Metabolic Reprogramming in Hematologic Malignancies: Advances and Clinical Perspectives

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ABSTRACT

Metabolic reprogramming is a hallmark of cancer progression. Metabolic activity supports tumorigenesis and tumor progression, allowing cells to uptake essential nutrients from the environment and use the nutrients to maintain viability and support proliferation. The metabolic pathways of malignant cells are altered to accommodate increased demand for energy, reducing equivalents, and biosynthetic precursors. Activated oncogenes coordinate with altered metabolism to control cell-autonomous pathways, which can lead to tumorigenesis when abnormalities accumulate. Clinical and preclinical studies have shown that targeting metabolic features of hematologic malignancies is an appealing therapeutic approach. This review provides a comprehensive overview of the mechanisms of metabolic reprogramming in hematologic malignancies and potential therapeutic strategies to target cancer metabolism.

Introduction

It has been widely observed that metabolic reprogramming can confer the ability for cancer cells to survive and proliferate, even under stressful conditions like nutritional deficiency (1). These metabolic changes result from structural and functional alterations in tumor cells, manifested as increased glycolysis, increased lipid synthesis, as well as increased amino acid uptake and catabolism such as glutamine (2, 3). Metabolic reprogramming parallels tumor cell proliferation, invasion, and survival (4–6).

Cancer cells destroy the bone marrow microenvironment in hematologic disease, accelerating disorders into hematologic malignancies (7, 8). Several studies have emphasized the role of particular metabolic enzymes and metabolites in normal hematopoietic stem cell homeostasis and leukemogenesis via direct effects on energy generation and macromolecular biosynthesis (9–11). In some circumstances, reprogrammed metabolic activities can be used to diagnose, monitor, and treat cancer. With the rise of metabolomics and metabolic imaging, potential biomarkers can diagnose malignancies. Tracking metabolic changes in tumors can provide monitoring information not available from traditional methods (12). Several metabolic inhibitors targeting these metabolic pathways and associated metabolic enzymes are currently in clinical trials. Our focus is on the mechanisms of metabolic reprogramming in hematologic diseases. In this article, we discuss how these features may provide new drug targets and potential tools for detecting and monitoring disease.

Altered Metabolism in Hematologic Malignancies

Glucose metabolism

Aerobic glycolysis

Tumor cells utilize glucose aerobically as an energy source and an intermediate for other metabolic pathways (13). Understanding how aerobic glycolysis is regulated enables the development of glycolysis inhibitors as anticancer drugs (14). To avoid adverse reactions, since the common glycolysis enzymes in tumors are the same as in normal cells, we can only target the metabolic reactions and corresponding metabolic enzymes that are preferred by tumor cells.

Glycolysis of tumor cells requires a large intake of glucose, and water-soluble glucose enters the cytoplasm through the phospholipid bilayer with the help of glucose receptors (GLUT). Currently, 14 gene-encoded subtypes (15) have been identified. Different subtypes of transporters have a distinct affinity for glucose and other hexoses and selectively transport different sugar molecules (16). It has been found that these transporters are overexpressed in most tumors, and GLUT1 is closely related to lymphoma (17, 18) and leukemia (19). Multiple myeloma cells predominantly express GLUT4 (20), which is responsible for maintaining adequate glucose intake.

The classical glycolysis process includes numerous reversible enzymes and three irreversible enzymes. The first irreversible enzyme is hexokinase (HK), which catalyzes the conversion of glucose to G-6-P. The expression of HK is significantly upregulated in tumor cells. The upregulation of HK expression in multiple myeloma can promote glucose intake and multiple metabolic pathways (21, 22). The second rate-limiting enzymes are phosphofructokinase 1 (PFK1) and PFK2, which can catalyze fructose-6-phosphate to fructose-1-diphosphate. PFK2 is overexpressed in tumor cells, producing excess fructose-2-diphosphate and activating PFK1 to maintain a high glycolysis rate (23). The third rate-limiting enzyme is pyruvate kinase (PK), which converts phosphoenolpyruvate into enol pyruvate. The activity of the rate-limiting step of PK catalytic glycolysis is affected by the pH of cells and the ratio of ATP/AMP. In chronic lymphocytic leukemia

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(CLL), weakening the rate-limiting enzyme reaction in the third step leads to metabolites entering the pentose phosphate pathway and serine synthesis, forming metabolic intermediates (24).

The glycolysis process produces metabolic intermediates and precursors that contribute to the biosynthesis of macromolecules required for cell proliferation and tumor progression (25). By overexpressing lactate dehydrogenase (LDH), lactate dehydrogenase in neoplasms, this process maintains a high glycolysis flux (26). Although glycolysis generates 18 times less ATP than mitochondrial oxidation, it accelerates ATP production 100 times faster than oxidative phosphorylation, resulting in competition for energy with neoplasms. To avoid the accumulation of lactic acid in the cell, LDH combines with monocarboxylate transporter (MCT) to excrete lactic acid out of the cell to prevent the formation of a robust acid environment (27). MCT1 and MCT4 play a critical role in the transport of lactic acid, with MCT4 releasing lactic acid and MCT1 absorbing it, which prevents cellular acidosis while maintaining a weakly acidic tumor microenvironment (**Fig. 1A**; refs. 28, 29). Highly expressed MCT tends to be associated with poor prognosis, and overexpression of MCT1 in human multiple myeloma cell lines significantly reduces the efficacy of lenalidomide (30).

Amino acid metabolism

Glutamine

Glutamine promotes the tricarboxylic acid (TCA) cycle of tricarboxylic acid, produces metabolic intermediates, is involved in the biosynthesis of nucleotides, glutathione, and other amino acids (31, 32), and can also be converted to α-ketoglutarate (αKG) for oxidative phosphorylation to produce ATP. In addition to glucose, glutamine plays a vital role in anabolism (33, 34). 25 patients with different types of cancer have been tested with fluorine 18-(2S,4R)-4-fluoroglutamine (FGln) PET, and all have shown abnormal glutamine metabolism (35).

Neoplasms rely on the solute carrier (SLC) superfamily transporters on the cell membrane to absorb glutamine from the extracellular environment (36). Upon entering the mitochondria, glutamine is decomposed into glutamate by MYC-driven glutaminase (GLS), promoting lymphoma cell proliferation (37). Glutamate can be oxidatively deaminated to αKG and ammonia by glutamate dehydrogenase (GDH) and transaminase. Subsequently, αKG participates in the TCA cycle in mitochondria (38, 39) to form malic acid, which is then transported into the cytoplasm and finally provides the material basis by aerobic glycolysis for energy or further conversion to aspartate or citric acid.

Arginine

Arginine contributes to cell division, wound healing, ammonia treatment, immune system, and hormone biosynthesis. It is also a precursor to polyamines. The *de novo* synthesis of arginine in cancer cells is insufficient to meet the needs of malignant cells (40). As a result, there is an urgent requirement to provide arginine outside the cell. It can make cancer cells auxotrophic or partially auxotrophic by introducing arginine-depleting agents.

Serine

Serine deficiency significantly inhibits the growth of several cancer cells and suppresses the ab initio synthesis of serine, which may lead to tumor cell tolerance. Alteration in the serine *ab initio* biosynthesis pathway (SSP) is common in cancers. The conversion from glycolysis intermediate 3-phosphoglyceric acid (3-PG) to serine is regulated by three enzymes: glycerol 3-phosphate dehydrogenase (PHGDH), phosphoserine aminotransferase 1 (PSAT1), and

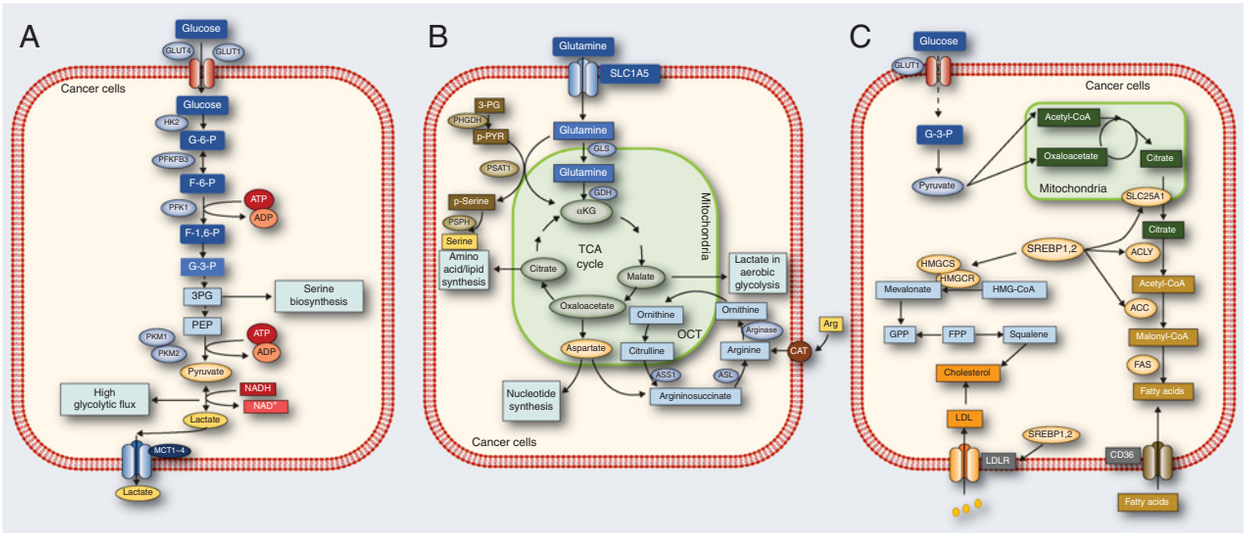

Figure 1.

Reprogrammed metabolic activities in cancer. **A,** The flux of glucose metabolism and glycolysis is accelerated in cancer cells by preferential expression of transporters and irreversible enzymes that drive glucose flux forward and satisfy the anabolic demands of cancer cells. Transporters and enzymes that are predominant in cancer cells are shown in red. **B,** Cancer cells rely on the exogenous supply of Arg and are regulated by arginase, ASL, and ASS1. Glutamine can be converted by GLS and GDH. The serine synthesis pathway utilizes the glycolytic intermediate 3P-glycerate, which is converted by PHGDH, PSAT-1, and PSPH into serine. Enzymes that are predominant in cancer cells are shown in red. **C,** In cancer cells, glucose uptake and glycolysis are markedly upregulated, generating large amounts of pyruvate. Pyruvate is converted to citrate in mitochondria, which is transported by SLC25A1 from the mitochondria into the cytoplasm. The citrate serves as a precursor for *de novo* synthesis of fatty acids and cholesterol in the cytoplasm. Acetate is converted to acetyl-CoA by the ACSS2 enzyme, serving as another source of lipid synthesis. Related enzymes upregulation promotes fatty acid and cholesterol synthesis, while the low-density lipoprotein receptor (LDLR) and CD36 upregulation increase fatty acid and cholesterol uptake.

phosphoserine phosphatase (PSPH). PHGDH and PSAT1 are overexpressed in Burkitt lymphoma. Both genes are controlled by MYC-dependent ATF4 transcription factors (41). Exogenous serine intake is converted to glycine by serine hydroxymethyl-transferase (SHMT1, or SHMT2), providing a carbon unit to participate in the one-carbon cycle for nucleotide biosynthesis. The carbon flux needed to promote 1C metabolism comes from serine, so serine deprivation can theoretically treat Burkitt lymphoma (**Fig. 1B**).

Lipid metabolism

De novo lipid synthesis

Endogenous fatty acids are synthesized by acetyl-CoA decomposed by glucose. ATP citrate lyase (ACLY) is a critical enzyme in the *de novo* synthesis of fatty acids, cleaving sodium citrate into acetyl-CoA and oxaloacetic acid (42). Then, acetyl-CoA carboxylase (ACC) irreversibly converts acetyl-CoA to malonyl-CoA. Then malonyl-CoA and acetyl-CoA were converted into carbon-saturated fatty acids composed of 16-carbon by fatty acid synthase (FAS). Under metabolic stress conditions such as hypoxia or lipid depletion, cancer cells upregulate acetyl-CoA synthase 2 (ACSS2) to produce acetyl-CoA from acetate (43–45). Cholesterol is synthesized by the mevalonate acid (MVA) pathway, squalene biosynthesis, and subsequent transformation. Among them, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase (HMGCR) and squalene epoxidase (SQLE) is the key rate-limiting enzymes that catalyze the oxidation of squalene to 3-epoxy squalene and the reduction of HMG-CoA to MVA. The expression of all enzymes involved in *de novo* lipid synthesis is regulated by the transcriptional family of sterol regulatory element-binding proteins (SREBP; ref. 46).

Lipid uptake

Because tumor cells are usually in the hypoxic microenvironment, and tumor cells may be more dependent on fatty acid uptake under hypoxic conditions, exogenous fatty acid uptake is lipolysis by lipoprotein lipase (LPL) and then introduced into cells through fatty acid transporters (including CD36, FATP, and FABPpm; ref. 47). The exogenous intake of cholesterol is processed and recycled into the surrounding tissue. Cells absorb low-density lipoprotein (LDL) from the bloodstream through the low-density lipoprotein receptor (48). After LDL binds to the LDL receptor, the complex is internalized into the endosome by endocytosis. After being ingested by cells, LDL macromolecules are wholly and quickly degraded in lysosomes to produce cholesterol (**Fig. 1C**).

Potential Clinical Application of Metabolic Reprogramming

Early diagnosis

Although next-generation sequencing has improved the diagnosis of malignant hematologic tumors, the use of biomarkers and imaging is currently inadequate. Metabolomics-based biomarker signatures could be used to aid in the early detection of hematologic malignancies. The initiation of leukemia development is sensitive to some aspects of early reprogramming. Mutations in the isocitrate dehydrogenase (IDH) isoforms IDH1 and IDH2 cause transcriptional reprogramming and enhanced mitochondrial oxidative metabolism in patients with acute myeloid leukemia (AML; ref. 49). In addition, serum metabolomic analysis has been used to identify metabolites associated with the outcome of children with AML receiving chemotherapy (50, 51). According to a recent urine metabolomics study of patients with non–Hodgkin lymphoma (NHL; 15 samples), 18 metabolites were detected by gas chromatography–mass spectroscopy (GC-MS) and gave a satisfying diagnostic value with an area under the ROC > 0.998 (52). Similarly, there were significant metabolic differences between patients with multiple myeloma and healthy controls in bone marrow supernatant and peripheral plasma. ROC curves showed that aspartic acid achieved the highest sensitivity and specificity in both, suggesting that aspartic acid could be used as a potential biomarker for diagnosis (53). Various tumors are affected by lipid metabolism (54), and lipidomics can be used as an alternative diagnostic tool. Magdalena and colleagues found that phospholipids had the best discriminating power for prostate cancer diagnosis (55). According to metabolomics and lipidomics studies conducted by Hiroyuki Shimizu and colleagues, spermine was the best discriminator between IgG4-ROD and orbital MALT lymphoma under the ROC curve value of 0.983 (56).

Metabolic tracer monitoring

PET is a noninvasive imaging method widely used for early tumor detection, disease extent assessment, and image-guided treatment evaluation (57). In tumor cells, the primary imaging agent for PET is the glucose analog 18F-fluorodeoxyglucose (FDG), which takes advantage of the observation of abnormal glucose uptake. Large randomized trials have shown that FDG-PET can distinguish individuals who need intensive therapy early in treatment from good responders by assessing changes in metabolism in Hodgkin lymphoma and diffuse large B-cell lymphoma (DLBCL), demonstrating high sensitivity (58). The [^{18}F]-FDG, however, is not a highly tumor-specific tracer and has a rather low sensitivity for detecting diffuse bone marrow infiltration (59). Sylvain Chantepie and colleagues studied and introduced [^{18}F]-fludarabine to find a more lymphoma-specific tracer. The study results showed that 18 F-fludarabine PET could sensitively monitor the extent of bone marrow infiltration in indolent lymphoma at lower doses (60). Fluorine FGln PET is another promising investigational radiological probe for *in vivo* tumor glutamine flux and metabolism, which has been successfully tested in patients with lymphoma (35, 61). Based on the fact that [^{18}F]FDG-PET is a false negative in some patients with multiple myeloma and glutamine addiction is famously described as a typical metabolic feature of multiple myeloma cells, Silvia Valtorta and colleagues explored the possibilities of novel tracers and determined that [^{18}F]4-FGln proved to be a highly effective tool for research and potential clinical applications (62).

Therapeutic opportunities

Treatment resistance is an essential issue in the management of many cancers, including hematologic malignancies. While commonly used chemotherapeutic agents such as bendamustine, nitrogen mustard phenylbutyrate, and rituximab show an initial response, patients continue to be resistant to these regimens, therefore limiting their efficacy (63, 64). A therapeutic approach that targets metabolic enzymes or metabolites may be promising for improving cancer treatment outcomes.

Targeting glucose metabolism

Clinical studies have found that multiple myeloma is sensitive to glycolysis inhibitors such as GLUT and inhibitors of key glycolysis enzymes (65). Several studies on the use of GLUT inhibitors combined with chemotherapy agents such as doxorubicin, paclitaxel, and cytarabine have shown synergistic or cumulative anticancer effects (66). Inhibitors of GLUT1/4, furyl-2-methylene thiazolidinediones (TZD) can block the growth of the cell cycle of leukemic cells and promote cell necrosis and apoptosis (24, 67). BAY-876 can selectively inhibit the

activity of GLUT1. 2-deoxy-D-glucose (2-DG) can competitively inhibit the phosphorylation of GLUT1 and HK and enhance the antiproliferation ability of venetoclax to AML in clinical (68–70).

$HK1^{-}HK2^{+}$ cancer subtypes exist in many types of cancer (22). This study identified an antisense oligonucleotide (ASO) that was targeted to human HK2 (HK2-ASO1), which inhibits HK2 expression in human multiple myeloma cell cultures (71, 72). The mitochondrial complex I inhibitor diphenyleneiodonium (DPI) was ascertained as the optimal synthetic lethal partner for cultured $HK1^{-}HK2^{+}$ Hep3B hepatoma cells (73). On the other hand, Metformin has been clinically approved for the treatment of $HK1^{-}HK2^{+}$ cancer. This hHK2-ASO/MET combination inhibited the subcutaneous and disseminated xenograft models of human $HK1^{-}HK2^{+}$ multiple myeloma growth (71). PFK1 is the critical kinase in glycolysis, and fructose-2,6-bisphosphate is the allosteric activator of PFK1, which comes from the PFKFB of spacer activator and phosphatase activity. Therefore, glycolysis can be regulated by inhibiting the activity of PFKFB (74). It had established appropriate inhibitory concentrations of two chemical inhibitors of PFKFB3, 3-(3-pyridinyl)-1-(4pyridinyl)-2-propen-1-one (3PO) and the more specific PFK158 (75). PFKFB3 inhibitors (PFK158) are currently in phase I clinical trials, which have the potential to target the treatment of solid tumors, AML, and other tumors (76, 77).

Recent studies have shown that lactate/H^{+} export is sufficient to induce cell growth, a widely utilized mechanism in malignancies. MCT4 exports excess lactate and protons during the effects of glycolysis (78). Inhibition of MCT4 reduces intracellular pH, carbon flux and eliminates AML-initiating cells without cytotoxic chemotherapy. Dual MCT1/4 inhibition leads to lymphoblastoid cell lines (LCL) growth arrest and lactate accumulation, emphasizing the metabolic vulnerabilities of virally infected lymphomas (79). In the clinical study of targeting lactic acid efflux, it was found that monocarboxylate transporter protein one inhibitor AZD3965 could inhibit the growth of Burkitt lymphoid tumor and diffuse large DLBCL in tumor cells lacking monocarboxylate transporter 4 (80–82). The novel MCT1 inhibitor BAY-8002 significantly increased intracellular lactate levels and transient regulated pyruvate levels in DLBCL (**Table 1**; ref. 83).

Targeting amino acid metabolism.

The development of drugs targeting glutamine metabolism in cancer cells is focused on glutamine depletion, glutaminase inhibition, membrane glutamine transporter inhibition, and GLS inhibitors (84–87). L-asparaginase (L-asp) is the most common glutamate depletion agent with significant glutaminase activity. It is the cornerstone for treating children with acute lymphoblastic leukemia (ALL; refs. 88, 89). In lymphoma, clinical trials show that chemotherapy containing L-asp is the critical component of first-line treatment of systemic extranodal natural killer/T-cell lymphoma, nasal type (ENKL; refs. 90–92). Jianhui Sun and colleagues found that although L-asp is a commonly used targeted drug for childhood ALL, SLC can produce resistance to the drug's therapeutic effect. Therefore, the combination of SLC inhibitors to restrict cell transport of glutamine has a better therapeutic effect on tumors (93). V-9302 is a competitive fraction antagonist of transmembrane glutamine flux, which can selectively and effectively target amino acid transporter ASCT2 (SLC1A5; ref. 94). GLS is the most intensely studied enzyme in the glutamine decomposition pathway. At present, various GLS inhibitors have been developed in basic research, such as Bis-2-(5-phenylacetamido-1,2,4-thiadazol-2yl) ethyl sulfide (BPTES), CB-839, and 968 compounds (95). CB-839 is a small molecular GLS inhibitor being studied clinically (96), and it is a selective and noncompetitive inhibitor (97). Gregory and colleagues found that the use of CB-839 to block glutamine metabolism can significantly weaken the production of glutathione, resulting in the increase of mitochondrial active oxygen (mitoROS) and the death of apoptotic cells (98, 99).

Arginine deiminase (ADI) can convert arginine to citrulline, which needs to be recycled to arginine through arginine succinate synthase (ASS1) and argininosuccinate lyase (ASL). The absence of ASS1 in

Table 1. Targeting metabolism by anticancer drug candidates.

Drugs	Target	Cancer type	References
Targeting glucose metabolism			
Furyl-2-Methylene Thiazolidinediones	GLUT1/4	Leukemia	(24, 67)
BAY-876, 2-DG	GLUT1	AML	(68–70)
ASO, MET	HK2	MM	(71, 72)
3PO, PFK158	PFKFB3/ PFK1	AML	(76, 77)
AZD3965	MCT4	Burkitt lymphoma and DLBCL	(80–82)
BAY-8002	MCT1	DLBCL	(83)
Targeting amino acid metabolism			
L-asp	Glutaminase	ENKL and ALL	(90–92)
V-9302	SLC	Various cancer types	(94)
BPTES, 968, CB-839	GLS	Various cancer types	(97–99)
ADI	ASS1	Various cancer types	(100, 101)
ADI-PEG20		AML	(104)
BCT-100, HuArgI, HuArgI (Co)-PEG5000	ARGase	Various cancer types	(107, 109, 111)
CBR-5884, BTZ	PHGDH	Various cancer types	(114, 116)
SHIN1	SHMT1/2	DLBCL	(117)
Targeting lipid metabolism			
Orlistat, Fasnall, C75	FASN	T-ALL, DLBCL, and B-NHL	(120–124)
SB-204990	ACLY	AML	(126–128)
Statins	HMGCR	Various cancer types	(132–135)
Bisphosphonate	MVA	Various cancer types	(136)
Terbinafine	SQLE	ALK +ALCL	(141, 142)
Itraconazole	NPC1	Various cancer types	(141)
mirRNAs	SREBPs	Various cancer types	(145)

Abbreviations: MET, metformin; MM, multiple myeloma; SHIN1, SHMT inhibitor 1.

tumor cells is equivalent to the exhaustion of arginine in serum, which prevents cell growth. Therefore, identifiable tumor cells lacking ASS1 are highly lethal (100, 101). ADI-PEG20 combined with docetaxel can inhibit arginine in solid tumors, making the patient's condition remission or relatively stable (102, 103). Arginine consumption through ADI-PEG20 can ease the burden of primary AML *in vivo* and *in vitro* (104). Another strategy to consume arginine (Arg) is ARGase. Therefore, ARGase may show an anticancer effect on ASS1 or Ornithine transcarbamylase (OTC) deficiency (105, 106). BCT-100 is a pegylated recombinant human arginase that consumes arginine. In acute lymphatic leukemia, BCT-100 results in reduced implantation of all ALL and prolonged survival for all xenografts (107). After BCT-100 treatment, extracellular and intracellular Arg is rapidly exhausted, thus reducing the proliferation of AML primordial cells (108). Synthesized human arginase 1 (HuArgI) is another arginine deprivation agent (109). Due to its short half-life limitation, PEG can be added, and $Co2^{+}$ substituted for $Mn2^{+}$ to enhance its cytotoxicity against l-arginine nutrient-deficient cancer cell lines (110), making it HuArgI (Co)-PEG5000 (111). Autophagy is activated after arginine deprivation induced by HuArgI (Co)-PEG5000.

PHGDH is the first and only rate-limiting enzyme in serine's de novo biosynthesis pathway (112). Inhibition or depletion of PHGDH can lead to apoptosis in many cancers (113). CBR-5884 inhibits PHGDH noncompetitively and time-dependently, interferes with its oligomerization, and inhibits the growth of cancer cells in a dose-dependent manner (114). The proteasome inhibitor bortezomib (BTZ) is widely used in multiple myeloma. After inhibiting serine metabolism, BTZ can enhance the cytotoxicity of bortezomib, which indicates that inhibition of PHGDH interference with serine may become a novel strategy to improve BTZ therapy for BTZ resistance (115). Florence Polet and colleagues also found that *in vitro* PHGDH silencing and nonexogenous serine intake can also inhibit the survival of leukemic cells (116). The inhibition of small molecule SHMT can prevent the growth of many cancer cells (117). Increased levels of SHMT1 and SHMT2 were observed in transgenic mice susceptible to carcinogen Myc-driven B-cell lymphoma (118). Ducker and colleagues found that SHIN1 has an inhibitory effect on SHMT1/2 when using small-molecule inhibitors of SHIN1, and cancer cells are sensitive to low concentrations of SHIN1 (**Table 1**; ref. 117).

Targeting lipid metabolism

FAS is a multienzyme protein complex encoded by the FASN gene. Inhibition of FASN inhibits the proliferation and accelerates the death of a wide range of tumors (119). Orlistat can reduce the activity of FASN and the growth potential of tumor cells in a variety of cancers, including T-ALL (120–122). Gifford and colleagues studies have found that the new drug Fasnall selectively inhibits fatty acid synthase and demonstrates the therapeutic potential of inhibiting the fatty acid synthesis in some DLBCL cells (123). Studies have shown that FAS inhibitor C75 reduces the activity of B-NHL (124, 125). ACLY was proved to be a potential target for anticancer therapy in 2005, and ACLY chemical inhibitor (SB-204990) impaired the proliferation and survival of tumor cells (126–128). Subsequently, some studies have shown that the expression of ACLY is related to the prognosis of AML (129).

Targeted cholesterol biosynthesis and uptake is a promising method for treating hematologic malignant tumors (130, 131). Numerous basic studies and several clinical trials have investigated the potential efficacy of statins, which act in cancer by inhibiting the activity of HMGCR (132–135). Bisphosphonates, another well-studied inhibitor of the MVA pathway, have been reported to inhibit the survival of various tumors (136). HMGCS1, SQLE, and lanosterol synthase (LSS) are potential metabolic targets for the treatment of cancer (137). Dipyridamole, inhibition of HMGCS1, could inhibit the activation of MEK1 and reduce the expression of pluripotent genes Oct4 and Sox2 (138–140). In anaplastic lymphoma kinase (ALK) + anaplastic large cell lymphoma (ALCL), SQLE can alter cells' lipid profile, protecting cancer cells from fattening cytostatic death. Some studies have shown that terbinafine targeting SQLE may be a promising method for tumor prevention and treatment (141, 142). Numerous studies have shown that inhibition of cholesterol release from lysosomes can remarkably inhibit tumor development and angiogenesis (143). Itraconazole is the most widely studied cholesterol transport inhibitor, which directly binds to the sterol-sensitive region of nasopharyngeal carcinoma (NPC) intracellular cholesterol transporter 1 (NPC1) and inhibits its function. During the rapid proliferation of tumor cells, high density lipoprotein cholesterol (HDL-C) decreases, thus preventing the loss of the intracellular cholesterol pool. The inhibition of SREBPs by small-molecule drugs such as fatostatin and mirRNAs has been widely reported to exert multiple antitumor effects in various cancers (144–146; **Table 1**).

Conclusion

Hematologic malignancies are closely associated with metabolic reprogramming, according to recent research. A wide range of nutrients are necessary for hematologic malignancies to survive, and the nutrient deficiencies resulting in metabolic vulnerability offer therapeutic possibilities. As part of the wide range of targeted metabolic reprogramming approaches, enzyme depletion and rate-limiting enzyme strategies are promising therapeutic approaches with good clinical results. Unfortunately, there are still some problems, such as low specificity and easy emergence of drug resistance, which can have great adverse effects on the human body. The application of drugs *in vivo* and *in vitro* is very limited because of a particular metabolic phenotypic gap between various cancer cells. Furthermore, research is now exploring a personalized medicine approach to target metabolism for cancer treatment. As such, there is a need to select appropriate therapeutic targets for more targeted treatment of metabolic reprogramming of tumor cells between antitumor cell growth and maintenance of normal cell growth in the body. In addition, there has been renewed interest in the use of cancer genetic analysis for patient stratification and/or dietary intervention in combination with metabolically targeted therapies.

Authors' Disclosures

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