribonucleotide reductase (RnR)
Leflunomide	Dihydroorotate dehydrogenase (DHODH)
CB-839	Glutaminase (GLS)
PEG-BCT-100 (ADI-PEG20) AEB-1102	Depletion of circulating arginine
L-Asparaginase	Depletion of circulating asparagine
TVB-2640	Fatty-acid synthase (FASN)
AG-120 (Ivosidenib) IDH305 BAY1436032 FT-2102 AG-221 (Enasidenib) AG-881	mutant IDH1 mutant IDH2 mutant IDH1/2
AZD3965	Monocarboxylate transporter 1 (MCT1)
CPI-613	Pyruvate dehydrogenase (PDH)/α-ketoglutarate dehydrogenase
Metformin	Mitochondrial complex I