Oncogenic Mechanisms and Therapeutic Targeting of Metabolism in Leukemia and Lymphoma

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Leukemias and lymphomas acquire the capacity for unrestrained cell growth and proliferation in conjunction with loss of responsiveness to molecular programs that promote terminal differentiation. Malignant cells generate the building blocks required for rapid cell division through both increased acquisition of nutrients from the environment and reprogrammed intermediary metabolism to shunt these molecules into producing the protein, lipids, and nucleic acids that comprise cell biomass. These accelerated metabolic processes require energy in the form of ATP and reducing equivalents in the form of NADPH, which power biosynthetic reactions and buffer oxidative stress encountered by the metabolically active cancer cell. Cancer-associated metabolic alterations can also promote accumulation or depletion of specific metabolites that directly regulate cell fate and function, thereby coupling metabolic reprogramming to dedifferentiation and stemness. This review will focus on the mechanisms by which leukemia and lymphoma cells rewire cellular metabolism to support: (1) bioenergetics, (2) biomass accumulation, (3) redox balance, and (4) differentiation blockade. We will further highlight examples of how specific pathways of leukemia and lymphoma metabolism confer therapeutic vulnerabilities that can be targeted to inhibit growth or promote differentiation.

At a fundamental level, cancer is a problem of hijacked cellular metabolism (Vander Heiden et al. 2009). Normally, metazoan cells require “permission” from growth factors, cytokines, hormones, or antigen/costimulatory receptors to increase nutrient uptake. All cancers, including leukemias and lymphomas, acquire the capacity for cell-autonomous uptake of nutrients that circumvents normal regulatory

mechanisms (Palm and Thompson 2017). Such unrestricted nutrient uptake is critical to build the cellular biomass (protein, lipids, nucleic acids) necessary for rapid cell doubling (Fig. 1). Because the availability of specific nutrients in the environment does not precisely match the necessary outputs, cancer cells must rewire metabolic circuits to rapidly convert available nutrients into precursor metabolites

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Figure 1. Key functions of reprogrammed cancer metabolism. Leukemias and lymphomas reprogram cellular metabolism to meet the anabolic demands of malignant growth and proliferation. Glycolysis and mitochondrial oxidative phosphorylation provide energy in the form of ATP and GTP (Bioenergetics). Metabolic intermediates are shunted into biosynthetic pathways that produce the protein, lipids, and nucleic acids required for cell doubling and division (Biomass). Malignant cells require increased regeneration of NAD^+ to enable oxidative biosynthetic reactions (e.g., nucleotides), as well as increased production of NADPH to fuel reductive biosynthetic reactions (e.g., lipids) and buffer oxidative stress (redox balance). Deregulation of specific metabolites or metabolic pathways can also disrupt chromatin marks, resulting in impaired differentiation and/or enhanced self-renewal (differentiation). (ATP) Adenosine triphosphate, (GTP) guanosine triphosphate, (NAD) nicotinamide adenine dinucleotide, (NADP) nicotinamide adenine dinucleotide phosphate, (FAD) flavin adenine dinucleotide.

that can be used to synthesize the macromolecules that comprise cell biomass. This intensive metabolic activity requires energy in the form of adenosine triphosphate (ATP) and reducing equivalents in the form of nicotinamide adenine dinucleotide phosphate (NADPH) to fuel biosynthetic reactions (Fig. 1).

As first described by Otto Warburg almost 100 years ago, most cancer cells rapidly ferment glucose to lactate regardless of oxygen availability (Warburg 1924, 1956). A high rate of glycolysis by cancer cells serves at least two important functions, which are often difficult to dissociate mechanistically: (1) ATP production and (2) generation of precursor molecules and reducing equivalents required for biosynthesis of macromolecules (Fig. 2; Vander Heiden et al. 2009). Surprisingly, the limited amount of ATP (maximum of 2 ATP per glucose) generated by glycolysis can be sufficient to support cell proliferation in highly glycolytic cancer cells without a requirement for additional ATP generated by mitochondrial oxidative phosphorylation (OXPHOS) (Birsoy et al. 2015; Sullivan et al. 2015). Running glycolysis at a high rate appears to necessitate the Warburg effect, which drives conversion of pyruvate to lactate by lactate dehydrogenase (LDH) in order to rapidly regener-

ate the cytosolic NAD^+ required to maintain glycolytic flux. However, despite the ability of glycolysis to provide adequate ATP, mitochondrial electron transport remains essential for virtually all cancer cells in order to regenerate the electron acceptors (NAD^+) required for macromolecular biosynthesis (Hosios and Vander Heiden 2018). Moreover, certain cancer cells without high glycolytic flux, including leukemic stem cells and a subset of diffuse large B-cell lymphoma (DLBCL), appear to be particularly dependent on OXPHOS, which may be related to their preferential oxidation of alternative fuels that can only generate ATP through the mitochondria (Caro et al. 2012; Ye et al. 2016; Jones et al. 2018).

Proliferating cells must double their biomass in order to divide, which requires assembling all of the proteins, lipids, and nucleic acids that comprise the cell (Fig. 1; Hosios et al. 2016). A subset of carbohydrates, amino acids, lipids, and nucleotides can be acquired from the microenvironment for direct incorporation into macromolecules. However, a major function of cancer metabolism involves conversion of available nutrients, such as glucose and glutamine, into metabolic intermediates that can be directed into macromolecular biosynthetic pathways (Fig. 2;

Figure 2. Simplified overview of metabolic pathways in leukemia and lymphoma. Altered and/or enhanced glycolysis, pentose phosphate pathway (PPP), serine biosynthetic pathway, folate/one-carbon cycles, tricarboxylic acid (TCA) cycle, oxidative phosphorylation (OXPHOS), lipid synthesis, and amino acid (AA) metabolism support bioenergetics (red), biomass accumulation (green), redox balance (blue), and differentiation blockade (purple). Most precursors, products, cofactors, and enzymes are intentionally absent for simplicity. (ATP) Adenosine triphosphate, (GTP) guanosine triphosphate, (NAD) nicotinamide adenine dinucleotide, (NADPH) nicotinamide adenine dinucleotide phosphate, (SAM) S-adenosyl methionine, (α KG) alpha-ketoglutarate, (GSH) reduced glutathione.

Vander Heiden and DeBerardinis 2017). Glycolytic intermediates provide a key pool of substrates for biosynthetic reactions: The pentose phosphate shunt produces ribose sugars for nucleotide biosynthesis; dihydroxyacetone phosphate can be converted into glycerol for lipid biosynthesis; serine biosynthesis from 3-phosphoglycerate operates in conjunction with the folate pathway to form one-carbon units for nucleotide production; and multiple glycolytic intermediates can be used for the synthesis of nonessential amino acids. Moreover, glucose- or acetate-derived acetyl-CoA functions as a key building block for fatty acid and cholesterol biosynthesis.

Analogous to enhanced glucose consumption and glycolytic flux, most leukemias and lymphomas exhibit increased uptake and consumption of glutamine, or glutaminolysis (Fig. 2; Wise and Thompson 2010). Glutamine serves as a nitrogen donor for nucleotide synthesis and for transamination reactions to generate nonessential amino acids. Likewise, glutamine-derived aspartate functions as a key building block for nucleotide biosynthesis (Wise and Thompson 2010). Glutamine also serves as a carbon backbone to generate nonessential amino acids and glutathione, an exchange factor for the import of essential amino acids from the environment, a key anaplerotic

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substrate to maintain pools of tricarboxylic acid (TCA) cycle intermediates, and an alternative source of acetyl-CoA for lipid biosynthesis via reductive carboxylation. In addition, glutamine and glucose together supply hexosamine biosynthesis for N- and O-linked glycosylation reactions.

Many of the common oncogenic pathways in leukemia and lymphoma (and other cancers) coordinate proliferation with reprogramming of cellular metabolism to meet the anabolic demands of growth and cell division. MYC oncoproteins are frequently overexpressed in leukemias and lymphomas through variety of mechanisms, including enhancer hijacking (Bahr et al. 2018; Schuijers et al. 2018), NOTCH1 activation (Sanchez-Martin and Ferrando 2017), or chromosomal translocations (Altman and Dang 2012). MYC exerts pleiotropic metabolic effects by promoting glucose uptake, glycolytic flux, glutamine uptake, glutaminolysis, nucleotide biosynthesis, lipid synthesis, and mitochondrial and ribosomal biogenesis (Stine et al. 2015). Likewise, RAS pathway activation enhances glucose uptake, increases flux through glycolysis and the nonoxidative pentose phosphate pathway, and promotes macropinocytosis of proteins/lipids that can be metabolized in lysosomes (Kimmelman 2015). Many genetic alterations in leukemias and lymphomas lead to constitutive PI3K/AKT/TOR pathway activation, enhancing glucose uptake, glycolytic flux, amino acid uptake, acetyl-CoA production, and synthesis of lipids and nucleotides (Saxton and Sabatini 2017). Additional leukemia- and lymphoma-specific genetic alterations that reprogram metabolism will be discussed throughout the review where relevant.

Redox balance refers to the relative availability of electron donors (NADH, FADH₂, NADPH) and electron acceptors (NAD⁺, FAD, NADP⁺) to perform reduction and oxidation reactions, respectively (Fig. 1). In simplistic terms, cancer cells must maintain sufficient supplies of NADPH and NAD⁺ to meet the redox demands of anabolic proliferative metabolism (Hosios and Vander Heiden 2018). NADPH serves a crucial role in regenerating reduced glutathione and other antioxidants that can

buffer oxidative damage from reactive oxygen species (ROS) (Sullivan and Chandel 2014). In addition, NADPH functions as an electron donor for key biosynthetic reactions such as lipid synthesis. NADPH can be produced by the oxidative pentose phosphate pathway, isocitrate dehydrogenase enzymes, malic enzyme, or serine-driven one-carbon metabolism in conjunction with the folate pathway (Fan et al. 2014). The relative importance of each source of NADPH varies depending on the cellular context. For example, RAS activation promotes NADPH production via malic enzyme, whereas loss of p53 enhances NADPH production through malic enzyme and the oxidative pentose phosphate pathway (Jiang et al. 2011, 2013; Son et al. 2013). The redox requirements for biosynthetic reactions have been an area of intense investigation in recent years (Hosios and Vander Heiden 2018). Emerging evidence demonstrates that NAD⁺ can often be limiting for tumor growth, given its essential function in the biosynthesis of macromolecules (e.g., nucleic acids), which are more oxidized than glucose itself (Garcia-Bermudez et al. 2018; Sullivan et al. 2018; Diehl et al. 2019). Because aerobic glycolysis is redox neutral, glycolysis alone provides no means to generate the “extra” oxidized NAD⁺ molecules required for macromolecular biosynthesis. This necessitates some degree of mitochondrial electron transport chain (ETC) activity to eliminate the excess electrons produced during glycolysis by reduction of molecular oxygen to water, which is coupled to regeneration of NAD⁺ (Birsoy et al. 2015; Sullivan et al. 2015).

To sustain continuous proliferation, cancer cells or subpopulations of cancer stem-like cells must also avoid terminal differentiation (Fig. 1; Intlekofer and Finley 2019). In both leukemia and lymphoma, impaired differentiation frequently results from genetic alterations in chromatin-modifying enzymes (Feinberg et al. 2016). The discovery of somatic isocitrate dehydrogenase (*IDH*) mutations and the oncometabolite 2-hydroxyglutarate (2HG) demonstrated that aberrant regulation of specific metabolites or metabolic pathways can directly drive dedifferentiation and “stemness” through inhibitory

effects on chromatin-modifying enzymes (Fig. 3; Losman and Kaelin 2013). Whereas succinate, fumarate, and 2HG can inhibit demethylation reactions, deposition of methyl marks requires S-adenosyl-methionine (SAM) produced by the interlinked methionine and folate cycles (Locasale 2013). Likewise, acetyl-CoA derived from glucose, fatty acids, or free acetate regulates acetylation of histones and other proteins, which can influence gene expression and cell differentiation states (Kinnaird et al. 2016). As will be discussed below, recent discoveries have revealed unexpected new connections between the differentiation state of leukemias and lymphomas with the metabolism of branched chain

amino acids, alpha-ketoglutarate, cholesterol, and nucleic acids. Thus, the push and pull to meet anabolic proliferative demands can have downstream effects on metabolites and metabolic pathways that influence chromatin dynamics and cell fate decisions.

Given the breadth of diversity within leukemias and the more than 70 different kinds of lymphoma with distinct cells of origin and lineage-specific metabolic networks, it is difficult to make generalizations that apply to all cases. For example, the metabolic features of aggressive acute leukemias and lymphomas differ substantially from indolent, chronic variants. Notably, even among acute leukemias, there are major

Figure 3. Metabolic inputs into demethylation reactions. Alpha-ketoglutarate (α KG), vitamin C (VitC)/ascorbate, and oxygen (O_2) are required for the demethylation of histones and DNA by histone lysine demethylases (KDM) and ten-eleven-translocation (TET) enzymes, respectively. Fumarate, succinate, and 2-hydroxyglutarate (2HG) inhibit demethylases, resulting in accumulation of repressive methyl marks and impaired cell differentiation. Mutations in isocitrate dehydrogenase 1 or 2 (mutIDH1 or mutIDH2) result in enhanced production of 2HG, which can be suppressed by isoform-specific inhibitors (mutIDH1i/mutIDH2i). Overexpression of branched chain amino acid transaminase 1 (BCAT1) results in excessive transfer of α -amino groups from branched chain amino acids (BCAA) to α KG, depletion of α KG, decreased demethylase activity, and impaired differentiation. (OAA) Oxaloacetate, (Me) methyl mark, (BCKA) branched-chain alpha-keto acid.

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differences in the metabolic states of myeloid and lymphoid leukemias, with lymphocyte-specific transcriptional programs conferring an energy-poor metabolic state that must be surmounted for transformation and progression (Müschen 2019). Nonetheless, reprogrammed cancer metabolism generally serves at least four important needs of the cancer cell: (1) bioenergetics, (2) biomass accumulation, (3) redox balance, and (4) differentiation blockade (Fig. 1). In this review, we will discuss these hallmarks of cancer metabolism with a focus on leukemia and lymphoma, highlight their clinical relevance, and outline potential strategies for therapeutic targeting.

LEUKEMIA BIOENERGETICS

Glycolysis

Increased glycolysis is a well-recognized hallmark of leukemias (Fig. 2; Boag et al. 2006; Herst et al. 2011; Chen et al. 2014). Oncogenic pathways, such as RAS, MYC, and PI3K/ATK/TOR each induce expression of glucose transporters and glycolytic enzymes and increase glycolytic flux in a wide variety of cancer types, including leukemia and lymphoma (Shim et al. 1997; Osthus et al. 2000; Yun et al. 2009; Coloff et al. 2011; Ying et al. 2012; Poulain et al. 2017). In addition, leukemia-specific genetic alterations, such as BCR-ABL fusions or FLT3 alterations, enhance glycolytic flux and confer oncogenic dependence on glycolysis (Gottschalk et al. 2004; Liu et al. 2014; Ju et al. 2017). Genetic ablation or pharmacologic inhibition of glycolytic machinery, such as glucose transporters, lactate dehydrogenase A (LDHA), or pyruvate kinase M2 (PKM2), can deplete ATP levels, induce cell death, and/or impair proliferation of leukemia cells (Xu et al. 2005; Liu et al. 2014; Wang et al. 2014).

Notably, the B-cell lineage harbors an intrinsic transcriptional program driven by PAX5 and IKZF that suppresses access to glucose and keeps B cells in a relatively energy-poor state compared to myeloid cells (Chan et al. 2017; Martín-Lorenzo et al. 2018; Xiao et al. 2018). Progression of B-cell acute lymphoblastic

leukemia (ALL) is associated with genetic events leading to the loss of these transcription factors to allow for increased glucose import, enhanced glycolytic flux, and elevated levels of ATP (Mullighan et al. 2007, 2008; Chan et al. 2017). Interestingly, *PTEN* deletion in B-cell ALL results in enhanced glucose uptake coupled with excessive kinase activation leading to depletion of cellular ATP stores and cell death, thereby conferring a unique oncogenic dependence on PTEN in B-lineage leukemias (Shojaee et al. 2016).

The importance of glycolysis for leukemogenesis and progression is also evident at the level of systemic glucose metabolism. Epidemiologic studies have identified a direct correlation between hyperglycemia and poor response to chemotherapy in ALL (Weiser et al. 2004). Strikingly, acute myeloid leukemia (AML) was shown to induce production of insulin-like growth factor binding protein 1 (IGFBP1) by adipocytes, resulting in systemic insulin resistance, hyperglycemia, and increased glucose availability for the leukemia cells; interventions aimed at reducing hyperglycemia were able to inhibit leukemic progression (Ye et al. 2018b). Likewise, fasting prevented initiation and progression of B- and T-cell ALL via up-regulation of leptin signaling, which exerted a tumor-suppressive effect (Lu et al. 2017). In contrast, a ketogenic diet accelerated leukemic progression in experimental models of AML (Hopkins et al. 2018). This suggests that different dietary strategies to limit systemic glucose availability may have lineage-specific utility or be counteracted by other poorly understood pro-leukemic effects.

The highly glycolytic phenotype of leukemia cells might result in a limited supply of glucose within the bone marrow microenvironment, as significantly lower glucose levels have been measured in leukemic bone marrow compared to peripheral blood (Tiziani et al. 2013). As one strategy to adapt to an insufficient glucose supply, AML cells were shown to enhance fructose uptake by increasing transcription and expression of the GLUT5 fructose transporter, which correlated with inferior survival (Chen et al. 2016). This is of particular importance as high

fructose corn syrup, commonly used as a sweetener in processed foods, has been shown to enhance intestinal tumor growth in mice (Goncalves et al. 2019). Of note, pharmacologic inhibition of fructose uptake by AML cells inhibited leukemia growth and synergized with cytarabine chemotherapy (Chen et al. 2016).

Therapeutic targeting of aerobic glycolysis in leukemia has shown minimal success to date. Although 2-deoxyglucose (2-DG) is a useful experimental tool that can inhibit glycolysis and synergize with cytarabine chemotherapy in vitro, it cannot be employed clinically because the high dose of 2-DG required to achieve target inhibition in vivo results in hypoglycemia, as well as cardiac and red blood cell toxicities (Larue et al. 2015). Furthermore, although highly glycolytic cells appear to be most susceptible to traditional cytotoxic chemotherapies, rare leukemia cell populations dependent on OXPHOS grow out under the pressure of chemotherapy and mediate therapy resistance and relapse (Fig. 4; Farge et al. 2017). More promising results have been shown in AML by targeting altered mitochondrial metabolism, as will be discussed below.

Oxidative Phosphorylation

In contrast to Warburg's initial hypothesis, it is now well established that mitochondrial oxidative phosphorylation (OXPHOS) is essential for leukemia survival and proliferation. Inhibiting mitochondrial function by disrupting mitochondrial protein synthesis (Škrčić et al. 2011), mitochondrial DNA replication (Liyanage et al. 2017), or mitochondrial protein degradation (Cole et al. 2015) effectively kills leukemia stem cells (LSCs) (Fig. 4). The antimicrobial tigecycline was demonstrated to inhibit mitochondrial translation, resulting in selective elimination of leukemia stem and progenitor cells but not their normal counterparts (Škrčić et al. 2011). Likewise, inhibiting mitochondrial DNA replication in leukemia cell lines and primary AML cells disrupted OXPHOS and induced cell death (Liyanage et al. 2017). The mitochondrial protease ClpP was identified as an important regulator of OXPHOS and mitochondrial metabolism in leukemia cells but not normal cells (Cole et al. 2015). Puzzlingly, although AML cells possess a higher mitochondrial mass compared to normal hematopoietic cells,

Figure 4. Metabolic vulnerabilities of bulk leukemia and leukemia stem cells. (A) Rapidly dividing bulk leukemia cells exhibit high glycolytic activity and high levels of reactive oxygen species (ROS), whereas (B) quiescent leukemia stem cells exhibit low levels of ROS and depend on mitochondrial oxidation of alternative fuels, such as amino acids (AAs) or fatty acids. Cytotoxic chemotherapies (Chemo) and inhibitors of mutant *fms*-like tyrosine kinase 3 (FLT3i) target highly glycolytic bulk leukemia cells, but leukemia stem cells are resistant to these therapies and contribute to disease relapse. (B) Mitochondrial metabolism of leukemia stem cells can be targeted by BCL-2 inhibition (BCL2i) in combination with DNA hypomethylating agents, such as azacitidine (Aza). (C) Leukemia stem cells can develop therapeutic resistance by changing their mitochondrial fuel source from AAs to fatty acids. Novel metabolic targeted therapeutics such as inhibitors of glutamine metabolism (GLSi), TCA cycle enzymes (CPI-613), or fatty acid oxidation (FAOi) are under investigation in clinical trials.

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this does not seem to correspond with an enhanced capacity for respiratory chain complex activity (Sriskanthadevan et al. 2015).

Selective utilization of OXPHOS has also been identified as a key feature of AML cells that are resistant to cytotoxic chemotherapy (Fig. 4; Farge et al. 2017; Baccelli et al. 2019). AML cells resistant to cytarabine treatment in mouse xenografts were found to be primarily reliant on OXPHOS for their survival (Farge et al. 2017), and ETC inhibitors were selectively toxic to a distinct subset of chemotherapy-resistant AML (Baccelli et al. 2019). Furthermore, OXPHOS was demonstrated to be required for tyrosine kinase inhibitor (TKI)-resistant chronic myeloid leukemia (CML) stem cells; inhibition of mitochondrial protein translation with tigecycline in combination with TKIs was able to eliminate these resistant stem cells (Kuntz et al. 2017).

Several recent publications have shown that disrupting OXPHOS by targeting mitochondrial ETC has therapeutic potential in AML. Targeting the ETC complex I with the small-molecule inhibitor IACS-010759 resulted in potent inhibition of proliferation and induction of apoptosis in vitro and improved leukemia-specific survival in mouse models of AML (Molina et al. 2018). These promising preclinical findings resulted in a phase I clinical trial of IACS-010759 for patients with relapsed and treatment-refractory AML (NCT02882321). Additionally, the ERBB2 inhibitor mubritinib, which was recently shown to inhibit ETC complex I activity, exerted significant antileukemic activity against chemotherapy-resistant AML cells with OXPHOS hyperactivity (Baccelli et al. 2019).

The therapeutic benefit achieved by targeting OXPHOS in AML has further been demonstrated by the recently U.S. Federal Drug Administration (FDA)-approved combination of the BCL2 inhibitor venetoclax with the DNA hypomethylating agent azacitidine (DiNardo et al. 2019). This drug combination, which results in unprecedented high response rates, was recently shown to eliminate LSCs by targeting mitochondrial OXPHOS (Fig. 4; Lagadinou et al. 2013; Pollyea et al. 2018; DiNardo et al. 2019). Mechanistically, venetoclax in combination with azacitidine appears to inhibit ETC complex II activity by dis-

rupting glutathionylation of succinate dehydrogenase (Pollyea et al. 2018). It was further demonstrated that venetoclax can directly inhibit ETC complex I (Sharon et al. 2019). Additionally, disrupted heme biosynthesis could potentiate venetoclax-induced apoptosis through the loss of ETC activity (Lin et al. 2019). Further clinical evidence for the importance of the ETC in mediating sensitivity of leukemia cells to venetoclax + azacitidine comes from the observation that *IDH* mutations induce a dependence on BCL2, likely explaining the especially high response rates of *IDH*-mutated AML to this treatment combination (Chan et al. 2015). Mutant *IDH*-derived 2HG, among many other effects, inhibited the activity of cytochrome *c* oxidase (COX) in the ETC, thereby lowering the mitochondrial threshold to trigger apoptosis upon BCL2 inhibition (Chan et al. 2015).

An alternative strategy to inhibit mitochondrial metabolism is to directly interfere with the activity of the TCA cycle. Glutamine depletion or inhibition of glutamine metabolism by blocking the rate-limiting enzyme glutaminase impairs TCA anaplerosis and blocks OXPHOS (Fig. 4; Emadi 2015; Jacque et al. 2015; Matre et al. 2016; Gallipoli et al. 2018; Gregory et al. 2018). The lipoic acid analog CPI-613 is a first-in-class TCA cycle inhibitor purported to disrupt lipoylation of pyruvate dehydrogenase (PDH) and α -KG dehydrogenase (OGDH) (Stuart et al. 2014). CPI-613 showed modest activity in early-phase clinical trials in patients with advanced hematological malignancies (Pardee et al. 2014) and AML (Pardee et al. 2018). CPI-613 is currently being tested in combination with chemotherapy for patients with relapsed/refractory AML in randomized phase III clinical trial (NCT03504410).

Fatty Acid Oxidation

Fatty acid oxidation (FAO) provides electron donors NADH and FADH₂ to ETC complex I and complex II, respectively, and produces acetyl-CoA, which can be oxidized in the TCA cycle or deposited on histones for regulation of gene expression (Carracedo et al. 2013; Ye et al. 2016; Farge et al. 2017). FAO has been shown to me-

diate resistance to a variety of antileukemic agents (Fig. 4; German et al. 2016; Jones et al. 2018). Chemotherapy-resistant CML LSCs were demonstrated to induce lipolysis in the gonadal adipose tissue niche and capture free fatty acids through increased expression of the fatty acid transporter CD36 (Ye et al. 2016). Utilizing patient-derived xenograft models of primary human AML, it was shown that the cytarabine-resistant residual AML cells were characterized by high OXPHOS activity, increased FAO, and up-regulated CD36 expression; inhibiting FAO induced an energetic shift toward low OXPHOS status and significantly augmented the antileukemic effects of cytarabine (Farge et al. 2017). Notably, whereas newly diagnosed AML exhibited impressively high response rates to venetoclax + azacitidine, response rates in relapsed/refractory AML were much lower (Di Nardo et al. 2019; Bewersdorf et al. 2020). One possible explanation for this observation could be differences in the metabolism of LSCs at diagnosis versus at time of disease relapse (Jones et al. 2018). Treatment-naïve LSCs exhibited dependence on amino acid uptake for OXPHOS maintenance and could not up-regulate FAO metabolism to preserve TCA cycle activity, whereas LSCs from patients at the time of relapse were able to compensate for the loss of amino acids by rewiring their metabolism toward FAO (Jones et al. 2018). Several different inhibitors of FAO have exhibited promising activity in preclinical AML models. Inhibition of FAO with the carnitine palmitoyltransferase 1 (CPT1) inhibitor etomoxir induced apoptosis in AML cells, which was synergistic with the BCL2 inhibitor ABT-731 and cytarabine (Samudio et al. 2010). Likewise, a novel CPT1b inhibitor ST1326 (Teglicar) demonstrated significant activity against both AML cell lines and primary samples, in conjunction with a more favorable safety profile (Ricciardi et al. 2015).

LEUKEMIA BIOMASS

Amino Acids

Asparaginase exploits the unusual dependency of ALL cells on exogenous supply of the nones-

sential amino acid asparagine and represents of the best-known metabolic dependencies in cancer (Clavell et al. 1986; Akagi et al. 2006; Williams et al. 2020). Compared to ALL cells, AML cells demonstrate reduced sensitivity to asparagine depletion, and asparaginase is not part of standard therapeutic regimens in AML. Asparaginase resistance in AML appears to be attributable to both variable expression levels of asparagine synthetase (ASNS) levels in AML cells as well as production of cathepsin B, a protease that inactivates L-asparaginase, by mesenchymal stromal cells and monocytes/macrophages in the bone marrow microenvironment of AML cells (Michelozzi et al. 2019). Additionally, bone marrow adipocytes have been shown mediate resistance to asparaginase by producing glutamine that can be captured by AML cells (Ehsanipour et al. 2013). However, there has been an intense search for other amino acid dependencies in AML and glutamine, arginine, and cysteine have been shown to represent potential metabolic dependencies in AML, as will be discussed below.

Inhibition of glutamine utilization in leukemia cells by genetic or pharmacological targeting of glutaminase exerted potent antileukemic activity, which could be augmented by chemotherapy (Fig. 4; Jacque et al. 2015). Although FLT3 inhibitors potently down-regulated glycolysis in myeloid leukemia cells, glutamine metabolism remained unaffected (Gallipoli et al. 2018). However, combining FLT3 inhibitors with the glutaminase inhibitor CB-839 resulted in synergistic antileukemic activity (Gallipoli et al. 2018; Gregory et al. 2018). Furthermore, inhibition of glutaminase depleted cellular stores of reduced glutathione, leading to increased mitochondrial ROS and synergistic toxicity when combined with arsenic trioxide (Gregory et al. 2019) or venetoclax (Emadi 2015; Jacque et al. 2015). Likewise, glutaminase inhibition synergized with NOTCH inhibition in T-ALL, although this effect could be counteracted by *PTEN* loss, which induced a switch to a hyperglycolytic state (Herranz et al. 2015). As an alternative strategy, genetic or pharmacological inhibition of the amino acid transporter ASCT2, whose preferred substrate is glutamine, blocked TOR signaling and induced apoptosis in MLL-

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AF9-driven leukemia cells (Ni et al. 2019). These preclinical findings prompted several clinical trials attempting to target glutamine metabolism in myeloid neoplasms, either alone or in combination with other agents (NCT02071927; NCT03047993) (Wang et al. 2015b).

Arginine is important for the synthesis of protein, nitric oxide, polyamines, and other amino acids, such as glutamate and proline; cells can either import arginine or synthesize it from citrulline by utilizing argininosuccinate synthetase-1 (ASS1) (Szlosarek 2014). A subgroup of AML lacks ASS1 expression and relies on the import of arginine, potentially conferring susceptibility to arginine deprivation therapy (Miraki-Moud et al. 2015). Moreover, AML with overexpression of ecotropic virus integration site 1 protein (EV11) relies on a functional creatine kinase pathway, which in turn depends on sufficient supply of arginine, to maintain cytosolic ATP levels and mitochondrial OXPHOS activity (Fenouille et al. 2017). Arginine-depleting enzymes, arginine deiminase (ADI-PEG 20) and arginase (BCT-100), demonstrated antileukemic activity in AML models with low or absent expression levels of ASS1 (Miraki-Moud et al. 2015; Mussai et al. 2015). However, when ADI-PEG20 was tested in a phase II trial in RR-AML patients, only 9.5% of patients achieved a complete response despite almost all pretreatment tumor samples showing ASS1 deficiency (NCT01910012) (Tsai et al. 2017). Somewhat counterintuitively to the above described dependence of AML blasts on arginine for proliferation, AML blasts have also been shown to secrete arginase II leading to inhibition of arginine-dependent T cells and immune evasion (Mussai et al. 2013).

The combination of venetoclax + azacitidine was shown to decrease amino acid uptake in LSCs, which were uniquely reliant on amino acid metabolism for OXPHOS and survival (Fig. 4; Jones et al. 2018). Whereas the bulk population of leukemia cells were able to adapt to amino acid starvation by increasing FAO to supply TCA cycle intermediates and energy, LSCs appeared to be more metabolically inflexible and unable to compensate for the decreased amino acid uptake induced by venetoclax + azacitidine (Jones et al. 2018). Subsequent studies

demonstrated that cysteine was particularly important for the viability of LSCs (Jones et al. 2019). Depletion of cysteine resulted in impaired glutathione synthesis, loss of glutathionylation of succinate dehydrogenase A, impaired ETC complex II activity, and cell death (Jones et al. 2019).

Lipids

Rapidly dividing leukemia cells need to meet the high demand for phospholipids, cholesterol, and triglycerides required for the synthesis of cell membrane structures (Currie et al. 2013). Apoptosis of AML cells can be induced by inhibiting the lipogenic enzymes fatty acid synthase (FASN) and stearoyl CoA desaturase 1 (SCD1) (Pizer et al. 1996; Khanim et al. 2009; Southam et al. 2015). However, in a phase I trial testing combination of lipid-regulating bezafibrate and the sex hormone medroxyprogesterone acetate, which was shown to inhibit SCD1, only one of 19 patients with AML achieved a partial response (Murray et al. 2010).

Several studies have focused on redeploying statins as anticancer therapy after an antileukemic effect of statin drugs was recognized early on in AML (Newman et al. 1994; Clutterbuck et al. 1998; Dimitroulakos et al. 2000). Statins inhibit HMG-CoA reductase, the rate-limiting enzyme of the mevalonate pathway that produces cholesterol, ubiquinone, dolichol, and geranylgeranyl/farnesyl pyrophosphate (Wong et al. 2002). Although some early-phase nonrandomized clinical trials showed some encouraging response rates when combining pravastatin with idarubicin and cytarabine in patients with relapsed/refractory AML, a similar trial in the up-front treatment setting was unable to confirm these results (Kornblau et al. 2007; Shadman et al. 2015; Advani et al. 2018). It is possible the differential activity was due to alterations in cholesterol and lipid metabolism induced by prior chemotherapy, as described above (Kornblau et al. 2007; Shadman et al. 2015; Farge et al. 2017; Advani et al. 2018). Recently, statins were shown to prime leukemia and lymphoma cells for venetoclax-mediated apoptosis via suppressed protein geranylgeranylation, resulting in induction of the proapoptotic protein p53

up-regulated modulator of apoptosis (PUMA) (Lee et al. 2018). In a retrospective multivariate regression analysis of three studies examining venetoclax in patients with chronic lymphocytic leukemia (CLL), statins were associated with significantly increased odds of attaining a complete response (OR 2.68, $P = 0.0054$) (Lee et al. 2018).

Nucleotides

Mitochondrial electron transport function plays a vital role in regenerating NAD^+ to enable aspartate production and nucleotide biosynthesis (Birsoy et al. 2015; Sullivan et al. 2015, 2018; Garcia-Bermudez et al. 2018). The sensitivity to ETC inhibition varied across cancer cell lines, with cell lines resistant to ETC inhibition being able to maintain aspartate levels by import through the aspartate-glutamate transporter SLC1A3 (Garcia-Bermudez et al. 2018). Because ETC inhibition is under investigation as a promising antileukemic therapy (venetoclax and IACS-01075), the ability of a leukemic cell to maintain aspartate levels in response to ETC inhibition may determine sensitivity to this treatment strategy. Indeed, antileukemic activity of IACS-01075 was associated with reduced aspartate production and impaired nucleotide biosynthesis (Molina et al. 2018).

Antimetabolites, which mimic purines (e.g., fludarabine, 6-MP) or pyrimidines (e.g., cytarabine) required for DNA synthesis or interfere with folate-dependent nucleotide synthesis (e.g., methotrexate), represent the oldest effective treatments for leukemia (Farber and Diamond 1948). Modern genetic studies have confirmed the importance of nucleotide biosynthesis in leukemia. For example, ablation of methylenetetrahydrofolate dehydrogenase-cyclohydrolase 2 (MTHFD2), a key enzyme in the one-carbon folate metabolism and purine synthesis, inhibited leukemic growth and promoted differentiation of AML blasts in vivo (Pikman et al. 2016). Thiopurine-resistant ALL acquired gain-of-function mutations in the enzyme NT5C2, which facilitates removal of toxic nucleotide intermediates that build up in the context of thiopurine treatment; notably, NTC52 mutations created a new vulnerability to inosine-5'-monophosphate de-

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hydrogenase (IMPDH) inhibition (Meyer et al. 2013; Tzoneva et al. 2013, 2018; Dieck et al. 2018). Utilizing a large drug screening approach, inhibition of dihydro-orotate dehydrogenase (DHODH) with brequinar sodium was found to inhibit leukemia growth by promoting myeloid differentiation of AML blasts (Sykes et al. 2016). DHODH is a mitochondrial enzyme that catalyzes the ubiquinone-mediated conversion of dihydro-orotate to orotate in the pyrimidine biosynthetic pathway. Based on this promising pre-clinical activity, multiple DHODH inhibitors are being tested in early phase clinical trials for a variety of myeloid malignancies (Sykes et al. 2016; Ladds et al. 2018; Wu et al. 2018b; Cao et al. 2019; Christian et al. 2019).

LEUKEMIA REDOX

Conventional chemotherapy induces redox stress in the form of ROS (Trachootham et al. 2009). Significant differences in ROS levels distinguish the rapidly dividing bulk population of leukemia cells from quiescent LSCs, which have been proposed to drive chemotherapy resistance and relapse (Lagadinou et al. 2013). Functionally defined LSCs exhibited relatively low levels of ROS, increased BCL2 expression, and dependence on OXPHOS for survival (Lagadinou et al. 2013). Treatment of AML LSCs with the BCL2 inhibitor venetoclax in combination with azacitidine resulted in depletion of cysteine and the antioxidant glutathione, leading to increased ROS levels and disruption of ETC complex II function (Pollyea et al. 2018; DiNardo et al. 2019; Jones et al. 2019). Alternative strategies to disrupt cysteine metabolism can deplete intracellular pools of reduced glutathione, increased ROS, and blocked growth of CLL (Zhang et al. 2012; Cramer et al. 2017). Likewise, targeting the pentose phosphate pathway, an important source of NADPH for buffering oxidative stress, displayed antileukemic activity toward chemoresistant AML (Bhanot et al. 2017; Poulain et al. 2017).

LEUKEMIA DIFFERENTIATION

The discovery of leukemia-associated mutations in IDH enzymes provided seminal insights into

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the interplay between metabolism, epigenetics, and differentiation (Dang et al. 2009; Mardis et al. 2009; Ward et al. 2010). Mutant IDH enzymes lose normal enzyme function and gain the ability to produce the oncometabolite 2HG. 2HG inhibits the function of α KG-dependent chromatin-modifying enzymes, resulting in blockade of myeloid differentiation (Fig. 3; Figueroa et al. 2010; Lu et al. 2012; Turcan et al. 2012; Rohle et al. 2013; Wang et al. 2013; Yen et al. 2017). In addition, 2HG can inhibit the function of enzymes involved in RNA demethylation, DNA repair, hypoxia-inducible factor (HIF) stability, collagen maturation, and intermediary metabolism (Koivunen et al. 2012; Chan et al. 2015; Fu et al. 2015; Wang et al. 2015c; Sulkowski et al. 2017, 2020; McBrayer et al. 2018; Su et al. 2018). Because some of effects of 2HG can be tumor-suppressive, the net effect of *IDH* mutations and 2HG in a given cell lineage likely depends on the balance of oncogenic and tumor-suppressive activities (Elkashaf et al. 2017; Ye et al. 2018a). Importantly, small-molecule inhibitors of mutant IDH enzymes can suppress 2HG production, restore myeloid differentiation, and induce clinical responses in ~40% of patients with relapsed/refractory *IDH*-mutant AML, leading to their recent FDA approvals for this indication (Fig. 3; Stein et al. 2017; DiNardo et al. 2018).

The branched chain amino acid amino transferase 1 (BCAT1) also influences α KG levels and has been shown to regulate leukemogenesis and leukemia cell differentiation (Hattori et al. 2017; Raffel et al. 2017). In AML, overexpression of BCAT1 caused excessive transfer of α -amino groups from branched chain amino acids (BCAAs) to α KG, resulting in depletion of α KG stores, DNA hypermethylation, and impaired myeloid differentiation (Fig. 3; Raffel et al. 2017). This BCAT1-mediated mechanism can mimic the epigenetic effects of 2HG in *IDH*-wild-type AML. In contrast, in CML blast crisis, overexpression of BCAT1 promoted excessive conversion of branched chain keto acids to BCAAs, which promoted leukemogenesis through TOR activation (Hattori et al. 2017).

Vitamin C, or ascorbate, functions as an essential cofactor for a variety of α KG- and

Fe^{2+} -dependent enzymes, including TET enzymes involved in DNA demethylation (Fig. 3; Cimmino et al. 2018). Vitamin C promoted enhanced TET activity, promoted DNA demethylation, and restored differentiation in models of myeloid leukemia (Agathocleous et al. 2017; Cimmino et al. 2017). Vitamin C may also act by depleting glutathione and increasing ROS levels (Yun et al. 2015). It remains unclear whether vitamin C could be used clinically—for example, as a preventative strategy in TET2-mutant clonal hematopoiesis (Huijskens et al. 2016). Notably, prior attempts to use vitamin C as an antineoplastic agent were not successful (Moertel et al. 1985), but more recent work suggests that vitamin C may be effective in *KRAS/RAF*-mutant cancers (Yun et al. 2015). The vitamin B6 pathway was also recently identified as a metabolic dependence in AML; perturbation of the pathway with isoniazid resulted in antileukemic activity in vivo (Chen et al. 2020).

LYMPHOMA BIOENERGETICS

Glycolysis

Enhanced glycolysis in lymphoma is evident from the utility of fluorodeoxyglucose positron emission tomography (FDG PET) scans for staging and response assessment and the use of blood LDH levels for prognostication (Seam et al. 2007; Sehn et al. 2007). The degree of glucose uptake, as measured by FDG avidity, effectively distinguishes indolent and aggressive forms of lymphoma (Noy et al. 2009). Aggressive forms of B-cell lymphoma exhibit aberrant overexpression of MYC, either through chromosomal translocations or transcriptional deregulation (Stine et al. 2015). Numerous studies have demonstrated that MYC enhances glycolytic flux through direct transactivation of glucose transporters (GLUT1), glycolytic enzymes (e.g., PFK, enolase), and LDHA (Shim et al. 1997; Osthus et al. 2000). In a model of Burkitt lymphoma with inducible control of MYC expression, MYC drove Warburg-like aerobic glycolysis with increased glucose consumption and lactate production (Le et al. 2012). This effect of MYC was counteracted by the activity of the

energy-stress kinase AMPK, as deletion of AMPK accelerated MYC-induced lymphomagenesis (Faubert et al. 2013). Both PI3K/AKT/TOR and NF- κ B signaling can cooperate with MYC to enhance GLUT1 transporter expression and transport to the cell surface (Sommermann et al. 2011; Bhatt et al. 2012; Broecker-Preuss et al. 2017). Epstein-Barr virus (EBV)-driven lymphomagenesis is characterized by an initial energy-poor state sustained by autophagy with progression of disease associated with up-regulation of the GLUT1 transporter and increased glycolytic flux (Bhatt et al. 2012; McFadden et al. 2016). In addition, targeting glucose uptake and/or glycolysis was demonstrated to abolish MCL-1 expression and overcome resistance to BCL2 inhibitors in DLBCL (Coloff et al. 2011).

The glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH) has been identified as a metabolic marker of aggressive DLBCL, irrespective of MYC expression (Chiche et al. 2015). Despite having more aggressive pathologic features, DLBCL with high expression of GAPDH predicted for better outcomes in response to R-CHOP chemotherapy (Chiche et al. 2019). In contrast, GAPDH-low DLBCL produced less ATP from glycolysis, preferentially used mitochondrial OXPHOS, and exhibited higher TOR activity. Several patients with GAPDH-low DLBCL responded to a combination of metabolic agents, including asparaginase, temsirolimus (TOR inhibitor), and metformin (ETC complex I inhibitor). In contrast to GAPDH, overexpression of glycolytic enzyme hexokinase 2 (HK2) was shown to mediate therapeutic resistance in DLBCL and ablation of HK2 inhibited lymphoma growth (Gu et al. 2018). Interestingly, the histone deacetylase (HDAC) inhibitor panobinostat was shown to diminish HK2 expression and restore platinum chemosensitivity in DLBCL cells (Nakajima et al. 2019).

Diabetes has been associated with increased risk of non-Hodgkin lymphoma (NHL), possibly because of increased glucose availability for lymphoma cells (Mitri et al. 2008; Castillo et al. 2012). Compounds targeting glucose uptake pathways in cancer cells have yet to demonstrate viability for clinical practice as a result of unac-

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ceptably low target specificity (Montrose and Galluzzi 2019). However, emerging evidence suggests that glucocorticoids may act, at least in part, through inhibition of glucose uptake by malignant lymphoid cells (Holleman et al. 2004; Hulleman et al. 2009; Chan et al. 2017).

Oxidative Phosphorylation

Numerous studies have demonstrated that DLBCL can be segregated into distinct subtypes based on mitochondrial OXPHOS activity (Fig. 5; Monti et al. 2005; Caro et al. 2012). Mechanistic studies found that the OXPHOS subset of DLBCL had increased activity of and dependence on mitochondrial FAO. Intriguingly, when B-cell receptor (BCR) signaling was inhibited in other subtypes of DLBCL, there was a shift from glycolysis to increased FAO, suggesting that this might represent a metabolic mechanism of adaptation and/or resistance to targeted therapies in DLBCL (Fig. 5; Caro et al. 2012). Recent investigations demonstrated that the genes involved in OXPHOS (e.g., ETC complexes I, III, IV, V) were largely dependent on MYC for translation (Singh et al. 2019). Another line of evidence supports a role for glutamine-dependent OXPHOS as a mediator of ibrutinib resistance in mantle cell lymphoma (MCL), potentially driven by MYC and TOR activity (Lee et al. 2019; Zhang et al. 2019a). Ibrutinib-resistant MCL was uniquely dependent on glutamine uptake and glutaminolysis; disruption of glutamine metabolism or ETC complex I increased ROS, induced energetic stress, and overcame resistance to ibrutinib. Enhanced OXPHOS was recently identified as a mechanism of resistance to the BCL2 inhibitor venetoclax in lymphoma, and treatment with ETC inhibitors restored sensitivity to venetoclax (Chukkapalli et al. 2018; Guièze et al. 2019).

LYMPHOMA BIOMASS

Amino Acids

MYC drives glutamine uptake and glutaminolysis (Stine et al. 2015). In MYC-driven lymphomas, MYC-induced expression of the glutamine

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Figure 5. Metabolic subtypes of diffuse large B cell lymphoma (DLBCL). Gene expression and metabolic profiling distinguishes subtypes of DLBCL based on activity of and dependency on mitochondrial oxidative phosphorylation (OXPHOS). (A) OXPHOS DLBCL exhibits relatively low glycolytic flux and enhanced mitochondrial oxidation of glutamine and fatty acids. (B) B-cell receptor (BCR) DLBCL exhibits enhanced glycolytic flux and limited mitochondrial OXPHOS. (C) Inhibition of BCR signaling (BCRi) in BCR DLBCL results in decreased glycolysis and increased mitochondrial OXPHOS as a putative adaptive response.

transporters SLC7A5 and SLC1A5 and relieved microRNA-mediated inhibition of glutaminase expression (Gao et al. 2009). Glutamine deprivation depleted TCA cycle intermediates, ATP, and glutathione, resulting in lymphoma cell death (Gao et al. 2009). Likewise, in MYC-driven Burkitt lymphoma, glutamine deprivation activated the integrated stress response (e.g., GCN2-eIF2 α , ATF4) and proapoptotic pathways (e.g., PUMA, NOXA, BAX) (Qing et al. 2012). Additional evidence demonstrated that DLBCL requires the mitochondrial lysine deacetylase SIRT3 to maintain glutamine flux into the TCA cycle via glutamate dehydrogenase (Li et al. 2019).

In addition to MYC, direct mutations in genes that mediate amino acid sensing have been identified in follicular lymphoma (FL) (Okosun et al. 2016; Ying et al. 2016). Approximately 17% of patients with FL harbored mutations in *RRAGC*, which encodes for RagC. RagC normally forms a complex with Ragulator, V-ATPase, and SLC38A9 to activate TOR in response to amino acids. Lymphoma-associated *RRAGC* mutants aberrantly activated TOR even in conditions of amino acid deprivation, relieved dependency on activation/stimulation signals from CD4⁺ T cells, and conferred heightened sensitivity to TOR inhibitors (Ortega-Molina et al. 2019; Wang et al. 2019a). FL also harbors mutations in *ATP6V1B2* (V-ATPase subunit) or deletions of *SESTRIN1* (negative regulator of

TOR), which analogously function to stimulate aberrant TOR activity (Oricchio et al. 2017; Ortega-Molina et al. 2019; Wang et al. 2019a).

Analogous to its application in ALL, asparaginase demonstrates selective activity for natural killer (NK)-cell lymphoma, a relatively rare and aggressive form of EBV-driven lymphoma that depends on exogenous asparagine for survival (Chien et al. 2015; d'Amore et al. 2015). Asparagine depletion activated the integrated stress response (GCN2/eIF2 α /ATF4) and suppressed TOR activity, but failure to activate ATF-mediated ASNS expression and increase asparaginase synthesis resulted in cell death (Bunpo et al. 2009; Ye et al. 2010; Chien et al. 2015). Response to asparaginase was further associated with proteolytic cleavage of BCL2A1, which converted it from an antiapoptotic to a proapoptotic factor (Chien et al. 2015). Loss of critical genes involved in polyamine metabolism (AMD1, eIF5A) was shown to promote lymphomagenesis, suggesting that metabolism of amino acids in the urea cycle can exert tumor-suppressive effects in some lymphomas (Scuoppo et al. 2012).

Lipids

Up-regulated lipid synthesis has been observed across a range of lymphoma types, which can create a therapeutic vulnerability to fatty acid

synthase inhibitors (Bhatt et al. 2012). Lipid droplets have long been recognized as a pathologic hallmark of Burkitt lymphoma, the prototypical MYC-driven cancer (Morrish et al. 2010; Ambrosio et al. 2012; Eberlin et al. 2014). Mechanistically, MYC induces the transcription factor sterol-regulated element-binding protein (SREBP1) and cooperates with SREBP1 to drive expression of key enzymes involved in fatty acid synthesis, fatty acid elongation, and phospholipid synthesis; these effects were coordinated with MYC-induced glycolysis and glutaminolysis to provide acetyl-CoA building blocks for lipid synthesis (Southam et al. 2015; Gouw et al. 2019). Similarly, MYC was shown to induce phosphocholine synthesis in DLBCL through transcriptional activation of PCYT1A (Xiong et al. 2017). Inhibition of lipid synthesis impaired growth of MYC-dependent lymphomas (Xiong et al. 2017; Gouw et al. 2019). Cholesterol metabolism offers a potential vulnerability for some lymphomas. For example, ALK⁺ anaplastic large cell lymphoma (ALCL) lacks expression of squalene monooxygenase (SQLE), which catalyzes the rate-limiting step of cholesterol synthesis (Garcia-Bermudez et al. 2019). Thus, ALK⁺ ALCL cells were functionally auxotrophic for exogenous cholesterol and inhibition of cholesterol import was a therapeutic vulnerability. Interestingly, loss of SQLE was suggested to confer a fitness advantage by allowing accumulation of squalene, which could block ferroptotic cell death in response oxidative stress (Garcia-Bermudez et al. 2019).

Nucleotides

Nucleotide synthesis represents another therapeutic vulnerability in lymphomas, as evidenced by the long-standing use of methotrexate and pralatrexate in these diseases. Targeted inhibition of serine hydroxymethyltransferases 1 and 2 (SHMT1/2), key enzymes in serine-driven one-carbon folate metabolism, impeded purine biosynthesis, disrupted DNA/histone methylation, and arrested B-cell lymphoma proliferation; concurrent glycine restriction and/or inhibition of glycine uptake augmented this ef-

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fect (Ducker et al. 2017; Parsa et al. 2020). EBV-driven lymphomas exhibit increased uptake of serine and glycine and enhanced metabolic flux through the one-carbon folate pathway for nucleotide biosynthesis (Wang et al. 2019b, 2019c). These effects appear to be driven by the EBV protein EBNA2, and targeting one-carbon folate metabolism via inhibition of SHTM1/2 markedly decreased EBV-driven B-cell lymphoproliferation.

LYMPHOMA REDOX

Increased ETC activity created a potential metabolic vulnerability from mitochondrial ROS, such that OXPHOS DLBCL cells were particularly sensitive to depletion of antioxidants (Norberg et al. 2017). In a variety of B- and T-cell lymphoma lines, inhibition of ETC complex I by metformin or other agents increased ROS and impaired mitochondrial oxygen consumption (Khan et al. 2019). Mitochondrial ROS stabilized hypoxia-inducible factor (HIF) and increased glycolytic flux and glucose dependence; concomitant ablation of HIF induced cell death (Khan et al. 2019). Ferroptosis, a form of programmed cell death triggered by lipid peroxidation, could be induced in DLBCL cells by targeted inhibition of the cystine-glutamine antiporter xCT (Zhang et al. 2019b). In ALCL, oxidative stress induced a reversion to a more stem-like state driven by activation of the WNT/ β -catenin signaling; inhibiting WNT signaling reversed this effect and overcame chemoresistance (Wu et al. 2018a). In B-cell lymphomas and leukemias, the pentose phosphate pathway was shown to play a critical role in generating NADPH to buffer oxidative stress. For this reason, B-cell malignancies exhibited a unique dependency on the phosphatase PP2A, which inhibits PFK2B, limits production of fructose-2,6-bisphosphate, and ensures adequate glycolytic flux through glucose-6-phosphate dehydrogenase (G6PD) and the pentose phosphate shunt (Xiao et al. 2018). This created a therapeutic vulnerability such that combined inhibition of PP2A and G6PD dramatically depleted NADPH and glutathione pools, increased ROS, and synergized in lymphoma cell killing.

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LYMPHOMA DIFFERENTIATION

Of all lymphoid malignancies, only angioimmunoblastic T-cell lymphoma (AITL) exhibits recurrent mutations in IDH enzymes (Cairns et al. 2012; Wang et al. 2015a). *IDH2*-mutant AITL exhibited decreased 5-hydroxymethylcytosine and increased 5-methylcytosine because of inhibition of TET enzymes by the oncometabolite 2HG. Likewise, histone methylation was enhanced in *IDH2*-mutant versus wild-type cases. In mouse models, *IDH2* mutations were shown to impair T lymphocyte development and differentiation, decreasing thymocyte numbers and skewing mature T cells toward memory phenotypes (Lemmonier et al. 2016). This suggests that *IDH2* mutations may cause an arrest in T-cell development, analogous to the stemness promoting effects of *IDH* mutations in AML. Enzymes that regulate TCA cycle metabolites have also been explored in DLBCL, in which 9% of 69 tumor samples were shown to have loss-of-function mutations of the 2HG-disposal enzyme D2HGDH (Lin et al. 2015). Loss of D2HGDH was associated with increased 2HG and decreased α KG levels, which increased repressive methylation of histones and DNA. However, further work is needed to determine whether 2HG metabolism offers a viable therapeutic target in lymphomas.

CONCLUDING REMARKS

We have described how leukemias and lymphomas rewire metabolism to support rapid cell growth and proliferation and, in some cases, couple this to dedifferentiation and self-renewal. Investigations into blood cancer metabolism have led to promising new therapies that target mitochondrial oxidative function, mutant IDH enzymes, pyrimidine biosynthesis, or serine production. Furthermore, long-standing metabolically targeted therapies such as methotrexate remain cornerstones of treatment for many patients with leukemias and lymphomas. As novel therapies advance further in clinical development with concurrent laboratory-based studies, important new insights will be made into the mechanisms by which targeting cancer cell me-

tabolism can exert pleiotropic downstream effects. For example, it remains unclear how targeting specific metabolic pathways apparently involved in biosynthetic processes triggers differentiation in leukemia, such as DHODH.

Of particular interest are those metabolically targeted therapies that can specifically target cancer stem cells, which are hypothesized to drive resistance to conventional treatments and contribute to disease relapses. Why LSCs appear to be particularly dependent on mitochondrial oxidative metabolism remains unclear. It is possible that these cancer stem cells reside in microenvironmental niches with restricted access to glucose, necessitating the use of alternative fuels such as amino acids or fatty acids that can only generate ATP through mitochondrial oxidation. Because LSCs are not highly proliferative, they might not depend on the high glycolytic flux and Warburg-like metabolism required for rapidly doubling biomass. This would also make them inherently resistant to most conventional therapies that target macromolecular biosynthetic pathways, in particular nucleic acid biosynthesis and DNA replication. However, to truly understand the metabolic state of LSCs, new technologies that allow for in situ assessments of metabolite levels, metabolic flux, and mitochondrial function will be required.

Another emerging realm of importance is the complex interplay between cancer cell metabolism, the tumor microenvironment, and antitumor immune responses. For example, 2HG and lactate have been demonstrated to disrupt antitumor T-cell differentiation (Brand et al. 2016; Xia et al. 2017; Bunse et al. 2018), whereas lactate can also promote differentiation of suppressive macrophages (Colegio et al. 2014). Likewise, tumor microenvironmental factors, such as hypoxia and acidic pH, can disrupt T-cell differentiation and function (Eil et al. 2016). In addition to the emerging roles of lactate and other metabolites as immunoregulatory molecules, new in vivo metabolic tracing methodologies revealed the surprising discovery that circulating lactate functions as the major mitochondrial fuel for most normal and malignant cells (Hensley et al. 2016; Hui et al. 2017). Al-

though these findings have yet to be confirmed in blood cancers, it is conceivable that the unique dependency of LSCs on OXPHOS could, at least in part, be related to preferential oxidation of lactate.

Otto Warburg's early intuition regarding the importance of tumor metabolism has been validated by the recent explosion of scientific discoveries in this area. Nonetheless, significant work remains to successfully translate these discoveries into therapies that improve outcomes for patients. Future efforts will focus on identifying cancer-specific metabolic dependencies, such that targeting of these pathways does not cause prohibitive toxicities toward normal cells. These endeavors will require sophisticated new techniques to unravel complex and dynamically changing metabolic programs within specific cell populations in vivo. Despite the complexity of cancer metabolism and the challenges associated with manipulating these processes for therapeutic benefit, the future of metabolism research in leukemia and lymphoma appears bright. To paraphrase Anthelme Brillat-Savarin, who in 1825 wrote in his celebrated book *The Physiology of Taste*, "Tell me what you eat and I will tell you what you are"; indeed, investigating the metabolic circuitry of leukemia and lymphoma cells will both provide fundamental insights about cancer biology and guide development of novel therapeutic approaches to improve outcomes for these diseases.

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