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MINI REVIEW

Regulation of Amino Acid Metabolism in Hematological Malignancies: Advances from Transcriptomics and Metabolomics

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ABSTRACT

Tumor cells use amino acids to rewire metabolic pathways to meet increased demands for energy, reducing equivalents, and cellular biosynthesis. Aside acting as building blocks for protein synthesis, amino acids also function as metabolic intermediates for ATP generation and redox homeostasis, as well as fueling biosynthetic pathways. Tumor-related metabolic changes influence every stage of the interaction between cells and their metabolites. Over the years, advancements in molecular methods such as transcriptomics and metabolomics have emerged to provide in-depth knowledge into the functions, interactions, and actions of molecules in cells of organisms. These technologies surfaced as methods that provide a more complete picture of disease pathophysiology, facilitating the elucidation of disease mechanisms and identification of potential biomarkers (metabolites) and targets (genes) respectively. Though Omics in cancer research have been explored in different concepts, however, employing these methods in amino acid metabolism in hematological cancers still requires attention. Therefore, this mini review discusses an up-to-date knowledge of principal regulators and their role in amino acid metabolism in hematological malignancies. In that perspective, we cover relevant findings from transcriptomics and metabolomics, thereby constructing mechanistic insights associated with disease pathogenesis.

Abbreviations

2-HG: 2-hydroxyglutarate; AA: Amino Acid; AAT: Aspartate Aminotransferase; AC220: Quizartinib/ FLT3 Inhibitor; ALDH: Aldehyde Dehydrogenase; ALDH1A2: Aldehyde Dehydrogenase 1 Family Member A2; ALL: Acute Lymphoblastic Leukemic; ALT: Alanine Transferase; AML: Acute Myeloid/Myelogenous Leukemia; ASNS: Asparagine Synthetase; ASS1: Arginosuccinate Synthase; AST/GOT: Aspartate Transferases; ATF4: Activating Transcription Factor 4; ATP: Adenosine Triphosphate; BCAA: Branched Chain Amino Acids; BCAT1: Branched Chain Amino Acid Transaminase 1; BC-CML: Blast Crisis Phase-CML; BCKA Branched Chain α-keto Acids; BM: Bone Marrow; CML: Chronic Myeloid Leukemia; CpG: Cysteine-p-Glycine Oligonucleotides; CPS2: Carbamoyl Phosphate

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Synthetase II; EZH2: Enhancer of Zeste Homolog 2; FLT3: FMS-Like Tyrosine Kinase 3; FLT3-ITD: FLT3 Internal Tandem Duplication; GAC: Glutaminase A; GBC: Glutaminase B; GCN2: General control non-derepressible 2; GLDC: Glycine dehydrogenase; Gln: Glutamine; GLS1: Glutaminase 1; GSH: Glutathione; HSCs; Hematopoietic Stem Cells; IDH1 and IDH2: Isocitrate Dehydrogenase Isoforms 1 And 2; ITD: Internal Tandem Duplication; LC-HR-MS/MS: Liquid Chromatography--High Resolution Tandem Mass Spectrometry; L-DON: 6-diazo-5-oxo-L-norleucine; LSC: Leukemia Stem Cells; MDSCs: Myeloid-Derived Suppressor Cells; MRIAN: Metabolic Reprogrammed L-Phenylalanine Polymer; MRIAN-Dox: Metabolic Reprogramming Immunosurveillance Activation Nanomedicine assembled Doxorubicin; MS: Mass Spectrometry; NEAA: Non-Essential Amino Acids; NFE2L2: Nuclear Factor Erythroid 2-Related Factor 2; NMR: Nuclear Magnetic Resonance; Omics Transcriptomics/Metabolomics or Proteomics/ Genomics; OXPHOS: Oxidative Phosphorylation; P5C: D1-pyrroline-5-carboxylate; PPAT: Amidophosphoribosyltransferase; PSAT: Phosphohydroxythreonine Aminotransferase; PYCR1: Pyrroline-5-carboxylate Reductase; ROS: Reactive Oxygen Species; RTKs: Receptor Tyrosine Kinases; SLC: Solute Carrier; SLC1A5/ Slc38A1: Sodium Dependent Neutral Amino Acid Transporters; TAL1: T-Cell Acute Leukemia Protein 1; T-ALL: T-Cell Acute Lymphoblastic Leukemia; TCA: Tricarboxylic Acid Cycle; TKI: Tyrosine Kinase Inhibitor; ULK1: Unc-51 Like Autophagy Activating Kinase; xCT: Cystine/ glutamate antiporter; α-KG: α-ketoglutarate

Introduction

The phrase "hematological malignancies" refers to a class of diseases that affect the blood, bone marrow, and organs and have a wide variety of prognoses and post-treatment relapse rates. Given its high prevalence (7 percent of all newly diagnosed cancers), leukemia remains one of the largest group of hematological malignancies that start in blood-forming cells in the bone marrow resulting in cumulation of abnormal blood cells in tissues [1].

Metabolism, the process by which organisms obtain the energy required to power their cellular functions as well as the building blocks needed to make new cells, has become a focal point for understanding disease pathogenesis and finding treatments. The malignant characteristics of cancer cells, including rapid proliferation and aggressive invasion into normal tissues, differ from normal non-proliferating cells and requires altered metabolism to meet increased nutritional and biosynthetic demands [2,3]. The primary carbon source for metabolism is provided by amino acids, which are also significant building blocks required for cellular functions. They are vital for the production of intermediate metabolites that power biosynthetic and bioenergetic pathways and have been conventionally categorized as either essential or nonessential [4].

Recent studies focused on deciphering mechanisms of chemo-resistance caused by abnormal Amino Acids (AA) metabolism [5-8]. To considerably inhibit hematological malignancies, therapies that target tumor AA metabolism are crucial for overcoming drug resistance and boosting the effectiveness of diagnosis and treatment [9,10]. Tumorigenesis-related metabolic changes have been shown to influence every stage of the interaction between cells and their metabolites, particularly how nutrients are acquired and preferentially assigned to metabolic pathways in order to support cellular tumorigenic properties. Studies on the metabolism of cancer cells have enhanced our understanding of tumor-associated metabolic changes influenced by genetic or epigenetic cues as well as components of tumor microenvironment [11-15].

As high-throughput technologies advance, a flood of data is generated in order to address clinical and translational research questions, necessitating the employment of bioinformatic and computational tools to organize, interpret, and analyse the data [16]. Metabolomics data is increasingly being integrated with other omics data, such as gene expression data, to fully utilize and improve the interpretability of metabolomic profiles [17]. More specifically, integrating metabolomics with transcriptomics aids in elucidating disease mechanisms as well as identifying potential biomarkers (metabolites) and targets (genes) [18].

The use of several omics platforms in cancer research has also been explored in a number of studies and provides a broad overview of the state of the field today [19], but the outcomes and relevance from employing these methods in amino acid metabolism in hematological cancers is poorly addressed. Thus, in this mini review, we summarize an up-to-date knowledge of key regulators and their role in amino acid metabolism in hematological malignancies. In that perspective, we cover the most relevant findings

from transcriptomics and metabolomics, thereby constructing mechanistic insights related to disease pathogenesis.

Principal regulators and their role in AA metabolism associated with disease pathogenesis

***TAL1* and *ALDH1A2* deletion in T-cell acute lymphoblastic leukemia:** According to gene expression and mutational patterns, T-ALL patients can be divided into distinct subgroups based on the expression of numerous transcription factors TAL1 [20-22]. TAL1-positive leukemia is the most prevalent subtype, representing majority of all primary cases [21,23-27]. *ALDH1A2* [28,29] a member of the Aldehyde Dehydrogenase (*ALDH*) family of genes that encode oxidoreductases, is one of the recognised targets of TAL1 in ALL. ALDH detoxifies endogenous aldehydes generated by the metabolism of amino acids and other biomolecules [30].

TAL1 directly activates ALDH1A2, which guards against intracellular stress and promotes leukemia cell metabolism and survival by inhibiting apoptosis [31]. Global gene expression profiling by RNA-sequencing after *ALDH1A2* deletion showed that several enzymes involved in amino acid metabolism, including ASS1 and ASNS, were increased following ALDH1A2 deletion compared to control samples, while a number of metabolic enzymes and transporters involved in the glycolysis pathway were down regulated [31].

After ALDH1A2 was deleted in the human T-lymphocyte Jurkat cell line, the relative amounts of metabolites implicated in the main metabolomics pathways were assessed using a capillary electrophoresis time-of-flight MS technique. Unexpectedly, acetyl-CoA, one of the major carbon sources that power the TCA cycle, as well as TCA subcomponents like citric acid, cis-aconitic acid, and isocitric acid, were reduced by ALDH1A2 loss [31]. It is important to note that the TCA cycle's levels of 2-oxoglutarate-derived metabolites remained unaltered. This suggests that the TCA cycle, which is reduced by the lack of ALDH1A2, may be augmented by glutaminolysis, which transforms exogenous glutamine into 2-oxoglutarate. The predominant carbon source for T-ALL cells with activated NOTCH1 is known to be glutamine [32,33]. In fact, after 24 hours of doxycycline treatment, glutamine depletion in culture induced apoptosis, which was amplified by ALDH1A2 loss. When exogenous glutamine was present, ALDH1A2 deletion alone did not cause apoptosis to occur until 48 hours after induction. In light of these findings, it is possible that exogenous glutamine may be used to replace downstream metabolites and maintain the TCA cycle in the absence of this gene transcript, and that ALDH1A2 and glutaminolysis pathways could work in concert to make up for one another [31].

***IDH1/IDH2* in leukemic transformation:** Acute myeloid leukemia is most frequently associated with mutations in the Homologous Isocitrate Dehydrogenase Isoforms 1 And 2 (IDH1/IDH2) [34]. IDH1 and IDH2, localised in the cytoplasm and mitochondria respectively, are involved in a variety of metabolic processes in cells, such as Redox regulation, biosynthesis, and bioenergetics [34-37]. Active IDH enzymes take part in citrate metabolism by converting isocitrate to α-ketoglutarate (α-KG) and producing NADPH by reducing the cofactor NADP+ [34]. α-KG plays a vital role in metabolism a key intermediate in the TCA cycle and glutaminolysis [34].

Using Nuclear Magnetic Resonance (NMR) to access metabolic profile of the intracellular metabolite, 2-HG on mutant IDH1 and IDH2-expressing human primary leukemia cells from AML patients [38]. The Class III Receptor Tyrosine Kinase (FLT3) inhibitor quizartinib was observed to reduced 2-HG metabolite levels in mutant IDH1 cells. Thus, suggesting mutant IDH1 might be involved in activating Glutaminase 1 (GLS1) activity in the absence of FLT3 inhibitor. Treating mutant IDH2 with quizartinib, on the other hand, resulted in increased intracellular 2-HG levels [38], implying that mutant IDH2 may play a role in inhibiting GLS1 in the absence of the inhibitor.

Transcriptome-RNA-sequencing revealed elevated 2-HG induces cytotoxicity through regulation of several pathways including upregulation of apoptotic and P53 pathway, and downregulation of MYC pathway, mTOR affecting ATP synthesis [38,39]. In addition, studies have shown that accumulation of oncometabolites including 2-HG is associated with elevated glutamine metabolism hence supporting cancer transformation [40,41] (Figure 1).

Loss of *PRMT7* cooperates with specific mediators to alter AA metabolism in CML: To investigate the role of the protein arginine methyltransferase PRMT7 in CML mice [42], RNAseq of Leukemia Stem Cells (LSCs) isolated from the bone marrow *Prmt7*-Knockout CML mice revealed that several genes were differentially regulated. Because PRMT7 has oncogenic epigenetic

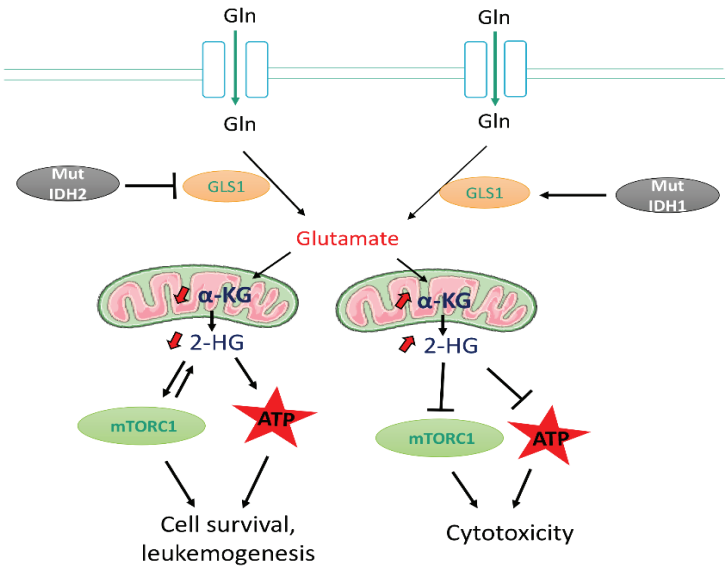

Figure 1 Mutations in IDH1/2 is associated with AA metabolism during leukemia transformation. The Presence of IDH1 mutation activates Glutaminase 1 (GLS1) which converts glutamine (Gln) to glutamate. The Excess glutamate is then catabolised increasing α-KG and 2-HG(hydroxyglutarate) metabolites. Elevated α-KG and 2-HG inhibits mTORC1 and ATP synthesis leading to cytotoxicity. On the other hand, mutated IDH2 blocks the activity of GLS1, inhibiting the formation of glutamate from Gln and as a result, decrease in α-KG and 2-HG. This leads to the activation of mTORC1, and synthesis of ATP required for cell survival and leukemogenesis.

regulation activity, the authors focused their attention on the genes that were downregulated in *Prmt7*-KO cells. Glycine Decarboxylase (GLDC) was one of the top ten down regulated genes, as confirmed by qRT-PCR analysis [42].

Additionally, functional enrichment analysis of the deregulated transcripts showed that *Prmt7*-deficient cells had a high enrichment of genes associated to glycine and serine metabolism. Because the proliferation of tumor-initiating cells and cancer depend on glycine decarboxylase, a rate-limiting enzyme in the network that controls glycine and serine metabolism [43], Liu's [42] group investigated this enzyme as a possible downstream target of Prmt7 in CML leukemia stem cells. In that perspective, they hypothesized that Prmt7 absence-mediated GLDC repression could be mediated by a downstream repressive transcription factor. As a result, RNA-seq results revealed GATA binding 1 (Trps1, a transcriptional repressor) among the upregulated genes in *Prmt7*-deleted cells.

According to Liu, et al. [42] the reduction in GLDC brought on by PRMT7-loss may allow the LSCs' glycine metabolism to be reprogrammed creating a hazardous metabolite, methylglyoxal. The outcome of glycine metabolism is determined by the balance of toxic product generation and clearance [44]. In terms of expulsion, glycine can be either converted by the decarboxylase into the nontoxic product 5,10-methylene-tetrahydrofolate (5,10-MTHF) or into toxic methylglyoxal by glycine C-acetyltransferase [44.45]. Zhang, et al. [43] suggested elevated glycine levels may be caused by excessive glycine generation from serine, mediated by Serine Hydroxymethyltransferase 2 (SHMT2). Furthermore, this transferase was found to be highly expressed in human CML-CD34 positive cells compared to normal cells and Prmt7 deletion had no effect on Shmt2 expression in leukemia mice. Most amino acids, including glycine and serine, have been reported to be higher in leukemia cells from newly diagnosed CML patients than in healthy individuals [46]. Following a time course assessment, High-Performance Liquid Chromatography-Mass Spectrometry (HPLC-MS) analysis showed that the intracellular contents of glycine and serine progressively increased as CML disease progressed. These findings demonstrate a potential link between altered glycine metabolism and the development of CML illness using transcriptomic and metabolomic methods [42].

***FLT3ITD* and glutamine metabolism in Leukemia:** FLT3 Internal Tandem Duplication (FLT3-ITD) mutations are common in AML and probably correlate with poor prognosis. Albeit current FLT3 Tyrosine Kinase Inhibitors (TKI) has been quite promising

in targeting this mutation, the consequences of this mutation in AML patients necessitate the identification of novel, specific and more effective therapeutic targets especially for the highly hostile AML subtype [47].

Combining metabolomics and gene expression analysis, studies have shown that by supporting both mitochondrial function and cellular redox function, glutamine metabolism becomes a metabolic dependence of FLT3ITD-leukemia, which is specifically revealed by treatment with FLT3 inhibitors.

Gallipoli, et al. [47] performed LC-MS analysis after incubation with stable isotope-labeled glutamine to understand the fate of glutamine metabolism in FLT3ITD cells after treatment with AC220 (FLT3 inhibitor). Intracellular levels of labeled glutamine were increased in treated cells, confirming that glutamine uptake was not impaired. However, given the antiproliferative properties of FLT3 inhibitors, incorporation of labeled glutamine in TCA intermediates was reduced likewise the total level of most TCA cycle intermediates as compared to control cells. Thus, despite a significant decrease in total TCA cycle activity, glutamine remains a major anaplerotic substrate in FLT3-treated cells.

In addition, glutamine (*via* glutamate) which supports the TCA cycle is also a precursor of glutathione, the primary cellular antioxidant [48]. It is noteworthy that the reduced/oxidized glutathione ratio (GSH/GSSG) was generally preserved in treated cells, and this treatment had no effect on glutathione metabolism genes, including the key regulator of antioxidant response NFE2L2. Taken together, these finding suggest glutamine supports the TCA cycle and glutathione production following FLT3 inhibition.

Following the work of Zarvoka Thomas, et al. [49] they sought to identify additional therapeutic targets that can be used to enhance the antileukemic effect of the tyrosine kinase inhibitor gilteritinib. Based on unbiased transcriptomic analyses, the glutamine transporter SNAT1 (SLC38A1) was identified as a potential target of gilteritinib that causes impaired glutamine uptake and utilization in leukemic cells. Furthermore, metabolomics and metabolic flux analyses in the presence of gilteritinib revealed reduced glutamine metabolism *via* the TCA cycle as well as cellular levels of the oncometabolite 2-HG. Finally, glutaminase inhibitor CB-839 improved gilteritinib antileukemic effect in ex vivo studies using human primary FLT3-ITD positive AML cells harboring mutations in the enzyme isocitrate dehydrogenase, which catalyses the oxidative decarboxylation of isocitrate to produce a-ketoglutarate. These findings have revealed a previously unknown gilteritinib-sensitive metabolic pathway downstream of SLC38A1 that causes decreased glutaminolysis and redox homeostasis disturbance [49] (Figure 2). Together, *via* transcriptomics and metabolomics, we can identify mechanistic insights connecting tyrosine kinase inhibition and glutaminolysis in AML treatment. Thus, providing a logical approach for the development and therapeutic investigation of targeted combinatorial treatment strategies for cases of relapse/refractory AML.

***BCAT1* and reprogrammed Branched Chain Amino acids (BCAA) metabolism in leukemia:** Blood AA levels in mouse models that replicate the chronic and blast crisis periods of human CML have been examined in order to better understand the role of AA metabolism in CML cancer growth [50,51].

Although BCAA amino acid transaminase 1, BCAT1, catalyzes transamination in the forward and reverse direction, in most cell types, the breakdown of BCAAs is the predominant reaction [52]. BCAT1 requires the presence of Branched-Chain Keto Acids (BCKAs) as well as glutamate as substrates in order to generate BCAAs. Hattori's group found the following BCKAs; keto-isovalerate, keto-isocaproate and keto-methylvalerate, in blood plasma and leukemia cells with significant amount of the corresponding BCAAs in blast crisis-CML cells, implying that intracellular BCKAs can serve as substrates for BCAA production. The authors then used stable-isotope tracer experiments with [^{13}C]-valine or [^{13}C]-KIV to see if BCAAs are produced in leukemia cells *via* BCAT1 transamination reactions. High-field NMR spectroscopy was used to examine intracellular 13C-labeled metabolites in K562 human BC-CML cells applying a one- and two-dimensional 1H-13C heteronuclear single bond correlation (HSQC) analysis. The production of strong [^{13}C]-valine signals was observed, indicating that valine is efficiently generated from KIV intracellularly as compared to cells in non-labeled KIV in which [^{13}C]-KIV was undetectable. This data indicated the transport of intracellular [^{13}C]-valine in these leukemic cells [53]. In equal concentrations of KIV and Val, Val is produced from KIV but not the reverse reaction (Val to KIV) as well as it was impossible to detect the formation of KIC from [^{13}C]-leucine. This

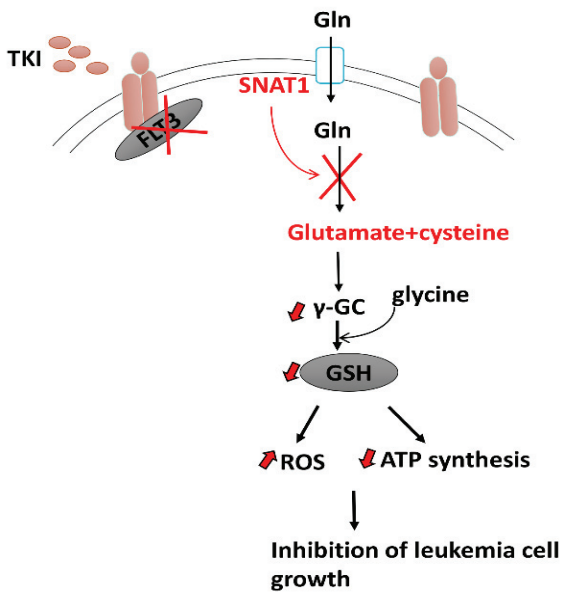

Figure 2 Action of Tyrosine kinase Inhibition on glutaminolysis in FLT3ITD-Leukemia. Tyrosine Kinase Inhibitors (TKI) blocks FLT3 activity. This enhances the uptake of glutamine transporter SNAT1 (or SLC38A1) which then blocks the utilization of glutamine by the cell leading to decrease Glutathione (GSH) and increase ROS. This accompanied by decrease ATP production thus inhibiting leukemia cell survival.

suggest that BCAAs are not converted to BCKAs in leukemia cells [53].

Furthermore, other labeling studies have been executed to monitor the fate of the glutamate amine group providing additional evidence for intracellular BCAA production *via* transamination. Human myelogenous leukemia K562 cells were cultured with [^{15}N]-amine-labeled glutamine, which is metabolized to [^{15}N]-amineglutamate by glutaminase upon cellular intake, and the labeling of BCAAs was examined using NMR. The authors identified [^{15}N]-amine-labeled BCAAs, indicating transamination from glutamine to BCAAs after 29h postlabeling. By 72 hours, the labeled BCAAs cumulated to a high abundance, suggesting that transamination made a significant contribution to the intracellular BCAA pool. These findings show that BCKA transamination by BCAT1 contributes to the pool of BCAAs in leukemia cells [53] (Figure 3a).

***EZH2* and *NRAS* in *BCAA* Metabolism:** EZH2, which is involved in histone-lysine methylation, is a frequent epigenetic regulator with high mutation rates in hematologic malignancies. Loss-of-function *EZH2* mutations have been identified in several myeloproliferative neoplasms and juvenile myelomonocytic leukemia [47,54-56]. Overexpression or gain-of-function *EZH2* mutations are also common in cancers [58,59], suggesting that EZH2 can cause tumors in both overactive and hypoactive states.

Alterations in *EZH2* and *RAS* together promote the progression of myeloproliferative neoplasms to highly penetrant, transplantable, and lethal myeloid leukemias in mice [54-56,59-61] BCAT1, which catalyzes the reversible transamination of BCAAs, is normally repressed by *EZH2* but abnormally activated in *EZH2*-deficient myeloid neoplasms in mice and humans. In addition, BCAT1 renewal collaborates with *mutant NRAS* to maintain intracellular BCAA pools, leading to increased mTOR signaling in leukemia cells lacking *EZH2* [59]. Gu, et al. [59] used WT, G12D, E2-KO, and G12D/E2-Knockout mice Hematopoietic Progenitor Cells (HSPCs) and performed RNA-seq to unravel the molecular link between *EZH2*, *BCAT1* and BCAA metabolism required for leukemogenesis. The levels of the BCAAs - Valine, Leucine and isoleucine were significantly higher in G12D/E2-KO compared to other genotypes, suggesting that increased BCAT1 in G12D/E2-KO HSPCs is associated with BCAA increase. These findings suggest that *EZH2* deficiency with $NRas^{G12D}$ reactivates BCAT1 to improve BCKA to BCAA conversion, resulting in increased BCAA pools in HSPCs. Thus, modulating the enzyme and substrates for BCAA metabolism is critical for targeting the epigenetic and metabolic vulnerabilities of leukemia cells.

Another critical question is where BCKAs and Glu, the two substrates for BCAT1 transamination, come from. Gu, et al. [59] speculated that BCKAs were imported from extracellular sources *via* monocarboxylate transporters MCT1,2 or 4. In light of this, RNA-seq analysis revealed that *MCT1* (or *Slc16a1*) was the most abundant transporter expressed in HSPCs. Strikingly, an MCT1 inhibitor AZD-3965 significantly reduced BCKAs and BCAAs in G12D/E2-KO HSPCs and mildly decreased BCAAs in wildtype and mutant *NRAS* HSPCs. In addition, *NRAS* activation resulted in elevated intracellular Glu in G12D and G12D/E2-KO cells. The authors then investigated whether $NRas^{G12D}$ increased Gln uptake and intracellular Glu pools *via* glutaminase (GLS)-mediated Gln to Glu conversion, which 'fuels' BCKA reamination catalyzed by BCAT1. Through [^{13}C]-Gln tracing they found that $NRas^{G12D}$ increased intracellular Gln to Glu conversion in G12D and G12D/E2-KO, whereas glutaminase inhibition by CB-839 significantly decreased Glu and BCAAs in G12D/E2-KO cells. Together, these findings

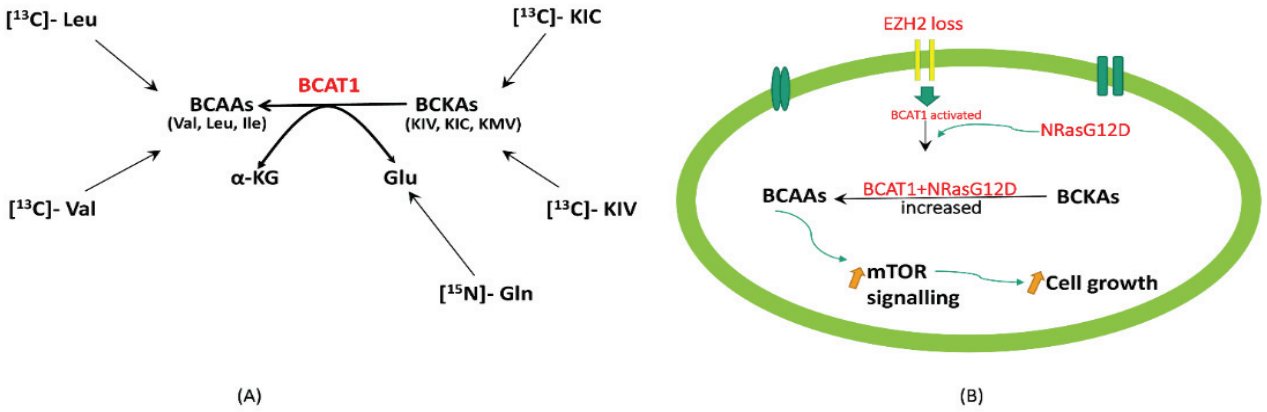

Figure 3 **(A)** BCAA metabolism is reprogrammed in leukemia cells. Branched Chain Amino Acids (BCAAs) including Valine, Leucine and isoleucine are formed from the transamination of Branched Chain A-Keto Acids (BCKA) catalysed by BCAA Transaminase 1 (BCAT1). In concert, Gln is also transaminated to BCAAs thus adding to the BCAA pool in leukemia cells.
(B) EZH2 mutation Reprograms BCAA Metabolism to Drive Leukemic Transformation. EZH2-deficient (loss) activates BCAT1 activity. Combined action of BCAT1 and NRasG12D enhances the conversion of BCKA to BCAAs. BCAAs such as Leucine increases mTOR signalling hence supporting cell growth and thus leukemia transformation.

show that MCT1-dependent BCKA transport and GLS dependent Gln to Glu conversion are required for BCAT1 transamination in EZH2-deficient leukemia cells [59]. In a related study, BCAAs, particularly Leu, were found to activate mTORC1 and promote cell growth. Since *BCAT1* activation increased BCAAs in *EZH2*-deficient cells, suggesting *BCAT1*-driven Leukemia is likely sensitive to mTOR inhibition [59]. In summary, these findings show that *EZH2* loss and RAS activation promote leukemic transformation by modulating the enzyme and metabolic substrates of BCAA metabolism (Figure 3b).

***KRAS* regulates the cysteine/glutamate antiporter:** Using B-ALL cell lines carrying $KRAS^{G12D}$ mutation, Isotope tracing revealed $KRAS^{G12D}$ mutation rewires methionine and arginine metabolism by boosting catabolism of these amino acids to enhance the anabolism of polyamines and proline, consequently inhibiting growth of the cells [62]. Overactivation of the AKT/mTOR pathway significantly increased the activity of KRAS12D. The effects of KRAS on amino acid metabolism were reversed when AKT/mTOR signaling was inhibited, and cell proliferation was restored [62]. According to the findings of Lim, et al. [63], the *xCT* gene expression was enhanced in KRAS transformed cells *via* the activation of ETS-1, which functions in conjunction with ATF4 to promote cell survival. On the other hand, knocking down this gene decreased tumor growth. This evidence suggests that the xCT (cysteine/glutamate antiporter) gene promotes tumor development, making it a possible therapeutic target.

***TKTL1* gene in hypoxia-induced AML cells:** The Transketolase (TKT) family's transketolase-like-1 gene has been linked to malignant transformation and a poor prognosis in many cancers [64-67]. The suppression of TKTL1 prevents THP-1 AML cells from switching to glycolysis in hypoxic circumstances by inhibiting hypoxia-induced transcription of genes that encode amino acid metabolism-related enzymes and transporters. In a study by Baptista and colleagues, metabolome data revealed considerable drop in concentrations of glutamate, glutamine, proline and ornithine in TKTL1-knockdown human monocytic leukemia THP-1 cells compared to wildtype cells [68,69]. Following transcriptome profiling, Proline dehydrogenase and arginase 1 were shown to have higher gene expression profiles in wildtype cells than in knockdown cells under hypoxic conditions. Furthermore, in control cells, Gln synthetase and SLC38A2 were modestly elevated, whereas glutaminase and SLC38A2 were dysregulated in THP-1 deficient cells. Likewise, still under hypoxic conditions, SLC1A3 and SLC17A7 were shown to be highly enhanced in the wildtype but decreased in the knockdown phenotype. Aside from the alterations in proline and ornithine, the investigators detected enhanced dimethylarginine secretion in the knockdown cells [69]. Taken together, this changes in metabolites and gene expression due to TKTL1 knockdown accounts for the amino acid metabolic adaptation observed in hypoxic induced AML cells.

***DNMT3A*, an epigenetic modulator controls AA metabolism:** DNA Methyltransferase 3A (DNMT3A) alterations have been found in the majority of AML patients [70-73]. DNA methylation transforms the cytosine of CpG dinucleotides by attaching a methyl group, making it an essential component of the regulation of gene epigenetics. RNA microarrays on k562 cells indicated that this mutation influences glutathione metabolism [74]. PSPH, SLC7A11, PSAT1, and CTH were shown to be considerably upregulated, raising glutathione levels [74]. This data suggests that, targeting genes involved in glutathione synthesis is crucial for understanding the role of DNMT3A mutation in AML pathogenesis.

***BCAT1* regulates αKG levels in AML cells:** Through MS-BCAA tracing Raffel, et al. [75] found that when BCAT1 was knocked down, a quantity of ^{15}N-labeled non-essential amino acids was significantly reduced, but the overall glutamate pool was unaffected, implying that leukaemia cells can compensate for the loss of BCAT1-dependent glutamate production from other sources. Given that BCAT1 uses αKG as a substrate, the authors speculated that BCAT1 could aid in regulating intracellular KG levels. Indeed, after *BCAT1-Knockdown*, KG levels increased significantly in several AML cell lines such as HL-60, SKM-1, and MOLM-13. In summary, this finding identifies BCAT1 as a critical regulator of αKG in distinct tumor cell types [75].

***SLC1A5* cooperates with Pten and BCR-ABL:** According to Ni, et al. [76] a constitutive deletion of *SLC1A5* reduced leukemia initiation spurred by *Pten* deficiency while a deletion of *SLC1A5* caused problems in bone marrow and mature blood cell formation. Interestingly, metabolomic analysis revealed that loss of this gene also impacted amino acid metabolism by impairing leucine influx which in turn interrupted mTOR signalling leading to cell death. BCR-ABL translocation mediates chronic leukemia [77-79]. Sontakkes' [80] group found that in normoxic conditions, BCR-ABL-transduced newborn blood cord cells had increased expression of the importer SLC1A5. This suggests that glutamine metabolism is a key target in BCR CML since BCR cells need glutaminolysis to sustain citric cycle intermediates in glycolysis.

AA metabolic reprogramming and clinical treatments in hematological malignancies

Tumor cells obtain and use nutrients to meet their biosynthetic and energetic requirements. Different genetic and epigenetic modulators, nutrient specificity, tumor microenvironment, and cell-matrix interaction have been shown to influence metabolic reprograming in tumor growth [81-83]. Despite the fact that tumor cells preferentially use glucose, glutamine and other AA metabolites play an important role in tumor cell growth by feeding the TCA cycle. In recent decades, metabolome and transcriptome research have identified potent metabolic inhibitors (some of which are in clinical trials) that target AA metabolic shift *via* various mechanisms, hence influencing proliferation, growth, and survival of malignant cells (Table 1).

AA metabolic reprograming and immunity

In fact, metabolic reprogramming is a feature of activated immune cells and is necessary for a vigorous anticancer immune response. Variations in AA metabolism can be found to affect a variety of cell types, including immune cells. Studies have demonstrated a link between AA metabolism, immunological control, and the impact on tumor cells [96-98,105].

Under normal circumstances, the tumor microenvironment harbors Myeloid-Derived Suppressor Cells (MDSCs) and Tumor-Associated Macrophages (TAM). By inhibiting GLS, ASNS, CPS2, and PPAT in malignant cells, MDSCs and DAMPs differentiate into pro-inflammatory macrophages, which improves antigen presentation to CD8+ CTLs. This causes a cascade of cancer-related immune responses, including increased cytokine production and decreased apoptosis, which inhibits tumor growth [97]. Furthermore, GLS inhibition has been demonstrated to boost CD4+ Th1 and CD8+ CTL differentiation, leading in increased cytokine production. Meanwhile, the same block reduces cytokine production in CD4 Th17 cells [106]. These changes have been connected to epigenetic markers of T cell subsets upon GLS inhibition [107].

Immunosuppressive cues must be eliminated in order to target hematological malignancies. Using isotope tracking, Hohtari, et al. [108] discovered that in T-ALL patients, MDSC levels were increased, impairing immune checkpoints, and contributing to chemoresistance. In this context, Li's group revealed that a metabolically reprogrammed L-phenylalanine polymer (MRIAN) degrades L-phenylalanine, triggering a chain of events that activate immune defence while suppressing MDSCs [99]. Given this knowledge, only a few metabolic targets have

demonstrated therapeutic potential in modulating immune response and tumor progression. As a result, more effective approaches employing Omics methods to better understanding the mechanisms linking these processes will aid in identifying novel metabolic-associated immunological markers.

Conclusion

Hematological cancers often become dependent on particular amino acids for survival, and a lack of these amino acids sets up a metabolic threat and therapeutic advantage [109]. Over the years, omics have proven quite useful in medicine. Despite the promising outcomes or findings from using these molecular techniques, there still exist some challenges and limitations. The majority of metabolomics research has focused on patient plasma or serum samples, with the exception of investigations needing invasive tumor biopsy samples. Measurements from one omics approach may not adequately correlate with data from other approaches when there is no considerable overlap between distinct omics datasets. It takes time and money to generate multi-omics data, and the value of the data generated is heavily reliant on the availability of biopsy samples and suitable tissue samples that can be effectively analyzed for their tissue transcriptome and metabolome [110].

Nonetheless, despite the challenges, transcriptomics and metabolomics remain among the most advanced techniques used today, with numerous applications spanning multiple fields of science. Findings have shown that these techniques have the potential to unlock ground-breaking discoveries in medicine, particularly in the treatment of life-threatening diseases such as cancer [19,111,112].

Presently, only in a few clinical settings have omics technologies (RNA-seq) been fully employed compared to traditional clinical tests. However, because the technologies allows for a more complete picture of health and disease, integration of these technologies should be a milestone in future clinical practice [111].

Most studies' findings have revealed the significant AA metabolites, TCA intermediates, pathways, and gene transcripts that, when altered, cause disease pathogenesis. The changes in particular metabolites can caused by specific mutations in genes encoding enzymes that regulate metabolism and other cellular processes including apoptosis, cell proliferation and differentiation and should be targeted against drug resistance in future studies.

Transcriptomics have revealed significant transcripts that drive AA metabolism including *PSAT1*, *ASNS*, *ASS1*, and *SLC1A5*, *ALDH1A2*, *GLS1*, SLC38A1, *GLDC*, *BCAT1* and others [31,38,42,49,52,53,74]. The dysregulation of these genes influenced by genetic and epigenetic mediators can either support or eradicate

Table 1: Metabolic targets in treatment of hematological malignancies.

Metabolic Inhibitors	Metabolite targets and off-targets	Mechanism of action	References
CB-839 (Telaglenastat)	GLS1,SLC7A11,c-MYC	Blocks GLS activity, decrease Gln utilization and flux into the TCA	[84-86]
V-9302 (GPNA derivative)	SLC38A2 (SNAT2),SLC1A5	Selectively binds and target AA transporters hence inhibiting glutamine uptake	[87-89]
BPTES	GLS1	Binding and stabilising the inactive state of GLS1 enzyme tetramer, Inhibiting tumor growth	[84,90-92]
Dibenzophenanthridine-968	GLS, GLS2	Selectively binds and inactivates the GAC and GBC tetramers in an inactive state	[93]
Alkyl benzoquinone AV-1	GLS1/2, mTORC1, AMPK	Inhibits glutaminase activity, stimulates autophagy, ULK1 activation and mtorc1 inhibition	[93]
ASNS/ GCN2 inhibitors	L-asparaginase, GCN2/eIF2a, mTORC1, ATF4, *ASS1, SLC1A4, SLC38A2, MTHFD1/2, and ATF5*	Induces stress-activated MAPK pathway hence triggering apoptosis	[94]
L-DON (JHU083)	Glutamine aminotransferases, glutaminases	Irreversibly competes with Gln for enzymes' binding site, inhibiting Gln metabolism and enhance antitumor immunity	[95-98]
MRIAN-Dox	L-phenylalanine polymer and MRIAN	Degrades MRIAN into Phenylalanine, inhibits PKM2, reduces ROS in MDSCs	[99]
PYCR1 inhibitors	P5C	Competitively binds to target enzyme's active site and inhibits proline utilisation	[100]
Aminooxyacetic acid/ hydrazinosuccinic acid	AST/GOT, ALT, AST	Inactivates pyridoxal phosphate-bound aminotransferases by reacting with the aldimine bond between these enzyme components	[101-104]

LSCs environment and leukemia development and progression. Because of their impact on multiple metabolic pathways, *SLC1A5* and xCT solute-carrier gene have been shown to interrupt AA metabolism *via* the mTOR signalling pathways [63,76].

Furthermore, the observed effects or changes in AA metabolism is associated with the cooperative effect of the downstream targets such as Trps1, Ets1,Atf4 on the AA biosynthesis [42,63] that drives the progression of the disease *via* mTOR and RAS signalling.

Among the non-essential AAs, glutamine has been shown to most prominent in refuelling (anaplerotic substrate) the Krebs cycle. As a result, it is well known to support mitochondrial function and redox mechanisms, making it an important metabolic target particularly in leukemia cells with FLT3-ITD mutations [47].

The BCAAs have been studied for their role in reprogramming cancer metabolism [53]. More importantly, BCAT1 was shown to cooperate with NRAS of RAS signalling causing activation of mTOR signalling resulting in the cumulation of BCAAs [59]. Thus, BCAAs' metabolism should be exploited in future research as they can reveal mechanistic insights that targets drug resistance and aid in developing effective chemotherapy against hematological cancers.

Metabolic inhibitors that target metabolites in the tumor stroma may produce encouraging results and should be evaluated for future clinical trial investigations.

The difficulty in immune-linked metabolic reprogramming is to always design metabolism-targeted therapies that are tumor-selective while protecting the host immune system. This will almost certainly necessitate a tailored therapeutic approach based on understanding the tumor and immune response determinants to certain metabolic disturbances.

To sum up, genetic and epigenetic modulators play crucial role in hematological cancer pathogenesis by altering amino acid metabolism. Employing an integrated system of transcriptomics and metabolomics has the potential to significantly advance understanding of the therapeutic mechanisms and metabolic pathways required for biomarker discovery, cancer diagnosis, and treatment.

Author Contributions

Conceptualization, original draft preparation: DB. Data collection and preparation of tables and figures: DB and GNN Neba Ambe. Supervision, revision, and manuscript editing: DB, GNN Neba Ambe and KD. Intellectual input and manuscript review: DB, GNN Neba Ambe, and KD. All authors have read and agreed to the published version of the manuscript.

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