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Review article

Targeting pivotal amino acids metabolism for treatment of leukemia

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ABSTRACT

Metabolic reprogramming is a crucial characteristic of cancer, allowing cancer cells to acquire metabolic properties that support their survival, immune evasion, and uncontrolled proliferation. Consequently, targeting cancer metabolism has become an essential therapeutic strategy. Abnormal amino acid metabolism is not only a key aspect of metabolic reprogramming but also plays a significant role in chemotherapy resistance and immune evasion, particularly in leukemia. Changes in amino acid metabolism in tumor cells are typically driven by a combination of signaling pathways and transcription factors. Current approaches to targeting amino acid metabolism in leukemia include inhibiting amino acid transporters, blocking amino acid biosynthesis, and depleting specific amino acids to induce apoptosis in leukemic cells. Different types of leukemic cells rely on the exogenous supply of specific amino acids, such as asparagine, glutamine, arginine, and tryptophan. Therefore, disrupting the supply of these amino acids may represent a vulnerability in leukemia. This review focuses on the pivotal role of amino acids in leukemia metabolism, their impact on leukemic stem cells, and their therapeutic potential.

1. Introduction

Leukemia is a hematological malignancy characterized by the uncontrolled proliferation of transformed blood cells in bone marrow or other hematopoietic tissues, leading to tissue invasion and organ destruction [1,2], causing anemia, bleeding, fever, and other symptoms [3,4]. Leukemia is classified based on two criteria: the pace of tumor progression (acute or chronic leukemia) and the origin of leukemia cells (myeloid or lymphoblastic leukemia) [5]. Advances in chemotherapy, stem cell transplantation, and targeted therapies have improved clinical outcomes for leukemia patients. However, individual differences, prolonged treatment duration, and the emergence of drug-resistant tumors can lead to severe toxicity and relapse in some patients [6–10]. Therefore, there is a need for effective and less toxic alternative therapies for leukemia.

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Cancer cells exhibit a metabolic shift from catabolism and oxidative phosphorylation (OXPHOS) to glycolysis and anabolic metabolism, enabling rapid synthesis of macromolecules necessary for cell duplication [11–14]. In contrast to normal cells, which rely on glycolysis under hypoxic conditions, cancer cells prefer cytoplasmic glycolysis in both aerobic and anaerobic environments due to their metabolic heterogeneity [15]. This complex process involves the activation of oncogenes like RAS and C-Myc, as well as the deletion of tumor suppressors such as p53 and PTEN, which collectively drive the metabolic transformation of cancer cells. Amino acid metabolism plays a crucial role in protein synthesis, small peptide production, and support for various biosynthetic pathways, particularly tryptophan metabolism [16–19]. Free tryptophan is used in protein synthesis and in the production of neurotransmitters (serotonin) and neuromodulators (tryptamine) [20]. The 20 amino acids and their metabolites are essential for various physiological functions, and disruptions in amino acid metabolism disturb homeostasis and impede cell growth, significantly impacting development [21,22]. Leukemic cells, for instance, are unable to synthesize sufficient amounts of amino acids on their own, leading to a reliance on specific amino acids. Consequently, amino acid deficiency is common in leukemic cells, presenting a metabolic vulnerability that can be targeted for amino acid metabolic therapies [23–27]. This review explores the significance of amino acids in cancer cell physiology and the potential of targeting amino acid metabolism in leukemia treatment.

2. Harnessing the power of amino acid deprivation as a novel strategy in the treatment of leukemia

Chemotherapy has been a widely used treatment for leukemia for many years. However, its effectiveness is limited due to the toxic side effects caused by the lack of specificity in most chemotherapeutic drugs [28]. To overcome this challenge, researchers have explored targeting amino acid metabolism as a potential approach for leukemia treatment [27]. This can be achieved by promoting amino acid depletion, inhibiting amino acid transporters, or inhibiting amino acid biosynthesis [27,29,30]. One of the main obstacles in targeting amino acid metabolism is the presence of solute carriers, which are proteins that transport amino acids and other substances. These carriers have hydrophobic alpha-helices connected by hydrophilic intra- and extracellular connections, allowing them to transport a wide range of substances including amino acids, nucleotides, inorganic ions, and drugs. However, this also leads to a functional redundancy of amino acid transporters [29]. In contrast, another approach to targeting amino acid metabolism is to promote amino acid consumption by activating enzymes in the pathway or inhibiting amino acid biosynthesis. For example, activating enzymes like phosphoglycerol dehydrogenase (PHGDH), asparagine synthetase (ASNS), and glutaminase (GLS) could be a promising direction for leukemia treatment [31]. Thus, exploring different strategies to target amino acid metabolism in leukemia treatment could potentially overcome the limitations of chemotherapy and improve patient outcomes.

Recent research has provided compelling evidence that amino acid starvation, specifically targeting glutamine, asparagine, arginine, and tryptophan, can effectively inhibit the growth of leukemia cells [29,32,33]. For instance, the use of ASNase (L-Asparaginase) and Navoximod (an inhibitor of tryptophan metabolizing enzyme) has shown promising results in the treatment of acute lymphoblastic leukemia [23,34]. The successful clinical applications of ASNase in acute lymphoblastic leukemia serve as a notable example of the efficacy of amino acid starvation therapy [35]. Additionally, glutaminase inhibitors such as CB-839, 987, and ADI (Arginine deiminase inhibitors) have been explored as potential treatments for leukemia [36–40]. The representative drugs of various amino acid inhibitors are shown in Table 1. These findings suggest that amino acid starvation therapy holds great potential as a novel approach to combat leukemia. In this discussion, we will delve into the significance of these four major amino acids as targets for amino acid starvation therapy.

2.1. Asparagine

ASN (L-Asparagine) is an amino acid that plays a crucial role in protein synthesis and serves as a source of energy for cell biosynthesis [26,41]. It is considered non-essential, but its presence is vital for cell survival and proliferation. The conversion of glutamine and aspartate into asparagine and glutamate is facilitated by asparagine synthase (ASNS) through ATP-dependent reactions [42]. This process requires the involvement of transaminase to supply amino groups from glutamine and consumes an ATP and two high-energy phosphoric acid bonds [43]. Leukemia cells heavily rely on ASN for survival due to inadequate ASNS expression, which hinders ASN synthesis [44]. Interestingly, recent research by KRALL et al. [45] has shown that exogenous aspartate can repair the damage caused by inhibition of the electron transport chain (ETC) without increasing intracellular aspartate levels. This suggests that aspartate may have a role in altering metabolic pathways during cellular injury and exclusively rescuing cells. Additionally, ASN plays a role in regulating ammonia metabolism and contributes to cell proliferation by increasing ASN transcription levels through endoplasmic reticulum stress [46–49]. These findings suggest that targeting ASN starvation could be a potential strategy for treating leukemia.

The clinical application of ASNase for the treatment of acute lymphoblastic leukemia (ALL) has shown promising results. In 1953, Kidd et al. [50,51] discovered the presence of L-asparaginase, an enzyme found in guinea pig serum but not in most mammals, which

Table 1
The representative drugs of various amino acid inhibitors.

ASNase	GLS inhibitor	Arginine deiminase inhibitor	IDO inhibitor
E. coil ASNase	CB-839	BCT-100	Navoximod
Peg-asparaginase	GP-1681	ADI-PEG20	BMS-986205
	Compound 968		Indoximod

converts asparagine to aspartate. The anti-leukemic effect of ASNase is primarily attributed to its high specificity for asparagine, leading to the conversion of most circulating asparagine into aspartic acid and ammonia [32]. This mechanism is particularly significant in (T-cell) leukemia, where cells often exhibit a deficiency in asparagine. As a result, cells must rely on dietary intake to obtain asparagine and other dependent amino acids. By blocking the cell's source of asparagine, ASNase leaves the cell undernourished and induces apoptosis (Fig. 1). To make ASNase more accessible for the treatment of childhood ALL, researchers have extracted it from *E. coli* and chrysanthemum and administered it through intravenous injection. This approach has been widely developed and has shown significant success when combined with other chemotherapeutic agents [23,52–54]. However, toxic side effects and allergic reactions have been observed in some ALL patients treated with *E. coli* ASNase [55–57]. This toxic side effect is mainly due to the limited purity of bacterial proteins and their pharmacokinetic distribution in mammalian systems (mainly in the central part of plasma volume), which are usually immunogenic to the host [32]. Therefore, bacterial proteins in ASNase must be extensively purified to eliminate toxic responses and reduce immune responses, as their biological distribution is limited and can be rapidly eliminated from circulation [32]. In 2006, the native *E. coli* ASNase was gradually replaced by peg-asparaginase, which is now used on a large scale as a first-line treatment for ALL [23]. This chemically modified ASNase has a long half-life, low antigenicity, and is more stable and efficient than the previous *E. coli* ASNase [58]. However, it is difficult to determine individual patient dosages due to asparaginase levels varying widely among patients. Recently, Kloos et al. [59] conducted an epidemiological investigation for peg-asparaginase using the pop-PK model to determine the clinical characteristics of patients associated with peg-asparaginase clearance [59]. It was observed that clearance was constant during the first 13 days after administration, after which clearance increased. A higher incidence of clearance and infection was demonstrated during the induction phase [59]. Other studies have concluded that asparaginase TDM (therapeutic drug monitoring) is effective in childhood acute lymphoblastic leukemia and that the dosage can be reduced without compromising the efficacy of ASNase.

The ASN starvation strategy is to provoke amino acid response and endoplasmic reticulum stress (ERS) by ASNase-induced ASN scarcity, which activates the unfolded protein response (UPR) [42] (Fig. 2). Initiation of UPR upregulates many survivals inhibition-related genes, leading to disruption of cellular metabolism. UPR proceeds in three pathways: EIF2AK3 (PERK), ERN1 (IRE1), and activating transcription factor 6 (ATF6) [49,60,61]. Next, we will introduce UPR in detail from the above three genes.

EIF2AK3 is a Ser/Thr protein kinase that is highly homologous to the eukaryotic initiation factor (EIF2). When unfolded proteins accumulate in the endoplasmic reticulum, heat shock protein family A (Hsp70) member 5 (HSPA5) is released, which causes EIF2AK3 to polymerize and phosphorylate in the ER membrane, inducing its activation [62,63]. Activating transcription factor 4 (ATF4) activation induces DDIT3 (CHOP) expression, which plays an important role in endoplasmic reticulum stress-mediated apoptosis [62,64]. Subsequently, activated DDIT3 induces *GADD34* (growth arrest and DNA damage-inducible gene 34) expression, thereby promoting apoptosis [65].

ERN1 is a transmembrane protein located in the ER with a unique mRNA splicing mechanism [62,66]. ERN1 is activated via heterodimer formation in response to URP signals. Activated ERN1 relieves ERS and inhibits the expression of heat-shock protein genes through upregulation of RIDD. When cells are under endoplasmic reticulum stress, X box binding protein-1 (*XBP1*) mRNA is sheared by ERN1 to produce the highly active transcription factor XBP1s (XBP1 small). *XBP1s* enter the nucleus to form a heterodimer with ATF6 and subsequently reduce endoplasmic reticulum stress through a series of reactions. Moreover, ATF6-XBP1 heterodimers can also activate XBP1 and thus deal with endoplasmic reticulum stress through XBP1 cycle activation [67–69]. Unlike the normal shearing mechanism, *XBP1* mRNA is sheared by ERN1 to excise an intron, which causes a change in the readable frame of the carboxyl terminus

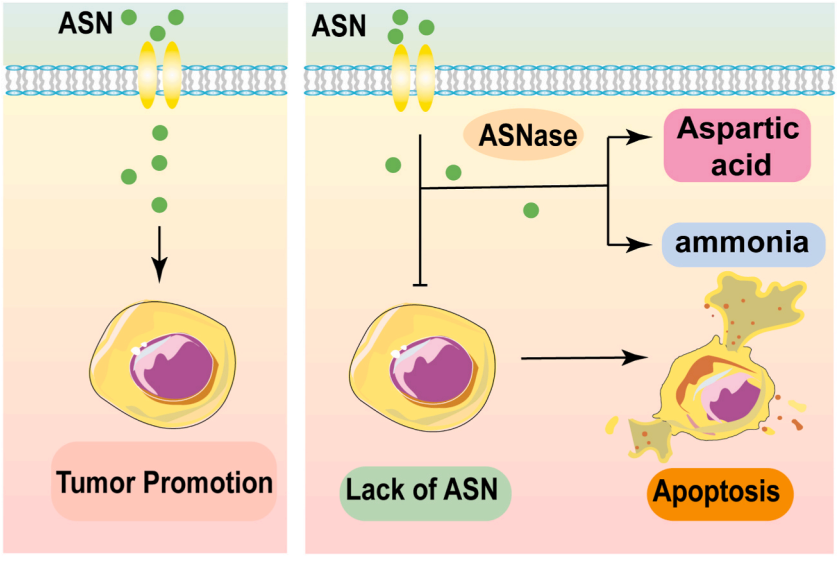

Fig. 1. Effects of ASNase on leukemia. ASNase rapidly converts ASN to aspartate and ammonia, resulting in an inadequate supply of ASN to leukemic cells, causing apoptosis.

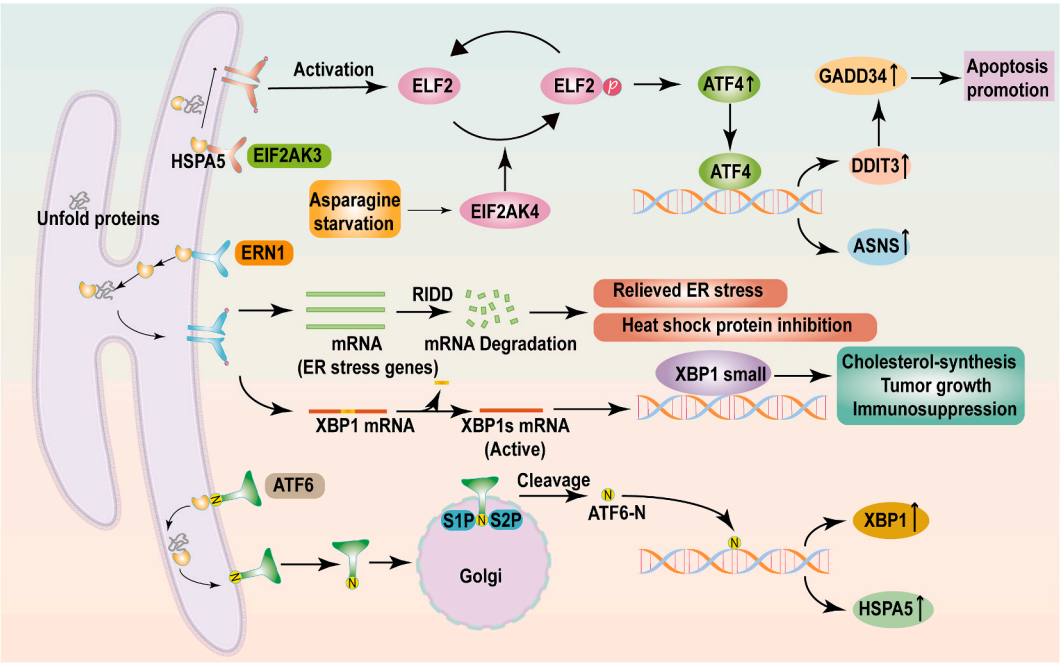

Fig. 2. Asparagine lack-induced stress and unfolded protein response. Asparagine deficiency causes ER stress and unfolded protein response, which leads to apoptosis of leukemia cells.

of the protein [68]. The type of shearing is called " readable frame splicing" [68]. A recent study has shown that the synthesis of *XBP1* facilitates cholesterol synthesis and secretion, thereby activating myeloid-derived suppressor cells, and causing immunosuppression [70]. In the case of unfolded protein accumulation, the release of HSPA5 induces *ATF6* (activating transcription factor 6) to translocate into the Golgi apparatus, where S1P (site1 protease) and S2P (site2 protease) located in the Golgi apparatus cleave ATF6, which upon hydrolysis releases the N-terminal structural domain and enters the nucleus to induce transcription of *XBP1* and *HSPA5*. Above findings imply that ASNase targeting amino acid stress pathways may be a promising strategy for leukemia therapy.

2.2. Glutamine

Glutamine, despite being a non-essential amino acid, is one of the most consumed nutrients after glucose. It is highly abundant in the blood, constituting over 20 % of the free amino acids present in serum [29,71]. Furthermore, glutamine plays a crucial role in the synthesis of other amino acids. It participates in metabolic processes such as the TCA cycle and the urea cycle, facilitating the metabolism of various amino acids [72] (Fig. 3). Glutamine undergoes deamidation catalyzed by glutaminase, resulting in its conversion to glutamate. Glutamate, in turn, is converted to alpha-ketoglutarate, which enters the TCA cycle. Additionally, glutamate can be transformed into asparagine and aspartate through the TCA cycle [72]. Moreover, glutamate can be converted to pyrroline-5-carboxylate (P5C) by pyrroline-5-carboxylate synthetase (P5CS). P5C can then be interconverted with proline by proline dehydrogenase (PRODH) and pyrroline-5-carboxylate reductase (PYCR) [73]. Glutamate acid serves as a substrate for the synthesis of serine and alanine. Alanine is produced by the conversion of glutamate to alanine through the action of alanine aminotransferase 1/2 (ALT1/2). Furthermore, glutamate and 3-phosphohydroxypyruvate, generated by the glycolytic pathway, undergo catalysis by phosphoserine aminotransferase 1 (PSAT1) and phosphoserine phosphatase (PSPH) to produce serine [43,74]. Serine, in turn, can be converted to glycine through one-carbon metabolism and to methionine via the trans-sulfuration pathway, ultimately leading to the production of cysteine [72]. In addition to its role in amino acid synthesis, glutamine plays a crucial role in providing nitrogen for purine and pyrimidine synthesis. This makes glutamine a critical factor influencing the proliferation of cancer cells [44,46,75,76].

Given the significant role of glutamine in the growth and proliferation of leukemia cells, the development of glutaminase (GLS) inhibitors has emerged as a promising approach for leukemia therapy [76,77]. One such inhibitor, CB-839, has shown efficacy in preclinical studies by effectively inhibiting glutamine hydrolysis and inhibiting tumor proliferation. Traditionally, it was believed that cells in the tumor microenvironment primarily relied on aerobic glycolysis (Warburg effect) to meet their energy demands for growth [78]. However, recent studies have demonstrated that leukemic stem cells (LSCs) in acute myeloid leukemia (AML) rely more on oxidative phosphorylation (OXPHOS), and GLS inhibitors have the potential to reduce mitochondrial OXPHOS and inhibit AML cell growth. In fact, both CB-839 and HHT (homoharringtonine) have been shown to enhance leukemia cell inhibition by exacerbating mitochondrial oxidation and inducing apoptosis [79–81]. Furthermore, when combined with FLT3 tyrosine kinase inhibitors like AC220, CB-839 has been found to induce reactive oxygen species production and deplete glutathione (GSH) in leukemia cells, leading to apoptosis in a murine model [82,83]. Additionally, the Bcl-2 inhibitor venetoclax has been found to synergize with GLS inhibitors in

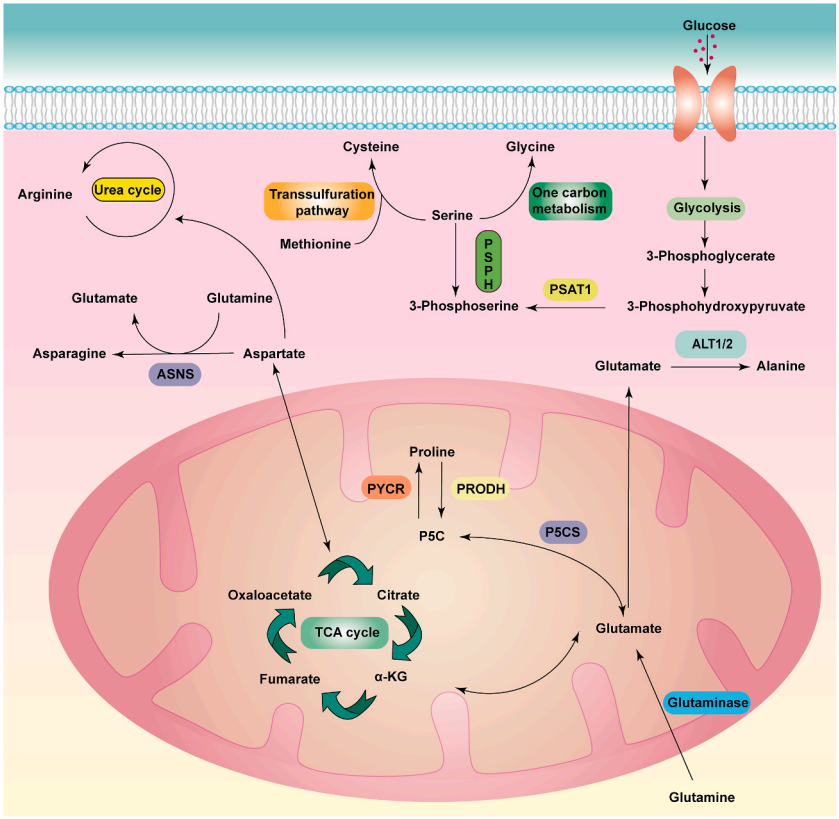

Fig. 3. Glutamine interconversions and metabolic pathways. Glutamine is essential for the synthesis of other amino acids. The details are shown in the figure. In vitro ingested glutamine is converted by glutamate as well as downstream enzymes to produce other amino acids that provide cell survival provide nutrients for cell survival.

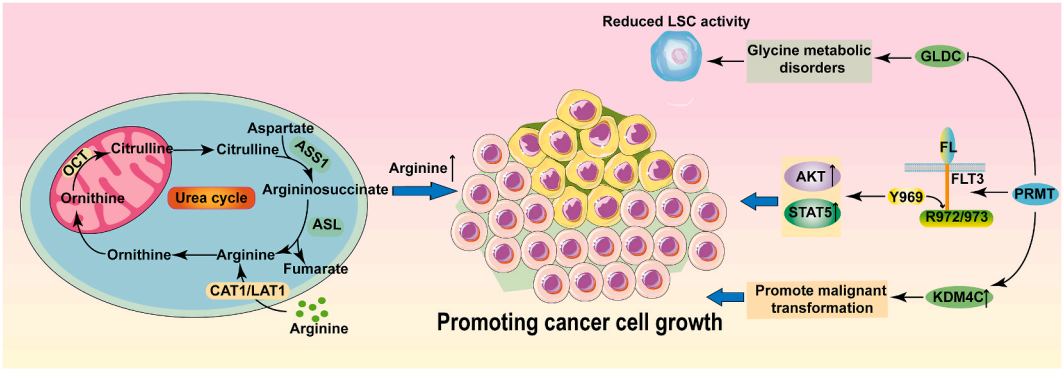

Fig. 4. The urea synthesis pathway involving arginine and PRMT-mediated FLT3 arginine methylation. Elevated intracellular arginine levels and PRMT1-mediated FLT3 arginine methylation accelerate the spread and proliferation of leukemia cells. The details are shown in the figure.

inducing apoptosis in AML cells [84]. Zhao et al. [85] discovered that BAG3, a gene associated with Bcl-2, specifically enhances GLS succinylation. BAG3 reduces SIRT5 levels and prevents GLS hydrolysis through ubiquitination labeling and subsequent enzymatic reactions, thereby promoting GLS stability [85]. However, the therapeutic effect of GLS inhibitors varies for different subtypes of leukemia. GLS inhibitors have achieved the effect of inhibiting cancer cells in AML by reducing GSH; Although GLS inhibitors can inhibit cancer cell proliferation in CLL, their therapeutic effect is limited; But for ALL, promoting GSH production by blocking glutamine metabolism is considered a therapeutic potential for ALL [77]. This suggests that different subtypes of leukemia may utilize differences in glutamine metabolism to develop appropriate treatment strategies. Consequently, there is a consensus in the scientific literature that GLS inhibitors effectively reduce leukemia cell survival.

2.3. Arginine

Arginine is a semi-essential amino acid that can be obtained through dietary intake, conversion of glutamine and proline, or protein degradation [86]. In pathological conditions, arginine is involved in various metabolic pathways, leading to the production of nitric oxide, polyamines, and other substances that are essential for cancer cell survival. In the urea cycle, ornithine is transported into the mitochondria and converted to citrulline by the enzyme ornithine carbamoyltransferase (OCT). Subsequently, citrulline is cleaved to argininosuccinate with the help of argininosuccinate synthetase 1 (ASS1) before being transported to the cytoplasm. Finally, argininosuccinate lyase (ASL) cleaves argininosuccinate to produce arginine. The transport of arginine is facilitated by CATs (cationic amino acid transporters) and L - amino acid transporters [86,87]. CAT1, a member of the CAT family, plays a role in maintaining the malignant characteristics associated with leukemia. Decreased expression of CAT1 can induce macrophage differentiation and reduce intracellular arginine transport in leukemia cells [27,88]. Studies have shown that low expression of OCT and ASS1, which are responsible for arginine synthesis, is observed in leukemia cells due to promoter hypermethylation, resulting in arginine deficiency [89–91]. Considering the dependence of leukemia cells on arginine, depletion of arginine has emerged as a promising therapeutic strategy.

Protein arginine methyltransferase (PRMT) plays a crucial role in the development of leukemia. As an H4R3 methyltransferase, PRMT is responsible for catalyzing the methylation of various substrate proteins, including protein inhibitor of activated STAT1 (PIAS1) and heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1), thereby influencing their activity, stability, and protein-protein interactions [92,93]. During arginine metabolism, PRMT shifts a methyl group from S-adenosylmethionine (SAM) to arginine's guanidino nitrogen atom, leading to the creation of monomethylarginine, symmetric dimethylarginine, and asymmetric dimethylarginine [93]. The relationship between arginine metabolism and PRMT genes is mainly evident in how arginine, serving as a substrate for PRMT catalysis, affects diverse cellular activities and physiological roles via its methylation alterations. The activity of PRMT is vital in preserving cell balance and controlling multiple biological functions, leukemia included.

As the one of the key players in leukemia pathogenesis, PRMT1 is essential for the induction of malignant transformation [94]. PRMT1 methylates FLT3 (Fms-like tyrosine kinase 3) at arginine residues 972 and 973 (R972/973), leading to the promotion of phosphor-tyrosine residue (Y) 969 (Y969) binding to FLT3. This, in turn, enhances the expression of Serine/threonine-protein kinase (AKT) and STAT (signal transduction and activator of transcription) 5, crucial factors for maintaining leukemia cell growth [94,95].

Furthermore, PRMT1 recruits KDM4C (lysine demethylase 4C) to dysregulate leukemia epigenetics and facilitate malignant transformation [96]. Recent research by Liu et al. [97] demonstrated that the knockout of PRMT7 in leukemia stem cells (LSCs) resulted in the suppression of glycine decarboxylase (GLDC) expression. This disruption of glycine metabolism inhibited the survival of LSCs, highlighting the potential of PRMT as a therapeutic target for leukemia treatment.

Interestingly, arginine, despite being essential for immune system cells, particularly T-cells, can also be exploited by cancer cells to evade immune control [98]. Elevated levels of arginine activate T-cells, promoting oxidative phosphorylation (OXPHOS) and supporting T-cell biosynthesis, proliferation, and differentiation, thereby enhancing the immune system's ability to combat cancer [99].

However, cancer cells can escape immune surveillance through arginine starvation therapy, primarily by targeting the NOS-ARGase pathway [100–102]. Activation of the NOS enzyme leads to the metabolism of arginine, producing nitric oxide (NO). The cytotoxicity of NO inhibits T-cell survival, facilitating immune evasion by cancer cells [102].

Nevertheless, studies have shown that the immunosuppression caused by arginine starvation can be mitigated or eliminated.

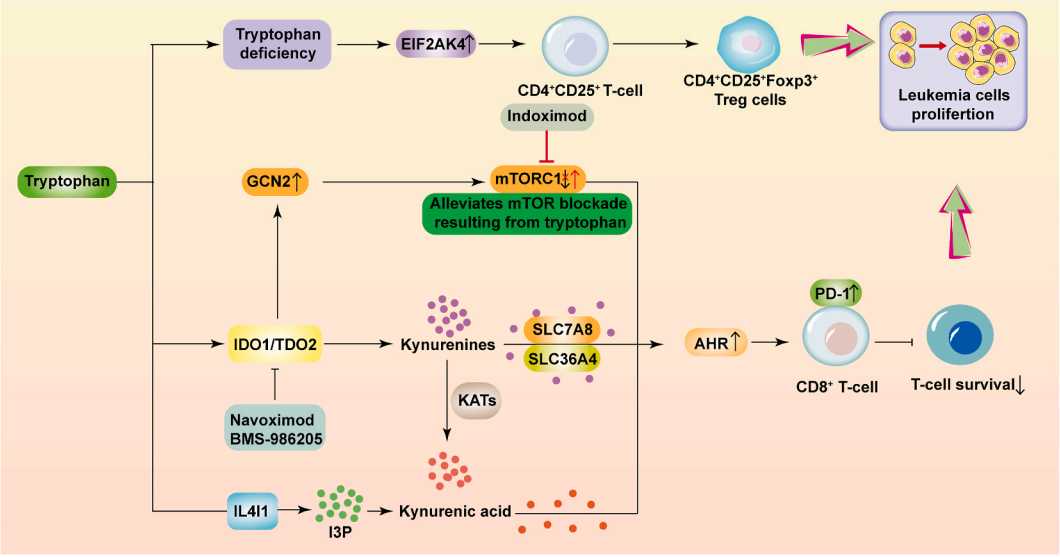

Fig. 5. Immunosuppressive pathways involving tryptophan. Tryptophan regulation of the Kynurenine pathway affects the activity of the immune system against leukemia cells. The details have been described in **1.4 Tryptophan.**

Fultaing et al. [98] suggest that the cytotoxicity of arginine starvation can be counteracted. De santo et al. [86] demonstrate that BCT-100, an arginine suppressor, exhibits cytotoxic effects on acute lymphoblastic leukemia (ALL) blasts in vitro and synergizes with dexamethasone. In ALL xenografts, BCT-100 reduces engraftment and prolongs survival. Another potential candidate for cancer treatment is ADI-PEG20 (polyethylene glycol-modified Arg deiminase), which has shown efficacy in clinical trials against various cancer types [103]. Clinical studies have indicated that ADI-PEG20 may be more effective than ASNase when applied to acute myeloid leukemia (AML), although the exact mechanism remains unclear. Consequently, ADI-PEG20 is considered a promising emerging anti-cancer agent [104–107].

It is important to note that ADI-induced arginine starvation, promotes autophagy and mitochondrial membrane potential depolarization, leading to the death of cancer cells deficient in argininosuccinate synthetase (ASS) [108–110]. In conclusion, targeting the arginine metabolic pathway holds significant potential for the treatment of hematopoietic malignancies (see Fig. 4).

2.4. Tryptophan

Tryptophan, an essential amino acid, plays a crucial role in cell survival. It is acquired through the diet and transported to cells via the amino acid transport system, which is involved in intracellular biosynthesis [111,112]. While tryptophan is utilized in protein synthesis like other amino acids, a significant portion of intracellular tryptophan is metabolized by the rate-limiting enzymes IDO1 (indoleamine-2,3-dioxygenase) and TDO2 (tryptophan 2,3-dioxygenase) to serve as a substrate for the Kynurenine pathway [112–118] (Fig. 5). Leukemia patients have been found to exhibit increased levels of Kynurenine metabolites, which activate the aryl hydrocarbon receptor (AHR) pathway downstream of the tryptophan metabolism pathway. AHR activation enables cells to adapt to the tumor microenvironment and inhibits T-cell survival [116,119,120]. In the absence of tryptophan, cancer cells activate the EIF2AK4 pathway, leading to the differentiation of $CD4^{+}CD25^{+}$ T-cells into $CD4^{+}CD25+Foxp3+$ regulatory T (Treg) cells and dampening T-cell activity against cancer cells [121,122].

Furthermore, studies have demonstrated that the Kynurenine pathway can activate the aryl hydrocarbon receptor (AHR) pathway, leading to the attenuation of the immune system's anti-tumor capacity [123–127]. Cancer cells, which exhibit high IDO1 activity, accumulate numerous Kynurenine metabolites intracellularly. These metabolites are then transported into T-cells by SLC7A8 and SLC36A4, activating the AHR pathway and upregulating programmed cell death protein 1 (PD-1) in $CD8^{+}$ T-cells [128,129]. This hampers immune functions and promotes immune evasion by cancer cells [130,131]. PD-1 is a crucial immunosuppressive molecule that regulates the immune system by suppressing inflammatory T-cell activity and promoting self-tolerance, thereby preventing autoimmune diseases. However, it can also prevent the immune system from effectively eliminating cancer cells [132,133]. Notably, Sadik A et al. [120] discovered that the tryptophan-metabolizing enzyme interleukin 4 induced 1 (IL4I1) also triggers the AHR pathway, suppressing the immune response and promoting malignant transformation in leukemia. Additionally, IL4I1 catalyzes the conversion of tryptophan to indole-3-pyruvate (I3P), an AHR-dependent substance that upregulates AHR expression. I3P further promotes AHR expression and suppresses T-cell growth [120,128] (Fig. 5). Overall, intracellular tryptophan levels play a significant role in the development of immune resistance in cancer cells, enhancing the population of regulatory T (Treg) cells while suppressing the survival of other immune cells.

Navoximod and BMS-986205 are novel IDO1 inhibitors that have shown promising results in combination with immunotherapy and are currently being evaluated in clinical trials for hematological malignancies [34]. Navoximod exhibits approximately 20-fold

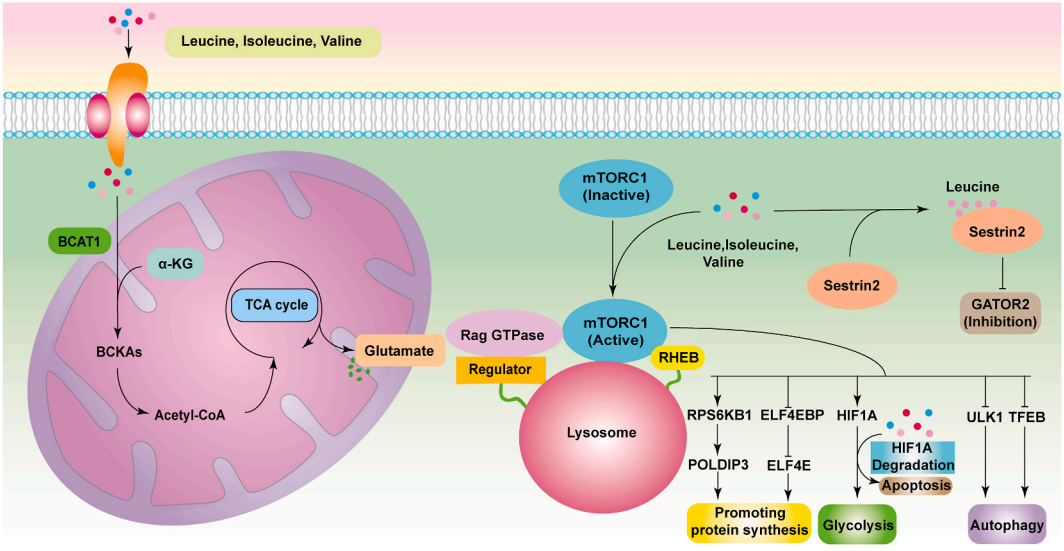

Fig. 6. Intracellular metabolic pathways of BCAAs and the mTORC1 signaling pathway. In addition to participating in the TCA cycle to supply energy to cells, BCAAs activate mTORC1 and promote lysosomal mTORC1 localization tumorigenesis.

selectivity for IDO1 over TDO2 and demonstrates noncompetitive inhibitory kinetics for tryptophan binding. On the other hand, BMS-986205 is an irreversible inhibitor of IDO1 that specifically targets this enzyme, without significant inhibition of TDO2. Indoximod, another compound, does not directly inhibit the IDO1 enzymes. Its mechanism of action is complex. In certain settings, indoximod indirectly inhibits TDO2 and/or IDO1. It can alleviate mTOR blockade caused by tryptophan deprivation, as depicted in Fig. 5 [134]. Indoximod acts as a potent tryptophan mimetic, which is interpreted by mTORC1 as tryptophan under conditions of high tryptophan catabolism and autophagy resulting from tryptophan deprivation caused by any catabolic enzyme [134].

3. Branched-chain amino acids

Branched-chain amino acids (BCAAs), including leucine, isoleucine, and valine, are essential amino acids that cannot be synthesized by the body but are abundant, accounting for approximately 35 % of the total essential amino acids (EAAs) [126,135–137]. The metabolism of BCAAs plays a crucial role in cancer cell growth. Similar to glutamine, BCAAs can provide carbon and nitrogen for the tricarboxylic acid (TCA) cycle and nucleotide synthesis, promoting oxidative phosphorylation and providing cellular energy [138–140]. Additionally, BCAAs are involved in the regulation of mammalian target of rapamycin complex 1 (mTORC1) [126,141,142]. In the presence of BCAAs, Rag GTPase binds to inactivated mTORC1, facilitating its localization to the lysosome. Activation of mTORC1 occurs through the small G protein Ras homolog, mTORC1 binding (RHEB), on the lysosomal surface, leading to increased mTORC1 expression, as depicted in Fig. 6 [143–146].

Once mTORC1 is initiated, it contributes to cancer cell growth and proliferation by promoting protein synthesis and autophagy [147] (Fig. 6). mTORC1 phosphorylates and activates ribosomal protein S6 kinase B1 (RPS6KB1) and promotes its interaction with DNA polymerase delta-interacting protein 3 (POLDIP3), a protein associated with translation [148]. Furthermore, mTORC1 phosphorylates eukaryotic translation initiation factor 4E binding protein (EIF4EBP1). When highly phosphorylated, EIF4EBP1 fails to bind with eukaryotic translation initiation factor (EIF4E) [149,150]. On the other hand, mTORC1 indirectly regulates autophagy by phosphorylating Unc-51 Like Autophagy Activating Kinase 1 (ULK1) to prevent its activation [151]. The ULK1 complex acts as a bridge between upstream trophic or energy receptors, such as mTOR, and downstream autophagy processes [151]. Phosphorylated ULK1 has been identified as a key regulator of autophagy [151,152]. In a nutrient-rich environment, mTOR binds to the 757th serine site of ULK1, inhibiting the interaction between ULK1 and AMP-activated protein kinase (AMPK), resulting in the inactivation of ULK1 and the subsequent suppression of autophagy signaling [152,153].

In addition, free BCAAs are metabolized by branched-chain amino acid transaminase 1 (BCAT1), which transfers nitrogen to α-ketoglutarate (α-KG) to produce glutamate and other branched-chain keto acids (BCKAs) [154,155]. BCAT1 is closely associated with α-KG homeostasis in leukemia [156]. Downregulation of BCAT1 leads to α-KG accumulation and degradation of hypoxia-inducible factor 1 subunit alpha (HIF1A), which interferes with leukemia cell glycolysis and induces apoptosis [156,157]. Kikushige et al. [158] demonstrated through isotope tracking experiments that the conversion of BCAAs to BCKAs provides a critical substrate for essential amino acid (EAA) biosynthesis and the TCA cycle in primary leukemia cells. They also showed that inhibiting BCAA catabolism specifically inactivates the function of polycomb repressive complex 2 (PRC2), an epigenetic regulator involved in stem cell signatures, by inhibiting the transcription of PRC components such as zeste homolog 2 (EZH2) and embryonic ectoderm development (EED). These studies suggest that BCAA catabolism plays an important role in maintaining stemness in leukemia, and molecules related to the BCAA metabolism pathway could be crucial targets for leukemia treatment.

4. Amino acids deficiency therapies in LSCs

Leukemia stem cells (LSCs) represent a subset of tumor stem cells characterized by their ability to self-renew and exhibit high heterogeneity [159–163]. Myeloid leukemia originating from LSCs is aggressive and is characterized by impaired differentiation of myeloid progenitor cells, leading to reduced numbers of normal blood cells [164,165]. LSCs have also been implicated in driving leukemia relapse, as they can migrate into protective microenvironments or utilize adipose tissue to evade the damage caused by chemotherapy, thereby contributing to the persistence of refractory leukemia [166–169]. The integrated stress response (ISR) pathway triggered by amino acid deficiency are observed in LSCs. Activation of the ISR results in eIF2α phosphorylation-dependent upregulation of activating ATF4 that facilitates apoptosis of LSCs [26]. A representative therapeutic approach targeting amino acid metabolism in LSCs is the combination of venetoclax and azacitidine, which has been shown to target amino acid metabolism and alleviate oxidative phosphorylation (OXPHOS) in LSCs [170]. In a subsequent study by Jones et al. [171] depletion of cysteine in LSCs demonstrated that the glutathione requirement of primary acute myeloid leukemia (AML) cells is driven by exogenous cysteine. They also confirmed that reactive oxygen species (ROS) induced by the combination of venetoclax and azacitidine may not be the primary cause of cell death [171–173]. Furthermore, OXPHOS is a preferred pathway for energy production in leukemia cells compared to glycolysis [174–176]. LSCs utilize amino acids to sustain the tricarboxylic acid (TCA) cycle for energy production and upregulate glycolysis and fatty acid oxidation to support biosynthesis in the absence of amino acids [177]. Therefore, OXPHOS is more efficient than the glycolytic pathway in supplying energy to leukemia cells. Importantly, post-chemotherapy LSCs in mice have been found to exhibit increased levels of glutamine and aspartate, which contribute to leukemia resistance through glutathione and nucleotide synthesis [178].

5. Conclusion

Thus, targeting amino acid metabolism holds promise as a therapeutic strategy for the treatment of leukemia. Amino acid

deprivation therapy offers advantages such as limited toxicity and absence of late effects associated with DNA damage. Current approaches focus on developing targeted inhibitors or agonists against key enzymes involved in specific amino acid metabolic pathways, such as aspartate lyase, aspartate synthase, glutaminase, and arginine deiminase. However, it is unlikely that inhibitors of amino acid metabolism alone will be sufficient to treat leukemia, as leukemic cells can develop resistance under conditions of amino acid starvation. Therefore, combination therapies involving targeted amino acid agents are being explored in clinical trials, such as the combination of glutaminase inhibitors with Venetoclax for leukemia stem cells. Before amino acid depletion can be widely applied in clinical practice, it is crucial to investigate the metabolic dependencies of specific cancer types and their tumor microenvironment in detail. This will enable the selection of the appropriate amino acid targets. Additionally, researchers need to consider the interaction of different amino acids with the tumor microenvironment, especially in the context of combination therapies that simultaneously target multiple metabolic and signaling pathways in leukemia cells. Further studies are needed to understand amino acid metabolism in specific cancers, identify pathways that promote amino acid depletion, and develop amino acid sensitizers to enhance therapeutic efficacy and durability.

CRediT authorship contribution statement

Jiankun Hong: Writing – review & editing, Writing – original draft, Conceptualization. **Wuling Liu:** Conceptualization. **Xiao Xiao:** Conceptualization. **Babu Gajendran:** Writing – review & editing, Conceptualization. **Yaacov Ben-David:** Writing – review & editing, Conceptualization.

Data and code availability statement

No data was used for the research described in the article.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

AHR (aryl hydrocarbon receptor)
AKT (protein kinase B, PKB)
ALT1/2 (alanine aminotransferase 1/2)
ASL (argininosuccinate lyase)
ASNS (asparagine synthetase)
ASNS (asparagine synthetase)
ASS1 (argininosuccinate synthetase 1)
ATF4 (activating transcription factor 4)
ATF6 (activating transcription factor 6)
BCAT1 (branched chain amino acid transaminase 1)
DDIT3 (DNA damage inducible transcript 3)
EIF2AK3 (eukaryotic translation initiation factor 2 alpha kinase 3)
EIF2AK4 (eukaryotic translation initiation factor 2 alpha kinase 4)
EIF2AK4 (eukaryotic translation initiation factor 2 alpha kinase 4)
ELF2 (E74 like ETS transcription factor 2)
ELF4E (eukaryotic translation initiation factor 4E)
ELF4EBP (eukaryotic translation initiation factor 4E binding protein)
ERN1 (endoplasmic reticulum to nucleus signaling 1)
FL (FLT3 ligand)
FLT3 (fms-related receptor tyrosine kinase 3)
GADD34 (growth arrest and DNA damage-inducible gene 34)

GATOR2 (GAP activity towards Rags 2)
GLDC (glycine decarboxylase)
HIF1A (hypoxia inducible factor 1 Subunit alpha)
HnRNPA1 (heterogeneous nuclear ribonucleoprotein A1)
HSPA5 (heat shock protein family A (Hsp70) member 5)
I3P (indole-3-pyruvate)
IDO1 (indoleamine-2,3-dioxygenase 1)
IL4I1 (interleukin 4 induced 1)
KATs (kynurenine aminotransferases I–III)
KDM4C (lysine demethylase 4C)
LAT1 (L-amino acid transporter 1)
MDSC (myeloid-derived suppressor cells)
OCT (ornithine carbamoyl transferase)
PIAS1 (Protein inhibitor ofactivated STAT1)
P5CS (pyrroline-5-carboxylate synthetase)
PD-1 (programmed cell death protein 1)
POLDIP3 (DNA polymerase delta interacting protein 3)
PRMT (protein arginine methyltransferase)
PRODH (proline dehydrogenase)
PSAT1 (phosphoserine aminotransferase 1)
PSPH (phosphoserine phosphatase)
PYCR (pyrroline-5-carboxylate reductase)
R972/973 (arginine residues-R 972/973)
RHEB (Ras homolog, mTORC1 binding)
RIDD (Regulated IRE1-dependent mRNA decay)
RPS6KB1 (ribosomal protein S6 kinase B1)
S1P (site1 protease)
S2P (site2 protease)
STAT5 (signal transduction and activator of transcription 5)
TDO2 (tryptophan 2,3-dioxygenase)
TFEB (transcription factor EB)
ULK1 (unc-51 like Autophagy activating kinase 1)
XBP1 (X box binding protein-1)
Y969 (phosphor-tyrosine residue-Y 969)
α-KG (α-ketoglutarate)

References

[1] M. Allison, J. Mathews, T. Gilliland, S.O. Mathew, Natural killer cell-mediated immunotherapy for leukemia, Cancers 14 (3) (2022), https://doi.org/10.3390/cancers14030843.
[2] M.M. Patnaik, A. Tefferi, Chronic myelomonocytic leukemia: 2024 update on diagnosis, risk stratification and management, Am. J. Hematol. 99 (6) (2024) 1142–1165, https://doi.org/10.1002/ajh.27271.
[3] R.A. Van Etten, R. Larson, H. Rosmarin, Clinical Manifestations and Diagnosis of Chronic Myeloid Leukemia, Uptodate, Waltham, MA, 2013. (Accessed 29 May 2012).
[4] R.A. Larson, S. Gurbuxani, Clinical Manifestations, Pathologic Features, and Diagnosis of Acute Promyelocytic Leukemia in Adults, UpToDate, 2018.
[5] G. Juliusson, R. Hough, Leukemia, Prog Tumor Res. 43 (2016) 87–100, https://doi.org/10.1159/000447076.
[6] M. Levin, M. Stark, Y. Ofran, Y.G. Assaraf, Deciphering molecular mechanisms underlying chemoresistance in relapsed AML patients: towards precision medicine overcoming drug resistance, Cancer Cell Int. 21 (1) (2021) 53, https://doi.org/10.1186/s12935-021-01746-w.
[7] K. Oshima, J. Zhao, P. Pérez-Durán, J.A. Brown, J.A. Patiño-Galindo, T. Chu, et al., Mutational and functional genetics mapping of chemotherapy resistance mechanisms in relapsed acute lymphoblastic leukemia, Nat Cancer 1 (11) (2020) 1113–1127, https://doi.org/10.1038/s43018-020-00124-1.
[8] B.D. Santomasso, J.H. Park, D. Salloum, I. Riviere, J. Flynn, E. Mead, et al., Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia, Cancer Discov. 8 (8) (2018) 958–971, https://doi.org/10.1158/2159-8290.Cd-17-1319.
[9] M. Martino, C. Alati, F.A. Canale, G. Musuraca, G. Martinelli, C. Cerchione, A review of clinical outcomes of CAR T-cell therapies for B-acute lymphoblastic leukemia, Int. J. Mol. Sci. 22 (4) (2021), https://doi.org/10.3390/ijms22042150.
[10] O.K. Weinberg, A. Porwit, A. Orazi, R.P. Hasserjian, K. Foucar, E.J. Duncavage, et al., The International Consensus Classification of acute myeloid leukemia, Virchows Arch. 482 (1) (2023) 27–37, https://doi.org/10.1007/s00428-022-03430-4.
[11] N.N. Pavlova, C.B. Thompson, The emerging hallmarks of cancer metabolism, Cell Metabol. 23 (1) (2016) 27–47, https://doi.org/10.1016/j.cmet.2015.12.006.
[12] D.R. Wise, C.B. Thompson, Glutamine addiction: a new therapeutic target in cancer, Trends Biochem. Sci. 35 (8) (2010) 427–433, https://doi.org/10.1016/j.tibs.2010.05.003.
[13] O. Cadassou, L.P. Jordheim, OXPHOS inhibitors, metabolism and targeted therapies in cancer, Biochem. Pharmacol. 211 (2023) 115531, https://doi.org/10.1016/j.bcp.2023.115531.
[14] B. Kalyanaraman, G. Cheng, M. Hardy, M. You, OXPHOS-targeting drugs in oncology: new perspectives, Expert Opin. Ther. Targets 27 (10) (2023) 939–952, https://doi.org/10.1080/14728222.2023.2261631.

[15] L. Xia, L. Oyang, J. Lin, S. Tan, Y. Han, N. Wu, et al., The cancer metabolic reprogramming and immune response, Mol. Cancer 20 (1) (2021) 28, https://doi.org/10.1186/s12943-021-01316-8.

[16] N.P. Curthoys, M. Watford, Regulation of glutaminase activity and glutamine metabolism, Annu. Rev. Nutr. 15 (1995) 133–159, https://doi.org/10.1146/annurev.nu.15.070195.001025.

[17] G. Wu, Amino acids: metabolism, functions, and nutrition, Amino Acids 37 (1) (2009) 1–17, https://doi.org/10.1007/s00726-009-0269-0.

[18] I. Martínez-Reyes, N.S. Chandel, Cancer metabolism: looking forward, Nat. Rev. Cancer 21 (10) (2021) 669–680, https://doi.org/10.1038/s41568-021-00378-6.

[19] Z.N. Ling, Y.F. Jiang, J.N. Ru, J.H. Lu, B. Ding, J. Wu, Amino acid metabolism in health and disease, Signal Transduct. Targeted Ther. 8 (1) (2023) 345, https://doi.org/10.1038/s41392-023-01569-3.

[20] A.S. Correia, N. Vale, Tryptophan metabolism in depression: a narrative review with a focus on serotonin and kynurenine pathways, Int. J. Mol. Sci. 23 (15) (2022), https://doi.org/10.3390/ijms23158493.

[21] Idrissi A. El, Taurine increases mitochondrial buffering of calcium: role in neuroprotection, Amino Acids 34 (2) (2008) 321–328, https://doi.org/10.1007/s00726-006-0396-9.

[22] A. Lupi, R. Tenni, A. Rossi, G. Cetta, A. Forlino, Human prolidase and prolidase deficiency: an overview on the characterization of the enzyme involved in proline recycling and on the effects of its mutations, Amino Acids 35 (4) (2008) 739–752, https://doi.org/10.1007/s00726-008-0055-4.

[23] H.S. Fernandes, C.S. Silva Teixeira, P.A. Fernandes, M.J. Ramos, N.M. Cerqueira, Amino acid deprivation using enzymes as a targeted therapy for cancer and viral infections, Expert Opin. Ther. Pat. 27 (3) (2017) 283–297, https://doi.org/10.1080/13543776.2017.1254194.

[24] J.R. Cantor, D.M. Sabatini, Cancer cell metabolism: one hallmark, many faces, Cancer Discov. 2 (10) (2012) 881–898, https://doi.org/10.1158/2159-8290.Cd-12-0345.

[25] K.L. Eales, K.E. Hollinshead, D.A. Tennant, Hypoxia and metabolic adaptation of cancer cells, Oncogenesis 5 (1) (2016) e190, https://doi.org/10.1038/oncsis.2015.50.

[26] Y. Tabe, P.L. Lorenzi, M. Konopleva, Amino acid metabolism in hematologic malignancies and the era of targeted therapy, Blood 134 (13) (2019) 1014–1023, https://doi.org/10.1182/blood.2019001034.

[27] C. Chen, J. Zhang, Enhancing leukemia treatment: the role of combined therapies based on amino acid starvation, Cancers 16 (6) (2024), https://doi.org/10.3390/cancers16061171.

[28] Z. Livshits, R.B. Rao, S.W. Smith, An approach to chemotherapy-associated toxicity, Emerg Med Clin North Am 32 (1) (2014) 167–203, https://doi.org/10.1016/j.emc.2013.09.002.

[29] M. Butler, L.T. van der Meer, F.N. van Leeuwen, Amino acid depletion therapies: starving cancer cells to death, Trends Endocrinol. Metabol. 32 (6) (2021) 367–381, https://doi.org/10.1016/j.tem.2021.03.003.

[30] E.L. Lieu, T. Nguyen, S. Rhyne, J. Kim, Amino acids in cancer, Exp. Mol. Med. 52 (1) (2020) 15–30, https://doi.org/10.1038/s12276-020-0375-3.

[31] J.L. Counihan, E.A. Grossman, D.K. Nomura, Cancer metabolism: current understanding and therapies, Chem. Rev. 118 (14) (2018) 6893–6923, https://doi.org/10.1021/acs.chemrev.7b00775.

[32] V.I. Avramis, P.N. Tiwari, Asparaginase (native ASNase or pegylated ASNase) in the treatment of acute lymphoblastic leukemia, Int. J. Nanomed. 1 (3) (2006) 241–254.

[33] Y. Shen, Y. Zhang, W. Li, K. Chen, M. Xiang, H. Ma, Glutamine metabolism: from proliferating cells to cardiomyocytes, Metabolism 121 (2021) 154778, https://doi.org/10.1016/j.metabol.2021.154778.

[34] P. Liao, N. Chang, B. Xu, Y. Qiu, S. Wang, L. Zhou, et al., Amino acid metabolism: challenges and opportunities for the therapeutic treatment of leukemia and lymphoma, Immunol. Cell Biol. 100 (7) (2022) 507–528, https://doi.org/10.1111/imcb.12557.

[35] P.A. Dinndorf, J. Gootenberg, M.H. Cohen, P. Keegan, R. Pazdur, FDA drug approval summary: pegaspargase (oncaspar) for the first-line treatment of children with acute lymphoblastic leukemia (ALL), Oncol. 12 (8) (2007) 991–998, https://doi.org/10.1634/theoncologist.12-8-991.

[36] M.I. Gross, S.D. Demo, J.B. Dennison, L. Chen, T. Chernov-Rogan, B. Goyal, et al., Antitumor activity of the glutaminase inhibitor CB-839 in triple-negative breast cancer, Mol. Cancer Therapeut. 13 (4) (2014) 890–901, https://doi.org/10.1158/1535-7163.Mct-13-0870.

[37] A. Le, A.N. Lane, M. Hamaker, S. Bose, A. Gouw, J. Barbi, et al., Glucose-independent glutamine metabolism via TCA cycling for proliferation and survival in B cells, Cell Metabol. 15 (1) (2012) 110–121, https://doi.org/10.1016/j.cmet.2011.12.009.

[38] C.A. Stalnecker, S.M. Ulrich, Y. Li, S. Ramachandran, M.K. McBrayer, R.J. DeBerardinis, et al., Mechanism by which a recently discovered allosteric inhibitor blocks glutamine metabolism in transformed cells, Proc. Natl. Acad. Sci. U.S.A. 112 (2) (2015) 394–399, https://doi.org/10.1073/pnas.1414056112.

[39] M.K.L. Fung, G.C. Chan, Drug-induced amino acid deprivation as strategy for cancer therapy, J. Hematol. Oncol. 10 (1) (2017) 144, https://doi.org/10.1186/s13045-017-0509-9.

[40] Y. Ju, Y. Ben-David, D. Rotin, E. Zacksenhaus, Inhibition of eEF2K synergizes with glutaminase inhibitors or 4EBP1 depletion to suppress growth of triple-negative breast cancer cells, Sci. Rep. 11 (1) (2021) 9181, https://doi.org/10.1038/s41598-021-88816-1.

[41] J. Jiang, S. Batra, J. Zhang, Asparagine: a metabolite to Be targeted in cancers, Metabolites 11 (6) (2021), https://doi.org/10.3390/metabo11060402.

[42] M. Chiu, G. Taurino, M.G. Bianchi, M.S. Kilberg, O. Bussolati, Asparagine synthetase in cancer: beyond acute lymphoblastic leukemia, Front. Oncol. 9 (2019) 1480, https://doi.org/10.3389/fonc.2019.01480.

[43] J. Zhang, N.N. Pavlova, C.B. Thompson, Cancer cell metabolism: the essential role of the nonessential amino acid, glutamine, EMBO J. 36 (10) (2017) 1302–1315, https://doi.org/10.15252/embj.201696151.

[44] G.C. Ligthart-Melis, M.A. Vermeulen, P.A. van Leeuwen, N.E. Deutz, Glutamine: precursor or nitrogen donor for citrulline synthesis? Am. J. Physiol. Endocrinol. Metab. 299 (4) (2010) E683, https://doi.org/10.1152/ajpendo.00425.2010, author reply E684.

[45] A.S. Krall, P.J. Mullen, F. Surjono, M. Momcilovic, E.W. Schmid, C.J. Halbrook, et al., Asparagine couples mitochondrial respiration to ATF4 activity and tumor growth, Cell Metabol. 33 (5) (2021) 1013–1026.e1016, https://doi.org/10.1016/j.cmet.2021.02.001.

[46] A.N. Lane, T.W. Fan, Regulation of mammalian nucleotide metabolism and biosynthesis, Nucleic Acids Res. 43 (4) (2015) 2466–2485, https://doi.org/10.1093/nar/gkv047.

[47] J.T. Cunningham, M.V. Moreno, A. Lodi, S.M. Ronen, D. Ruggero, Protein and nucleotide biosynthesis are coupled by a single rate-limiting enzyme, PRPS2, to drive cancer, Cell. 157 (5) (2014) 1088–1103, https://doi.org/10.1016/j.cell.2014.03.052.

[48] C. Bahr, L. von Paleske, V.V. Uslu, S. Remeseiro, N. Takayama, S.W. Ng, et al., A Myc enhancer cluster regulates normal and leukaemic haematopoietic stem cell hierarchies, Nature 553 (7689) (2018) 515–520, https://doi.org/10.1038/nature25193.

[49] K. Tsegaye, B.A. Tsehai, B. Getie, Desirable L-asparaginases for treating cancer and current research trends, Front. Microbiol. 15 (2024) 1269282, https://doi.org/10.3389/fmicb.2024.1269282.

[50] J.G. Kidd, Regression of transplanted lymphomas induced in vivo by means of normal Guinea pig serum. I. Course of transplanted cancers of various kinds in mice and rats given Guinea pig serum, horse serum, or rabbit serum, J. Exp. Med. 98 (6) (1953) 565–582, https://doi.org/10.1084/jem.98.6.565.

[51] J.G. Kidd, Regression of transplanted lymphomas induced in vivo by means of normal Guinea pig serum. II. Studies on the nature of the active serum constituent: histological mechanism of the regression: tests for effects of Guinea pig serum on lymphoma cells in vitro: discussion, J. Exp. Med. 98 (6) (1953) 583–606, https://doi.org/10.1084/jem.98.6.583.

[52] B. Clarkson, I. Krakoff, J. Burchenal, D. Karnofsky, R. Golbey, M. Dowling, et al., Clinical results of treatment with E. coli L-asparaginase in adults with leukemia, lymphoma, and solid tumors, Cancer 25 (2) (1970) 279–305, https://doi.org/10.1002/1097-0142(197002)25:2<279::aid-cncr2820250205>3.0.co;2-7.

[53] J.A. Ortega, M.E. Nesbit Jr., M.H. Donaldson, R.E. Hittle, J. Weiner, M. Karon, et al., L-Asparaginase, vincristine, and prednisone for induction of first remission in acute lymphocytic leukemia, Cancer Res. 37 (2) (1977) 535–540.

[54] C. Domenech, X. Thomas, S. Chabaud, A. Baruchel, F. Gueyffier, F. Mazingue, et al., l-asparaginase loaded red blood cells in refractory or relapsing acute lymphoblastic leukaemia in children and adults: results of the GRASPALL 2005-01 randomized trial, Br. J. Haematol. 153 (1) (2011) 58–65, https://doi.org/10.1111/j.1365-2141.2011.08588.x.

[55] V.I. Avramis, S. Sencer, A.P. Periclou, H. Sather, B.C. Bostrom, L.J. Cohen, et al., A randomized comparison of native Escherichia coli asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study, Blood 99 (6) (2002) 1986–1994, https://doi.org/10.1182/blood.v99.6.1986.

[56] A.S. Spiers, H.E. Wade, Achromobacter L-glutaminase-L-asparaginase: human pharmacology, toxicology, and activity in acute leukemias, Cancer Treat Rep. 63 (6) (1979) 1019–1024.

[57] R. Zhou, T. Liang, T. Li, J. Huang, C. Chen, Possible mechanism of metabolic and drug resistance with L-asparaginase therapy in childhood leukaemia, Front. Oncol. 13 (2023) 1070069, https://doi.org/10.3389/fonc.2023.1070069.

[58] D. Koerholz, M. Brueck, W. Nuernberger, H. Juergens, U. Goebel, V. Wahn, Chemical and immunological characteristics of four different L-asparaginase preparations, a 42 (5) (1989) 417–424, https://doi.org/10.1111/j.1600-0609.1989.tb01464.x.

[59] R.Q.H. Kloos, R. Mathôt, R. Pieters, I.M. van der Sluis, Individualized dosing guidelines for PEGasparaginase and factors influencing the clearance: a population pharmacokinetic model, Haematologica 106 (5) (2021) 1254–1261, https://doi.org/10.3324/haematol.2019.242289.

[60] D. Ron, P. Walter, Signal integration in the endoplasmic reticulum unfolded protein response, Nat. Rev. Mol. Cell Biol. 8 (7) (2007) 519–529, https://doi.org/10.1038/nrm2199.

[61] S. Wang, R.J. Kaufman, The impact of the unfolded protein response on human disease, J. Cell Biol. 197 (7) (2012) 857–867, https://doi.org/10.1083/jcb.201110131.

[62] S.A. Oakes, F.R. Papa, The role of endoplasmic reticulum stress in human pathology, Annu. Rev. Pathol. 10 (2015) 173–194, https://doi.org/10.1146/annurev-pathol-012513-104649.

[63] E.A.V. Beilankouhi, M.A. Sajadi, I. Alipourfard, P. Hassani, M. Valilo, R. Safaralizadeh, Role of the ER-induced UPR pathway, apoptosis, and autophagy in colorectal cancer, Pathol. Res. Pract. 248 (2023) 154706, https://doi.org/10.1016/j.prp.2023.154706.

[64] M. Śniegocka, F. Liccardo, F. Fazi, S. Masciarelli, Understanding ER homeostasis and the UPR to enhance treatment efficacy of acute myeloid leukemia, Drug Resist. Updates 64 (2022) 100853, https://doi.org/10.1016/j.drup.2022.100853.

[65] K. Liu, W. Fang, E. Sun, Y. Chen, Roles of endoplasmic reticulum stress and apoptosis signaling pathways in gynecologic tumor cells: a systematic review, Oncology 3 (2017).

[66] S. Le Goupil, H. Laprade, M. Aubry, E. Chevet, Exploring the IRE1 interactome: from canonical signaling functions to unexpected roles, J. Biol. Chem. 300 (4) (2024) 107169, https://doi.org/10.1016/j.jbc.2024.107169.

[67] M. Calfon, H. Zeng, F. Urano, J.H. Till, S.R. Hubbard, H.P. Harding, et al., IRE1 couples endoplasmic reticulum load to secretory capacity by processing the XBP-1 mRNA, Nature 415 (6867) (2002) 92–96, https://doi.org/10.1038/415092a.

[68] H. Yoshida, T. Matsui, A. Yamamoto, T. Okada, K. Mori, XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor, Cell 107 (7) (2001) 881–891, https://doi.org/10.1016/s0092-8674(01)00611-0.

[69] A. Almanza, K. Mnich, A. Blomme, C.M. Robinson, G. Rodriguez-Blanco, S. Kierszniowska, et al., Regulated IRE1α-dependent decay (RIDD)-mediated reprograming of lipid metabolism in cancer, Nat. Commun. 13 (1) (2022) 2493, https://doi.org/10.1038/s41467-022-30159-0.

[70] Z. Yang, Y. Huo, S. Zhou, J. Guo, X. Ma, T. Li, et al., Cancer cell-intrinsic XBP1 drives immunosuppressive reprogramming of intratumoral myeloid cells by promoting cholesterol production, Cell Metabol. (2022), https://doi.org/10.1016/j.cmet.2022.10.010.

[71] J. Bergström, P. Fürst, L.O. Norée, E. Vinnars, Intracellular free amino acid concentration in human muscle tissue, J. Appl. Physiol. 36 (6) (1974) 693–697, https://doi.org/10.1152/jappl.1974.36.6.693.

[72] B.H. Choi, J.L. Coloff, The diverse functions of non-essential amino acids in cancer, Cancers 11 (5) (2019), https://doi.org/10.3390/cancers11050675.

[73] W. Liu, A. Le, C. Hancock, A.N. Lane, C.V. Dang, T.W. Fan, et al., Reprogramming of proline and glutamine metabolism contributes to the proliferative and metabolic responses regulated by oncogenic transcription factor c-MYC, Proc. Natl. Acad. Sci. U.S.A. 109 (23) (2012) 8983–8988, https://doi.org/10.1073/pnas.1203244109.

[74] L.B. Sullivan, D.Y. Gui, A.M. Hosios, L.N. Bush, E. Freinkman, M.G. Vander Heiden, Supporting aspartate biosynthesis is an essential function of respiration in proliferating cells, Cell 162 (3) (2015) 552–563, https://doi.org/10.1016/j.cell.2015.07.017.

[75] R.J. DeBerardinis, T. Cheng, Q's next: the diverse functions of glutamine in metabolism, cell biology and cancer, Oncogene 29 (3) (2010) 313–324, https://doi.org/10.1038/onc.2009.358.

[76] Y. Xiao, B. Hu, Y. Guo, D. Zhang, Y. Zhao, Y. Chen, et al., Targeting glutamine metabolism as an attractive therapeutic strategy for acute myeloid leukemia, Curr. Treat. Options Oncol. 24 (8) (2023) 1021–1035, https://doi.org/10.1007/s11864-023-01104-0.

[77] Z. Wang, M. Liu, Q. Yang, Glutamine and leukemia research: progress and clinical prospects, Discov Oncol 15 (1) (2024) 391, https://doi.org/10.1007/s12672-024-01245-0.

[78] O. Warburg, On the origin of cancer cells, Science 123 (3191) (1956) 309–314, https://doi.org/10.1126/science.123.3191.309.

[79] M. Janiszewska, M.L. Suvà, N. Riggi, R.H. Houtkooper, J. Auwerx, V. Clément-Schatlo, et al., Imp2 controls oxidative phosphorylation and is crucial for preserving glioblastoma cancer stem cells, Genes Dev. 26 (17) (2012) 1926–1944, https://doi.org/10.1101/gad.188292.112.

[80] A. Roesch, A. Vultur, I. Bogeski, H. Wang, K.M. Zimmermann, D. Speicher, et al., Overcoming intrinsic multidrug resistance in melanoma by blocking the mitochondrial respiratory chain of slow-cycling JARID1B(high) cells, Cancer Cell 23 (6) (2013) 811–825, https://doi.org/10.1016/j.ccr.2013.05.003.

[81] M.A. Gregory, T. Nemkov, H.J. Park, V. Zaberezhnyy, S. Gehrke, B. Adane, et al., Targeting glutamine metabolism and redox state for leukemia therapy, Clin. Cancer Res. 25 (13) (2019) 4079–4090, https://doi.org/10.1158/1078-0432.Ccr-18-3223.

[82] M.A. Gregory, T. Nemkov, J.A. Reisz, V. Zaberezhnyy, K.C. Hansen, A. D'Alessandro, et al., Glutaminase inhibition improves FLT3 inhibitor therapy for acute myeloid leukemia, Exp. Hematol. 58 (2018) 52–58, https://doi.org/10.1016/j.exphem.2017.09.007.

[83] P. Gallipoli, G. Giotopoulos, K. Tzelepis, A.S.H. Costa, S. Vohra, P. Medina-Perez, et al., Glutaminolysis is a metabolic dependency in FLT3(ITD) acute myeloid leukemia unmasked by FLT3 tyrosine kinase inhibition, Blood 131 (15) (2018) 1639–1653, https://doi.org/10.1182/blood-2017-12-820035.

[84] N. Jacque, A.M. Ronchetti, C. Larrue, G. Meunier, R. Birsen, L. Willems, et al., Targeting glutaminolysis has antileukemic activity in acute myeloid leukemia and synergizes with BCL-2 inhibition, Blood 126 (11) (2015) 1346–1356, https://doi.org/10.1182/blood-2015-01-621870.

[85] S. Zhao, J.M. Wang, J. Yan, D.L. Zhang, B.Q. Liu, J.Y. Jiang, et al., BAG3 promotes autophagy and glutaminolysis via stabilizing glutaminase, Cell Death Dis. 10 (4) (2019) 284, https://doi.org/10.1038/s41419-019-1504-6.

[86] C. De Santo, S. Booth, A. Vardon, A. Cousins, V. Tubb, T. Perry, et al., The arginine metabolome in acute lymphoblastic leukemia can be targeted by the pegylated-recombinant arginase I BCT-100, Int. J. Cancer 142 (7) (2018) 1490–1502, https://doi.org/10.1002/ijc.31170.

[87] J. Szefel, A. Danielak, W.J. Kruszewski, Metabolic pathways of L-arginine and therapeutic consequences in tumors, Adv. Med. Sci. 64 (1) (2019) 104–110, https://doi.org/10.1016/j.advms.2018.08.018.

[88] A. Barilli, B.M. Rotoli, R. Visigalli, O. Bussolati, G.C. Gazzola, V. Dall'Asta, Arginine transport in human monocytic leukemia THP-1 cells during macrophage differentiation, J. Leukoc. Biol. 90 (2) (2011) 293–303, https://doi.org/10.1189/jlb.0910510.

[89] F. Mussai, S. Egan, J. Higginbotham-Jones, T. Perry, A. Beggs, E. Odintsova, et al., Arginine dependence of acute myeloid leukemia blast proliferation: a novel therapeutic target, Blood 125 (15) (2015) 2386–2396, https://doi.org/10.1182/blood-2014-09-600643.

[90] F. Miraki-Moud, E. Ghazaly, L. Ariza-McNaughton, K.A. Hodby, A. Clear, F. Anjos-Afonso, et al., Arginine deprivation using pegylated arginine deiminase has activity against primary acute myeloid leukemia cells in vivo, Blood 125 (26) (2015) 4060–4068, https://doi.org/10.1182/blood-2014-10-608133.

[91] B. Delage, P. Luong, L. Maharaj, C. O'Riain, N. Syed, T. Crook, et al., Promoter methylation of argininosuccinate synthetase-1 sensitises lymphomas to arginine deiminase treatment, autophagy and caspase-dependent apoptosis, Cell Death Dis. 3 (7) (2012) e342, https://doi.org/10.1038/cddis.2012.83.

[92] T.B. Nicholson, T. Chen, S. Richard, The physiological and pathophysiological role of PRMT1-mediated protein arginine methylation, Pharmacol. Res. 60 (6) (2009) 466–474, https://doi.org/10.1016/j.phrs.2009.07.006.

[93] C. Thiebaut, L. Eve, C. Poulard, M. Le Romancer, Structure, activity, and function of PRMT1, Life 11 (11) (2021), https://doi.org/10.3390/life11111147.
[94] K. Gritsman, FLT3-ITD gets by with a little help from PRMT1, Blood 134 (6) (2019) 498–500, https://doi.org/10.1182/blood.2019001876.
[95] Y. Zhu, X. He, Y.C. Lin, H. Dong, L. Zhang, X. Chen, et al., Targeting PRMT1-mediated FLT3 methylation disrupts maintenance of MLL-rearranged acute lymphoblastic leukemia, Blood 134 (15) (2019) 1257–1268, https://doi.org/10.1182/blood.2019002457.
[96] N. Cheung, T.K. Fung, B.B. Zeisig, K. Holmes, J.K. Rane, K.A. Mowen, et al., Targeting aberrant epigenetic networks mediated by PRMT1 and KDM4C in acute myeloid leukemia, Cancer Cell 29 (1) (2016) 32–48, https://doi.org/10.1016/j.ccell.2015.12.007.
[97] C. Liu, W. Zou, D. Nie, S. Li, C. Duan, M. Zhou, et al., Loss of PRMT7 reprograms glycine metabolism to selectively eradicate leukemia stem cells in CML, Cell Metabol. 34 (6) (2022) 818–835.e817, https://doi.org/10.1016/j.cmet.2022.04.004.
[98] L. Fultang, S. Booth, O. Yogev, B. Martins da Costa, V. Tubb, S. Panetti, et al., Metabolic engineering against the arginine microenvironment enhances CAR-T cell proliferation and therapeutic activity, Blood 136 (10) (2020) 1155–1160, https://doi.org/10.1182/blood.2019004500.
[99] R. Geiger, J.C. Rieckmann, T. Wolf, C. Basso, Y. Feng, T. Fuhrer, et al., L-arginine modulates T cell metabolism and enhances survival and anti-tumor activity, Cell 167 (3) (2016) 829–842.e813, https://doi.org/10.1016/j.cell.2016.09.031.
[100] F. Mussai, R. Wheat, E. Sarrou, S. Booth, V. Stavrou, L. Fultang, et al., Targeting the arginine metabolic brake enhances immunotherapy for leukaemia, Int. J. Cancer 145 (8) (2019) 2201–2208, https://doi.org/10.1002/ijc.32028.
[101] H. Lemos, L. Huang, G.C. Prendergast, A.L. Mellor, Immune control by amino acid catabolism during tumorigenesis and therapy, Nat. Rev. Cancer 19 (3) (2019) 162–175, https://doi.org/10.1038/s41568-019-0106-z.
[102] I. Marigo, S. Zilio, G. Desantis, B. Mlecnik, A.H.R. Agnellini, S. Ugel, et al., T cell cancer therapy requires CD40-CD40L activation of tumor necrosis factor and inducible nitric-oxide-synthase-producing dendritic cells, Cancer Cell 30 (3) (2016) 377–390, https://doi.org/10.1016/j.ccell.2016.08.004.
[103] Y. Ni, U. Schwaneberg, Z.H. Sun, Arginine deiminase, a potential anti-tumor drug, Cancer Lett. 261 (1) (2008) 1–11, https://doi.org/10.1016/j.canlet.2007.11.038.
[104] H. Gong, F. Zölzer, G. von Recklinghausen, W. Havers, L. Schweigerer, Arginine deiminase inhibits proliferation of human leukemia cells more potently than asparaginase by inducing cell cycle arrest and apoptosis, Leukemia 14 (5) (2000) 826–829, https://doi.org/10.1038/sj.leu.2401763.
[105] K. Beloussow, L. Wang, J. Wu, D. Ann, W.C. Shen, Recombinant arginine deiminase as a potential anti-angiogenic agent, Cancer Lett. 183 (2) (2002) 155–162, https://doi.org/10.1016/s0304-3835(01)00793-5.
[106] I.S. Park, S.W. Kang, Y.J. Shin, K.Y. Chae, M.O. Park, M.Y. Kim, et al., Arginine deiminase: a potential inhibitor of angiogenesis and tumour growth, Br. J. Cancer 89 (5) (2003) 907–914, https://doi.org/10.1038/sj.bjc.6601181.
[107] G.C. Field, I. Pavlyk, P.W. Szlosarek, Bench-to-Bedside studies of arginine deprivation in cancer, Molecules 28 (5) (2023), https://doi.org/10.3390/molecules28052150.
[108] H.J. Kung, C.A. Changou, C.F. Li, D.K. Ann, Chromatophagy: autophagy goes nuclear and captures broken chromatin during arginine-starvation, Autophagy 11 (2) (2015) 419–421, https://doi.org/10.1080/15548627.2015.1009789.
[109] C.A. Changou, Y.R. Chen, L. Xing, Y. Yen, F.Y. Chuang, R.H. Cheng, et al., Arginine starvation-associated atypical cellular death involves mitochondrial dysfunction, nuclear DNA leakage, and chromatin autophagy, Proc. Natl. Acad. Sci. U.S.A. 111 (39) (2014) 14147–14152, https://doi.org/10.1073/pnas.1404171111.
[110] Z. Wang, Q. Xie, H. Zhou, M. Zhang, J. Shen, D. Ju, Amino acid degrading enzymes and autophagy in cancer therapy, Front. Pharmacol. 11 (2020) 582587, https://doi.org/10.3389/fphar.2020.582587.
[111] J.D. Silk, S. Lakhal, R. Laynes, L. Vallius, I. Karydis, C. Marcea, et al., Ido induces expression of a novel tryptophan transporter in mouse and human tumor cells, J. Immunol. 187 (4) (2011) 1617–1625, https://doi.org/10.4049/jimmunol.1000815.
[112] M. Miyanokoshi, T. Yokosawa, K. Wakasugi, Tryptophanyl-tRNA synthetase mediates high-affinity tryptophan uptake into human cells, J. Biol. Chem. 293 (22) (2018) 8428–8438, https://doi.org/10.1074/jbc.RA117.001247.
[113] I. Cervenka, L.Z. Agudelo, J.L. Ruas, Kynurenines: tryptophan's metabolites in exercise, inflammation, and mental health, Science 357 (6349) (2017), https://doi.org/10.1126/science.aaf9794.
[114] N. Le Floc'h, W. Otten, E. Merlot, Tryptophan metabolism, from nutrition to potential therapeutic applications, Amino Acids 41 (5) (2011) 1195–1205, https://doi.org/10.1007/s00726-010-0752-7.
[115] T.W. Stone, N. Stoy, L.G. Darlington, An expanding range of targets for kynurenine metabolites of tryptophan, Trends Pharmacol. Sci. 34 (2) (2013) 136–143, https://doi.org/10.1016/j.tips.2012.09.006.
[116] A. Salminen, Activation of aryl hydrocarbon receptor (AhR) in Alzheimer's disease: role of tryptophan metabolites generated by gut host-microbiota, J. Mol. Med. (Berl.) 101 (3) (2023) 201–222, https://doi.org/10.1007/s00109-023-02289-5.
[117] T.W. Stone, R.O. Williams, Modulation of T cells by tryptophan metabolites in the kynurenine pathway, Trends Pharmacol. Sci. 44 (7) (2023) 442–456, https://doi.org/10.1016/j.tips.2023.04.006.
[118] C.A. Opitz, W. Wick, L. Steinman, M. Platten, Tryptophan degradation in autoimmune diseases, Cell. Mol. Life Sci. 64 (19–20) (2007) 2542–2563, https://doi.org/10.1007/s00018-007-7140-9.
[119] V. Vonka, Z. Humlova, H. Klamova, L. Kujovska-Krcmova, M. Petrackova, E. Hamsikova, et al., Kynurenine and uric acid levels in chronic myeloid leukemia patients, OncoImmunology 4 (3) (2015) e992646, https://doi.org/10.4161/2162402x.2014.992646.
[120] A. Sadik, L.F. Somarribas Patterson, S. Öztürk, S.R. Mohapatra, V. Panitz, P.F. Secker, et al., IL4I1 is a metabolic immune checkpoint that activates the AHR and promotes tumor progression, Cell 182 (5) (2020) 1252–1270.e1234, https://doi.org/10.1016/j.cell.2020.07.038.
[121] D.H. Munn, M.D. Sharma, B. Baban, H.P. Harding, Y. Zhang, D. Ron, et al., GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase, Immunity 22 (5) (2005) 633–642, https://doi.org/10.1016/j.immuni.2005.03.013.
[122] F. Fallarino, U. Grohmann, S. You, B.C. McGrath, D.R. Cavener, C. Vacca, et al., The combined effects of tryptophan starvation and tryptophan catabolites down-regulate T cell receptor zeta-chain and induce a regulatory phenotype in naive T cells, J. Immunol. 176 (11) (2006) 6752–6761, https://doi.org/10.4049/jimmunol.176.11.6752.
[123] Y. Yan, G.X. Zhang, B. Gran, F. Fallarino, S. Yu, H. Li, et al., Ido upregulates regulatory T cells via tryptophan catabolite and suppresses encephalitogenic T cell responses in experimental autoimmune encephalomyelitis, J. Immunol. 185 (10) (2010) 5953–5961, https://doi.org/10.4049/jimmunol.1001628.
[124] J.D. Mezrich, J.H. Fechner, X. Zhang, B.P. Johnson, W.J. Burlingham, C.A. Bradfield, An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells, J. Immunol. 185 (6) (2010) 3190–3198, https://doi.org/10.4049/jimmunol.0903670.
[125] B.C. DiNatale, I.A. Murray, J.C. Schroeder, C.A. Flaveny, T.S. Lahoti, E.M. Laurenzana, et al., Kynurenic acid is a potent endogenous aryl hydrocarbon receptor ligand that synergistically induces interleukin-6 in the presence of inflammatory signaling, Toxicol. Sci. 115 (1) (2010) 89–97, https://doi.org/10.1093/toxsci/kfq024.
[126] J.H.L. Pacheco, G. Elizondo, Interplay between Estrogen, Kynurenine, and AHR Pathways: an immunosuppressive axis with therapeutic potential for breast cancer treatment, Biochem. Pharmacol. 217 (2023) 115804, https://doi.org/10.1016/j.bcp.2023.115804.
[127] A. Shadboorestan, M. Koual, J. Dairou, X. Coumoul, The role of the kynurenine/AhR pathway in diseases related to metabolism and cancer, Int. J. Tryptophan Res. 16 (2023), https://doi.org/10.1177/11786469231185102, 11786469231185102.
[128] L. Zeitler, P.J. Murray, IL4i1 and Ido1: oxidases that control a tryptophan metabolic nexus in cancer, J. Biol. Chem. 299 (6) (2023) 104827, https://doi.org/10.1016/j.jbc.2023.104827.
[129] Y. Fujiwara, S. Kato, M.K. Nesline, J.M. Conroy, P. DePietro, S. Pabla, et al., Indoleamine 2,3-dioxygenase (Ido) inhibitors and cancer immunotherapy, Cancer Treat Rev. 110 (2022) 102461, https://doi.org/10.1016/j.ctrv.2022.102461.
[130] Y. Liu, X. Liang, W. Dong, Y. Fang, J. Lv, T. Zhang, et al., Tumor-repopulating cells induce PD-1 expression in CD8(+) T cells by transferring kynurenine and AhR activation, Cancer Cell 33 (3) (2018) 480–494.e487, https://doi.org/10.1016/j.ccell.2018.02.005.
[131] D.J. Elson, S.K. Kolluri, Tumor-suppressive functions of the aryl hydrocarbon receptor (AhR) and AhR as a therapeutic target in cancer, Biology 12 (4) (2023), https://doi.org/10.3390/biology12040526.

[132] F.K. Dermani, P. Samadi, G. Rahmani, A.K. Kohlan, R. Najafi, PD-1/PD-L1 immune checkpoint: potential target for cancer therapy, J. Cell. Physiol. 234 (2) (2019) 1313–1325, https://doi.org/10.1002/jcp.27172.
[133] Z.Y. Xu-Monette, J. Zhou, K.H. Young, PD-1 expression and clinical PD-1 blockade in B-cell lymphomas, Blood 131 (1) (2018) 68–83, https://doi.org/10.1182/blood-2017-07-740993.
[134] G.C. Prendergast, W.P. Malachowski, J.B. DuHadaway, A.J. Muller, Discovery of Ido1 inhibitors: from bench to bedside, Cancer Res. 77 (24) (2017) 6795–6811, https://doi.org/10.1158/0008-5472.Can-17-2285.
[135] M. Neinast, D. Murashige, Z. Arany, Branched chain amino acids, Annu. Rev. Physiol. 81 (2019) 139–164, https://doi.org/10.1146/annurev-physiol-020518-114455.
[136] A. Moura, M.A. Savageau, R. Alves, Relative amino acid composition signatures of organisms and environments, PLoS One 8 (10) (2013) e77319, https://doi.org/10.1371/journal.pone.0077319.
[137] J.J. Kamphorst, M. Nofal, C. Commisso, S.R. Hackett, W. Lu, E. Grabocka, et al., Human pancreatic cancer tumors are nutrient poor and tumor cells actively scavenge extracellular protein, Cancer Res. 75 (3) (2015) 544–553, https://doi.org/10.1158/0008-5472.Can-14-2211.
[138] S. Sivanand, M.G. Vander Heiden, Emerging roles for branched-chain amino acid metabolism in cancer, Cancer Cell 37 (2) (2020) 147–156, https://doi.org/10.1016/j.ccell.2019.12.011.
[139] T.J. Wetzel, S.C. Erfan, L.D. Figueroa, L.M. Wheeler, E.A. Ananieva, Crosstalk between arginine, glutamine, and the branched chain amino acid metabolism in the tumor microenvironment, Front. Oncol. 13 (2023) 1186539, https://doi.org/10.3389/fonc.2023.1186539.
[140] P.M. Van Pevenage, J.T. Birchmier, R.K. June, Utilizing metabolomics to identify potential biomarkers and perturbed metabolic pathways in osteoarthritis: a systematic review, Semin. Arthritis Rheum. 59 (2023) 152163, https://doi.org/10.1016/j.semarthrit.2023.152163.
[141] E.A. Ananieva, A.C. Wilkinson, Branched-chain amino acid metabolism in cancer, Curr. Opin. Clin. Nutr. Metab. Care 21 (1) (2018) 64–70, https://doi.org/10.1097/mco.0000000000000430.
[142] M.E. Trautman, N.E. Richardson, D.W. Lamming, Protein restriction and branched-chain amino acid restriction promote geroprotective shifts in metabolism, Aging Cell 21 (6) (2022) e13626, https://doi.org/10.1111/acel.13626.
[143] R.L. Wolfson, L. Chantranupong, R.A. Saxton, K. Shen, S.M. Scaria, J.R. Cantor, et al., Sestrin2 is a leucine sensor for the mTORC1 pathway, Science 351 (6268) (2016) 43–48, https://doi.org/10.1126/science.aab2674.
[144] L. Chantranupong, R.L. Wolfson, J.M. Orozco, R.A. Saxton, S.M. Scaria, L. Bar-Peled, et al., The Sestrins interact with GATOR2 to negatively regulate the amino-acid-sensing pathway upstream of mTORC1, Cell Rep. 9 (1) (2014) 1–8, https://doi.org/10.1016/j.celrep.2014.09.014.
[145] M. Zhu, F. Teng, N. Li, L. Zhang, S. Zhang, F. Xu, et al., Monomethyl branched-chain fatty acid mediates amino acid sensing upstream of mTORC1, Dev. Cell 56 (19) (2021) 2692–2702, https://doi.org/10.1016/j.devcel.2021.09.010, e2695.
[146] J.M. Han, S.J. Jeong, M.C. Park, G. Kim, N.H. Kwon, H.K. Kim, et al., Leucyl-tRNA synthetase is an intracellular leucine sensor for the mTORC1-signaling pathway, Cell 149 (2) (2012) 410–424, https://doi.org/10.1016/j.cell.2012.02.044.
[147] R.A. Saxton, D.M. Sabatini, mTOR signaling in growth, metabolism, and disease, Cell 168 (6) (2017) 960–976, https://doi.org/10.1016/j.cell.2017.02.004.
[148] X.M. Ma, S.O. Yoon, C.J. Richardson, K. Jülich, J. Blenis, SKAR links pre-mRNA splicing to mTOR/S6K1-mediated enhanced translation efficiency of spliced mRNAs, Cell 133 (2) (2008) 303–313, https://doi.org/10.1016/j.cell.2008.02.031.
[149] G.J. Brunn, C.C. Hudson, A. Sekulić, J.M. Williams, H. Hosoi, P.J. Houghton, et al., Phosphorylation of the translational repressor PHAS-I by the mammalian target of rapamycin, Science 277 (5322) (1997) 99–101, https://doi.org/10.1126/science.277.5322.99.
[150] A.C. Gingras, S.P. Gygi, B. Raught, R.D. Polakiewicz, R.T. Abraham, M.F. Hoekstra, et al., Regulation of 4E-BP1 phosphorylation: a novel two-step mechanism, Genes Dev. 13 (11) (1999) 1422–1437, https://doi.org/10.1101/gad.13.11.1422.
[151] S. Alers, A.S. Löffler, S. Wesselborg, B. Stork, Role of AMPK-mTOR-Ulk1/2 in the regulation of autophagy: cross talk, shortcuts, and feedbacks, Mol. Cell Biol. 32 (1) (2012) 2–11, https://doi.org/10.1128/mcb.06159-11.
[152] J. Kim, M. Kundu, B. Viollet, K.L. Guan, AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1, Nat. Cell Biol. 13 (2) (2011) 132–141, https://doi.org/10.1038/ncb2152.
[153] D.F. Egan, D.B. Shackelford, M.M. Mihaylova, S. Gelino, R.A. Kohnz, W. Mair, et al., Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to mitophagy, Science 331 (6016) (2011) 456–461, https://doi.org/10.1126/science.1196371.
[154] A.E. Harper, R.H. Miller, K.P. Block, Branched-chain amino acid metabolism, Annu. Rev. Nutr. 4 (1984) 409–454, https://doi.org/10.1146/annurev.nu.04.070184.002205.
[155] J. Wang, W. Wang, F. Zhu, Q. Duan, The role of branched chain amino acids metabolic disorders in tumorigenesis and progression, Biomed. Pharmacother. 153 (2022) 113390, https://doi.org/10.1016/j.biopha.2022.113390.
[156] S. Raffel, M. Falcone, N. Kneisel, J. Hansson, W. Wang, C. Lutz, et al., BCAT1 restricts αKG levels in AML stem cells leading to IDHmut-like DNA hypermethylation, Nature 551 (7680) (2017) 384–388, https://doi.org/10.1038/nature24294.
[157] A. Hattori, M. Tsunoda, T. Konuma, M. Kobayashi, T. Nagy, J. Glushka, et al., Cancer progression by reprogrammed BCAA metabolism in myeloid leukaemia, Nature 545 (7655) (2017) 500–504, https://doi.org/10.1038/nature22314.
[158] Y. Kikushige, T. Miyamoto, Y. Kochi, Y. Semba, M. Ohishi, H. Irifune, et al., Human acute leukemia utilizes branched-chain amino acid catabolism to maintain stemness through regulating PRC2 function, Blood Adv (2022), https://doi.org/10.1182/bloodadvances.2022008242.
[159] Y. Hu, S. Li, Survival regulation of leukemia stem cells, Cell. Mol. Life Sci. 73 (5) (2016) 1039–1050, https://doi.org/10.1007/s00018-015-2108-7.
[160] P. Valent, Targeting of leukemia-initiating cells to develop curative drug therapies: straightforward but nontrivial concept, Curr. Cancer Drug Targets 11 (1) (2011) 56–71, https://doi.org/10.2174/156800911793743655.
[161] M. Houshmand, G. Simonetti, P. Circosta, V. Gaidano, A. Cignetti, G. Martinelli, et al., Chronic myeloid leukemia stem cells, Leukemia 33 (7) (2019) 1543–1556, https://doi.org/10.1038/s41375-019-0490-0.
[162] R.G.A. Costa, S.L.R. Silva, I. Dias, M.S. Oliveira, A. Rodrigues, R.B. Dias, et al., Emerging drugs targeting cellular redox homeostasis to eliminate acute myeloid leukemia stem cells, Redox Biol. 62 (2023) 102692, https://doi.org/10.1016/j.redox.2023.102692.
[163] K. Barbosa, A.J. Deshpande, Therapeutic targeting of leukemia stem cells in acute myeloid leukemia, Front. Oncol. 13 (2023) 1204895, https://doi.org/10.3389/fonc.2023.1204895.
[164] B. Löwenberg, J.R. Downing, A. Burnett, Acute myeloid leukemia, N. Engl. J. Med. 341 (14) (1999) 1051–1062, https://doi.org/10.1056/nejm199909303411407.
[165] D. Vetrie, G.V. Helgason, M. Copland, The leukaemia stem cell: similarities, differences and clinical prospects in CML and AML, Nat. Rev. Cancer 20 (3) (2020) 158–173, https://doi.org/10.1038/s41568-019-0230-9.
[166] H. Ye, B. Adane, N. Khan, T. Sullivan, M. Minhajuddin, M. Gasparetto, et al., Leukemic stem cells evade chemotherapy by metabolic adaptation to an adipose tissue niche, Cell Stem Cell 19 (1) (2016) 23–37, https://doi.org/10.1016/j.stem.2016.06.001.
[167] F. Ishikawa, S. Yoshida, Y. Saito, A. Hijikata, H. Kitamura, S. Tanaka, et al., Chemotherapy-resistant human AML stem cells home to and engraft within the bone-marrow endosteal region, Nat. Biotechnol. 25 (11) (2007) 1315–1321, https://doi.org/10.1038/nbt1350.
[168] L.I. Shlush, A. Mitchell, L. Heisler, S. Abelson, S.W.K. Ng, A. Trotman-Grant, et al., Tracing the origins of relapse in acute myeloid leukaemia to stem cells, Nature 547 (7661) (2017) 104–108, https://doi.org/10.1038/nature22993.
[169] M.A. Essers, A. Trumpp, Targeting leukemic stem cells by breaking their dormancy, Mol. Oncol. 4 (5) (2010) 443–450, https://doi.org/10.1016/j.molonc.2010.06.001.
[170] C.L. Jones, B.M. Stevens, A. D'Alessandro, J.A. Reisz, R. Culp-Hill, T. Nemkov, et al., Inhibition of amino acid metabolism selectively targets human leukemia stem cells, Cancer Cell 35 (2) (2019) 333–335, https://doi.org/10.1016/j.ccell.2019.01.013.
[171] C.L. Jones, B.M. Stevens, A. D'Alessandro, R. Culp-Hill, J.A. Reisz, S. Pei, et al., Cysteine depletion targets leukemia stem cells through inhibition of electron transport complex II, Blood 134 (4) (2019) 389–394, https://doi.org/10.1182/blood.2019898114.

[172] C.L. Jones, B.M. Stevens, D.A. Pollyea, R. Culp-Hill, J.A. Reisz, T. Nemkov, et al., Nicotinamide metabolism mediates resistance to venetoclax in relapsed acute myeloid leukemia stem cells, Cell Stem Cell 27 (5) (2020) 748–764.e744, https://doi.org/10.1016/j.stem.2020.07.021.
[173] J.S. Khorashad, S. Rizzo, A. Tonks, Reactive oxygen species and its role in pathogenesis and resistance to therapy in acute myeloid leukemia, Cancer Drug Resist 7 (2024) 5, https://doi.org/10.20517/cdr.2023.125.
[174] E.D. Lagadinou, A. Sach, K. Callahan, R.M. Rossi, S.J. Neering, M. Minhajuddin, et al., BCL-2 inhibition targets oxidative phosphorylation and selectively eradicates quiescent human leukemia stem cells, Cell Stem Cell 12 (3) (2013) 329–341, https://doi.org/10.1016/j.stem.2012.12.013.
[175] A. Viale, P. Pettazzoni, C.A. Lyssiotis, H. Ying, N. Sánchez, M. Marchesini, et al., Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function, Nature 514 (7524) (2014) 628–632, https://doi.org/10.1038/nature13611.
[176] P. Sharma, G. Borthakur, Targeting metabolic vulnerabilities to overcome resistance to therapy in acute myeloid leukemia, Cancer Drug Resist 6 (3) (2023) 567–589, https://doi.org/10.20517/cdr.2023.12.
[177] C.L. Jones, A. Inguva, C.T. Jordan, Targeting energy metabolism in cancer stem cells: progress and challenges in leukemia and solid tumors, Cell Stem Cell 28 (3) (2021) 378–393, https://doi.org/10.1016/j.stem.2021.02.013.
[178] N. van Gastel, J.B. Spinelli, A. Sharda, A. Schajnovitz, N. Baryawno, C. Rhee, et al., Induction of a timed metabolic collapse to overcome cancer chemoresistance, Cell Metabol. 32 (3) (2020) 391–403.e396, https://doi.org/10.1016/j.cmet.2020.07.009.