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Review

Glutamine and leukemia research: progress and clinical prospects

Zexin Wang[1] · **Miao Liu**[1] · **Qiang Yang**[1]

Received: 25 March 2024 / Accepted: 14 August 2024
Published online: 31 August 2024

Abstract
Leukemia is an abnormal proliferation of white blood cells that occurs in bone marrow and expands through the blood. It arises from dysregulated differentiation, uncontrolled growth, and inhibition of apoptosis. Glutamine (GLN) is a "conditionally essential" amino acid that promotes growth and proliferation of leukemic cells. Recently, details about the role of GLN and its metabolism in the diagnosis and treatment of acute myeloid, chronic lymphocytic, and acute lymphoblastic leukemia have emerged. The uptake of GLN by leukemia cells and the dynamic changes of glutamine-related indexes in leukemia patients may be able to assist in determining whether the condition of leukemia is in a state of progression, remission or relapse. Utilizing the possible differences in GLN metabolism in different subtypes of leukemia may help to differentiate between different subtypes of leukemia, thus providing a basis for accurate diagnosis. Targeting GLN metabolism in leukemia requires simultaneous blockade of multiple metabolic pathways without interfering with the normal cellular and immune functions of the body to achieve effective leukemia therapy. The present review summarizes recent advances, possible applications, and clinical perspectives of GLN metabolism in leukemia. In particular, it focuses on the prospects of GLN metabolism in the diagnosis and treatment of acute myeloid leukemia. The review provides new directions and hints at potential roles for future clinical treatments and studies.

Keywords Glutamine · Leukemia · Glutamine metabolism · Glutaminase · Glutamine transporter protein

1 Introduction

Leukemias are a group of aggressive hematologic malignancies (also known as blood cancers) involving clonal proliferation of immature myeloid progenitor cells in the bone marrow and peripheral blood. They are caused by genetic mutations in hematopoietic stem cells. Presently, the treatment of choice includes chemotherapy and allogeneic stem cell transplantation [1]. With the development of time and technology, immunotherapeutic approaches for various leukemias have shown great promise, such as CD33 or CLL-1-specific chimeric antigen receptor (CAR)-T cell therapy[2, 3] and immune checkpoint inhibitor therapies such as TIM3, CD47, and anti-CD70 [4–6]. Regardless of therapy, relapse is common and shortens the survival of leukemia patients. Therefore, alternative treatment strategies are needed.

Growing evidence points to the critical role of amino acid metabolism on the diagnosis and treatment of leukemia. The metabolic pathways for GLN, arginine, isoleucine, tryptophan, cysteine, tyrosine, threonine, and L-serine play a crucial role in cancer. Moreover, amino acid metabolism is active in high-risk populations and the corresponding genes are associated with the immune microenvironment in acute myeloid leukemia (AML) patients [7]. Among the various amino acids, GLN metabolism seems to be an effective target against leukemia [8]. Leukemia cells have changes in the uptake and utilization

✉ Zexin Wang, wayen920326@163.com; Miao Liu, 583745693@qq.com; Qiang Yang, 15883779352@163.com | [1]Mianyang Central Hospital, Fucheng District, Mianyang 621000, Sichuan, China.

of GLN as well as metabolic pathways. Through the dynamic changes of GLN-related indexes in patients can help to determine whether the leukemia is in progress, remission or relapse, and the differences in glutamine metabolism in different subtypes of leukemia can help to differentiate between subtypes of leukemia. Therefore, this review discusses the role of GLN metabolism in three common types of leukemia: AML, chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL). Furthermore, it discusses the latest advances and developments in the field, as well as the therapeutic opportunities and challenges of GLN targeting.

2 Glutamine metabolism

GLN is a nonessential amino acid with two amino groups, the α-amino group and a readily hydrolysable side-chain amide group, with five carbons, a molecular weight of 146.15 kDa, and a chemical composition of C = 41.09%, H = 6.90%, O = 32.84%, and N = 19.17%. Classified as a neutral at physiological pH, it is the most abundant and versatile amino acid in the body (~ 0.6–0.8 mM) [9]. GLN is converted by glutaminase (GLS) to glutamate, which is then transformed to α-ketoglutarate (α-KG), an intermediate in the tricarboxylic acid (TCA) cycle and a core element in GLN metabolism [9, 10]. Glutamate can be directly converted to α-KG in two ways. The first is via glutamate dehydrogenase (GLDH), which produces the potential autophagy inducer ammonium and NADH or NADPH as cofactors. The second is via a group of transaminases, including glutamate–oxaloacetate transaminase, glutamate-pyruvate transaminase, and phosphoserine aminotransferase. Glutamate serves as a metabolite for the growth and proliferation of cancer cells via the TCA cycle. Moreover, glutamate can be deaminated in a number of reactions, thus providing a source of nitrogen for nonessential amino acids, purines and pyrimidines [11]. At the same time, intracellular glutathione (GSH) derived from GLN effectively scavenges intracellular reactive oxygen species (ROS), mediating ferroptosis and redox homeostasis in cancer cells [8]. Notably, GLN promotes the activation of rapamycin complex 1 (mTORC1), which is associated with apoptosis and autophagy in cancer cells.

GLN is as important in hematologic tumors as one of the nutrients on which cancer cells depend for survival. Given the need of tumor cells for glucose (for anaerobic glycolysis), GLN deficiency has been associated with cell death [12–14]. In both healthy and diseased states, immune cells consume as much GLN as possible, and its deprivation holds promise as a new therapeutic tool.

3 Glutaminase

GLS is a key enzyme involved in GLN metabolism. It comprises renal glutaminase-1 (GLS-1) and hepatic glutaminase-2 (GLS-2). GLS-1 has two variable splice isoforms: glutaminase C and renal glutaminase. The TCA cycle yields metabolic intermediates that are involved in the biosynthesis of nucleotides, GSH, and other amino acids [15]. In addition, GLN can be converted to α-KG for oxidative phosphorylation to produce ATP. Elevated expression of GLS-1 is directly or indirectly associated with poor prognosis in stem cell, colorectal, and breast cancers [16].

The *GLS-2* gene is located on chromosome 12q13 and contains 18 coding exons. GLS-2 is considered more of a tumor suppressor than GLS-1. GLS-2 has been shown to be a *p53* target as it contains two possible p53 binding sites [17]. The tumor suppressor *p53* activates GLS-2 expression, regulates intracellular ROS levels and reduced/oxidized GSH ratios, and removes intracellular ROS to protect cells from genomic damage and ROS-sensitive apoptosis [18, 19]. TAp63, TAp73, and long-chain non-coding RNAs can also regulate GLS-2 [20–22]. Meanwhile, increased mitochondrial GLS expression enhances GLN catabolism by Myc oncogene inhibition of miR-23, which in turn targets GLS [23]. GLS inhibition decreases the production of GSH in AML cell lines, leading to increased mitochondrial ROS and apoptosis [8, 24]. Thus. GLS-1 and GLS-2 may serve as diagnostic and therapeutic targets for certain cancers. Clinical studies should explore new chemotherapeutic combinations of GLS inhibitors in the treatment of leukemia.

4 Inhibitors of the GLN transporter limit tumor demand for GLN

Strong expression of alanine-serine-cysteine transporter protein 2 (ASCT2), a GLN transporter, helps meet the amino acid needs of tumors [25] (Fig. 1). However, ASCT2 has also anticancer properties [26], because its deletion can lead to apoptosis of leukemia cells [27]. Inhibition of ASCT2-mediated GLN uptake in human cells using a lead compound (V-9302) resulted in attenuation of cancer cell growth and proliferation, frequent cell death, and increased oxidative stress [28]. ASCT2 plays the same role in cell proliferation and apoptosis in several cancers [29–36]. In a study of 25 patients with

different clinically aggressive tumors (lung, breast, colon, or lymphoma), who underwent fluorine 18-(2S,4R)-4-fluoroglutamine positron emission tomography, all showed abnormal GLN metabolism [37]. Notably, ASCT2-mediated pharmacological inhibitors significantly reduced GLN uptake by triple-negative basal-like breast cancer cells, while having little effect on luminal breast cancer cells [38]. Taken together, this evidence implies that ASCT2 may serve as a potential target for antitumor drugs. ASCT2 inhibitors and the combination of ASCT2 inhibitors with other antitumor therapies may offer a promising antitumor strategy. However, more research is needed in this area of leukemia. Because GLN may be closely related to leukemogenesis and progression, it may directly or indirectly affect the diagnosis and treatment of leukemia.

5 GLN metabolism in leukemia

Leukemia is a myeloid malignancy characterized by abnormal proliferation and differentiation of hematopoietic precursor cells. Cancer cells are highly dependent on GLN metabolism and availability [39]. GLN metabolism is centered in the mitochondria. Mitochondria play a crucial role in the maintenance of hematopoietic stem cells, whose malignant transformation ultimately leads to leukemic stem cells [40]. The first evidence of impaired mitochondrial metabolism in AML was the presence of mutations in the gene encoding isocitrate dehydrogenase (IDH) in AML patients [41, 42].

Recent in vivo and in vitro studies have shown that GLN is restricted to the cancer cell environment [43]. Glutamine is used as an alternative fuel for the TCA cycle, with plasma concentrations of 0.6–0.8 mM, and is the most common amino acid in blood [9, 10]. As in other cancers, plasma GLN concentrations in AML patients are quite low, 0.3 mM or less, suggesting that GLN is rapidly depleted in AML cells [10, 44, 45]. A study of 55 newly diagnosed AML patients and 45 healthy individuals also showed that GLN levels were much lower in the former than in the latter [46]. AML cells are completely dependent on exogenous GLN, and knockdown of high-affinity ASCT2 leads to apoptosis in AML cell lines and inhibits tumor progression in AML xenografts and primary AML mouse models [47] Indeed, ASCT2 plays pleiotropic roles in cellular metabolism and serves as a promising molecular target for the treatment of leukemia [27].

GLS is a rate-limiting factor for TCA activity in AML and is highly expressed in AML patients [48]. The initial step required for glucose-independent oxidative phosphorylation is the conversion of GLN to glutamate. Subsequently,

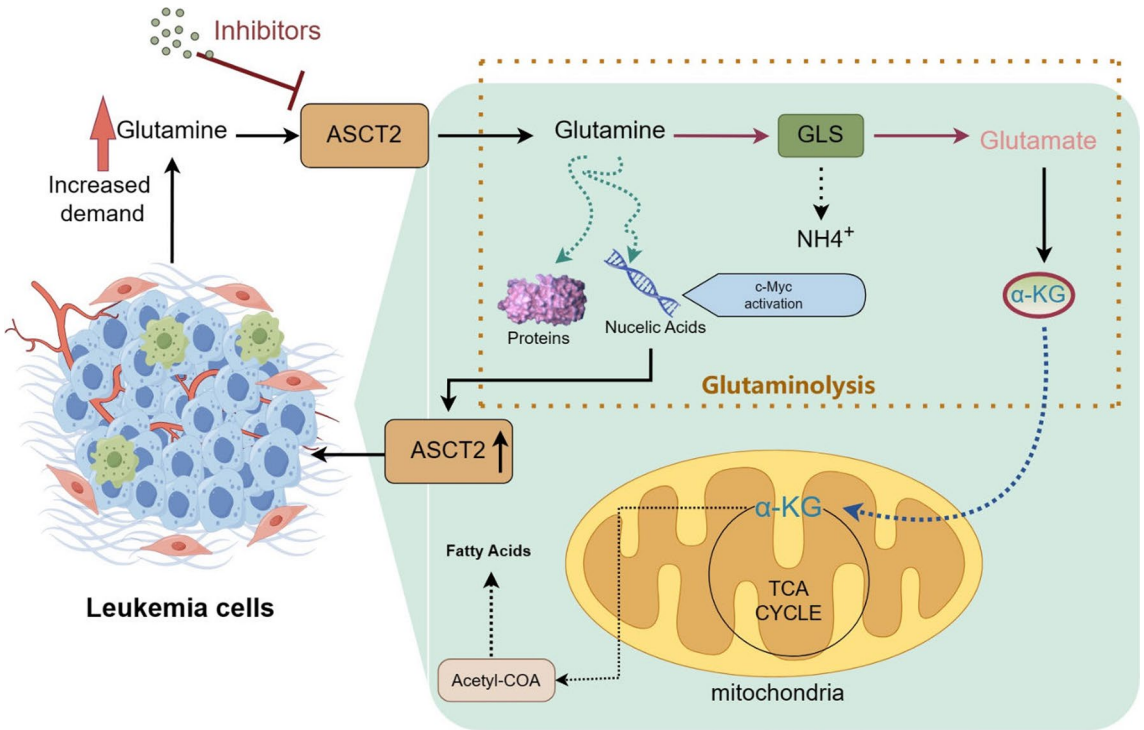

Fig. 1 Overview of glutamine metabolism in leukemia cells. The increased demand for glutamine by leukemia cells and simultaneous inhibition of the ASCT2 transporter, result in a declining hydrolysis of glutamine to glutamate. α-KG, α-ketoglutarate; ASCT2, alanine-serine-cysteine transporter protein 2; GLS, glutaminase; TCA, tricarboxylic acid. The Illustration was created in Figdraw

glutamate provides the substrate for the synthesis of α-KG. IDH catalyzes the oxidative decarboxylation of isocitrate to α-KG. Mutations in IDH result in the conversion of α-KG to R2-hydroxyglutarate, which is detected in approximately 2% of adult AML patients [42, 49] (Fig. 2). ATP and metabolic pathways localized to the mitochondria have been shown to play an important role in the progression of AML [50]. Elevated levels of 2-hydroxyglutarate, a metabolite associated with the TCA cycle, may promote tumorigenesis [51]. Meanwhile, the central nervous system is also involved in metabolic processes, posing a major challenge to the treatment of acute leukemia [52]. In addition, in studies on GLN metabolism, N6-methyladenosine (m^6A) regulates GLN metabolism through modification of insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2), which directly or indirectly promotes AML cell development and self-renewal, and higher levels of IGF2BP2 expression correlate with a poor prognosis for AML [53].

Taken together, changes in glutamine utilization and metabolic pathways in leukemia cells are expected to be potential prognostic markers. For example, GLS is highly expressed in AML patients and IGF2BP2 is associated with prognosis in AML. By detecting dynamic changes in glutamine-related markers, it is possible to understand the progression, remission or relapse of leukemia and provide diagnostic value. Glutaminolysis inhibits the conversion of GLN to circulating TCA metabolites by regulating various enzymes, and GLS is the first step in the process. Therefore, targeting GLS to block GLN degradation is a promising therapeutic strategy. Targeting of the two GLS isoforms, GLS-1 and GLS-2, will provide new insights on the treatment of leukemia. Hereafter, we discuss the relationship between GLN and AML, CLL, and ALL.

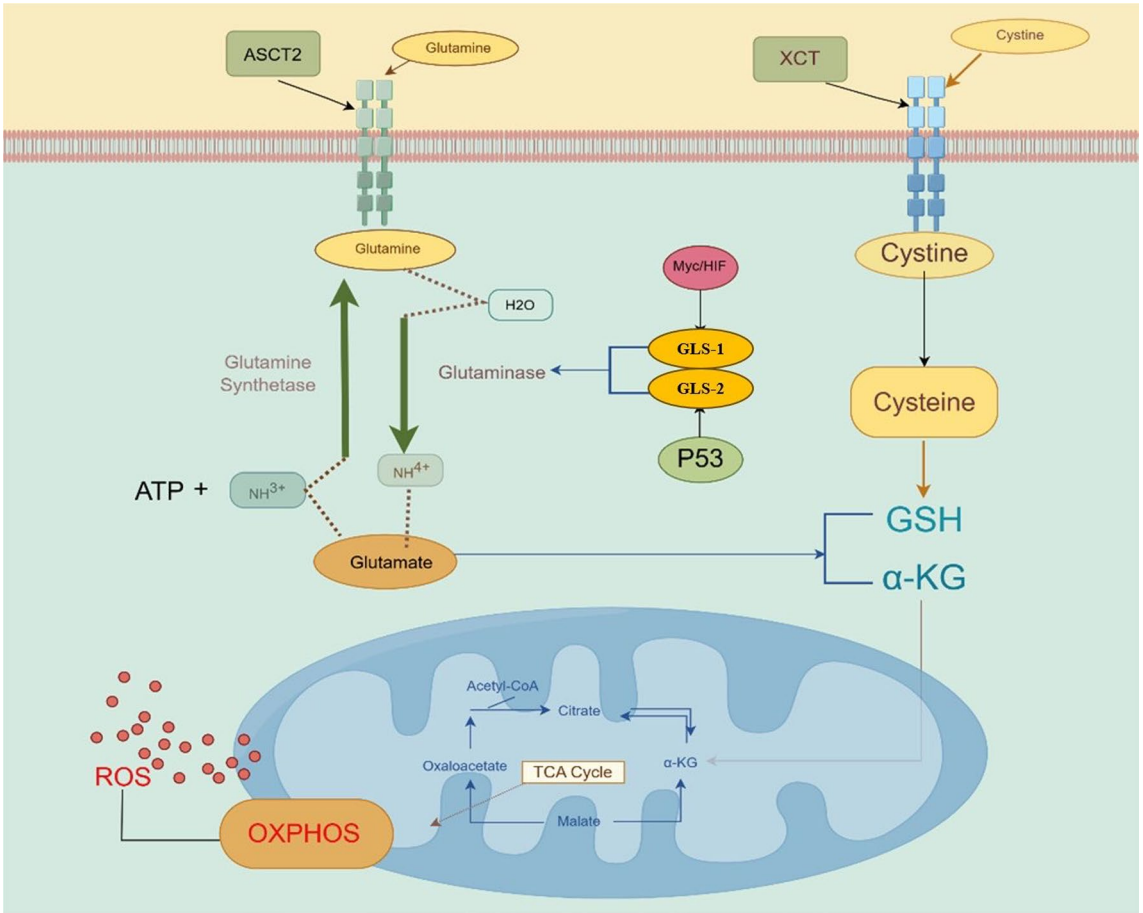

Fig. 2 Strategies for targeting glutamine metabolism in AML. L-asparaginase allows the hydrolysis of extracellular glutamine, impeding its synthesis and hydrolysis. Upon translocation to the cell, glutamine is transformed to glutamate by the two isoforms of glutaminase, GLS-1 and GLS-2. Glutamine is synthesized from glutamate and ammonia (NH_3) by glutamine synthetase. In this reaction, an ATP is consumed. The reverse reaction yields glutamate and ammonium ions (NH_4^+). Almost all cells in the body contain glutamine and ammonium ions, and express both glutamine synthetase and GLS. The predominant expression of one or the other of these enzymes will determine whether tissues are more likely to produce or consume glutamine. α-KG, α-ketoglutarate; ASCT2, alanine-serine-cysteine transporter protein 2; GLS, glutaminase; GSH, glutathione; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; TCA, tricarboxylic acid; XCT, cystine/glutamate transporter

6 Glutamine as a therapeutic strategy for leukemia

6.1 Acute myeloid leukemia

Reducing intracellular GLN levels in AML patients is one of the main strategies for AML treatment. The most important step in targeting GLN is the use of GLS to catalyze the deamination reaction of GLN to glutamate. Glutamate is further catabolized and metabolized to α-KG which feeds into the TCA cycle to provide energy. Therefore, glutaminase inhibitors are a popular antitumor strategy [54]. In particular, the renal-type GLS-1 form disrupts GLN-driven oxidative phosphorylation in AML cell lines, thereby preventing tumor growth and inducing apoptosis [55].

Blocking GLN metabolism with the GLS inhibitor CB-839 results in GSH depletion [56, 57]. In AML, where GSH acts as an antioxidant, a decrease in GSH leads to the accumulation of mitochondrial ROS and subsequent apoptosis [58, 59]. At the same time, the inhibitory effect of CB-839 makes AML cells more sensitive to adjuvants of the mitochondrial redox state, such as arsenic trioxide and hypertriglyceride [8]. Therefore, CB-839 applied together with the above adjuvants induces apoptosis in AML cells. In addition to inducing apoptosis in AML cells, CB-839 inhibits also the mTOR signaling pathway [54]. In AML cells, GLN condenses with cysteine and glycine to produce GSH, which maintains redox homeostasis, prevents ROS-induced damage, and provides a nitrogen source for DNA replication [55, 60]. In addition, many AML gene mutations have been shown to be associated with a number of mutations. In addition, many AML gene mutants are specific for GLN metabolism. For example, the glutaminase inhibitor BPTES was able to target and inhibit the unique metabolic profile of primary AML cells with IDH mutations (i.e., glutamine addiction), which in turn slowed the growth of primary AML cells with mutant IDH [49]. The fact that there is a unique selective inhibitory effect of interfering with glutamine metabolism on AML cells with IDH mutations is demonstrated. Other than this, aberrant expression of the FMS-like tyrosine kinase 3 (FLT3) gene in AML also leads to disorders of glutamate metabolism [61]. Approximately 25–30% of AML cases show hyperactivation due to mutations in tandem duplications within genes (FLT3–ITD) or in the structural domain of tyrosine kinase (FLT3–TKD) [62]. The FLT3 inhibitor AC220 (also known as Quizartinib) decreases GLN uptake and GSH production in AML cells, while increasing sensitivity to oxidative stress [63]. In addition, GLN is also used as a parenteral nutrient to assist in the treatment of AML. In a randomized, double-blind, controlled study including 45 adult AML patients and 127 cycles of chemotherapy, GLN improved the clinical course of patients after bone marrow transplantation and parenteral nutrition [64]. If in AML, the degree of GLN dependence of AML cells with specific gene mutations (e.g. IDH mutations and FLT3 mutations) is investigated. It is possible to assist in the diagnosis of such subtypes of AML with specific gene mutations by detecting GLN-related metabolic markers.

At present, the specific quantitative indicators and the exact extent of GLN dependence in AML subtypes with specific genetic mutations need to be investigated in further studies. In general, however, this dependence may be manifested by an increased rate of cellular uptake and utilization of GLN, increased activity of enzymes involved in intracellular GLN metabolism, and a more critical role of the GLN pathway in maintaining cell survival, proliferation, and energy supply. In conclusion, GLN is essential for the treatment of leukemia and is an effective therapeutic strategy. It is also important in medical research as a nutrient to support cell growth and repair, and as a potential antitumor agent for the treatment of leukemia.

6.2 Chronic lymphocytic leukemia

The 13q deletion is the most common cytogenetic mutation in CLL. Bruton's tyrosine kinase and B-cell lymphoma-2 inhibitors are widely used in the clinic for the treatment of CLL; however, CLL cells have developed resistance to these drugs. CB-839, a small-molecule GLS-1 inhibitor, decreases GLS-1 activity and inhibits CLL cell proliferation; however, the efficacy of CB-839 is limited in combination with conventional CLL drugs [65]. In addition, CLL lymphocytes in del11q-positive CLL cells exhibit altered glutamine metabolism [66]. Mitochondria in CLL have been reported to increase ROS production [67]. The role of GLN in preventing the overproduction of ROS underscores its importance in tumor growth and energy production [68].

6.3 Acute lymphoblastic leukemia

Acute lymphoblastic leukemia is a heterogeneous malignancy of immature B or T lymphoblastoid cells that is most prevalent in children [69, 70]. L-asparaginase (ASNase) is the first-line therapy for childhood ALL [71, 72], as well as adult ALL [73]. ASNase hydrolyzes GLN to produce glutamate and may be considered for patients with Notch1 ALL positivity [74]. The notch1 receptor is effective in the treatment of ALL. Notably, when GLN is secreted by adipocytes, its cytotoxicity towards ALL cells is blocked [75]. Therefore, targeting GLN and ASNase may also serve in the development of novel therapeutic agents [76, 77]. In addition, GLN nutritional therapy during chemotherapy can effectively improve and enhance the systemic nutritional status and immunity of pediatric patients with ALL [78]. Notably, there are genomic differences in relapsed ALL during treatment [79]. Among these differences, reduced dependence on GLN is an important cause of drug resistance in leukemia cells [80].

Mitochondria are one of the major sources of ROS production. Redox dysfunction plays a crucial role in leukemogenesis in ALL, and inhibition of ROS production via NADPH oxidases is a novel therapeutic tool for the treatment of ALL [81]. Many enzymes neutralize ROS, including superoxide dismutase, catalase, glutathione peroxidase (GPX), thioredoxin, peroxiredoxin, and glutathione transferase [82]. In addition, activating mutations in NOTCH1 are common in T-cell ALL, and inhibition of NOTCH1 signaling suppresses and promotes autophagy during GLN catabolism [83]. GLN metabolism regulates the expression of mitochondrial uncoupling protein 2 (UCP2) in T-cell ALL cell lines, and UCP2 is required for T-cell ALL proliferation [84]. A link between UCP2 and ROS production has been demonstrated [85]. Therefore, promoting GSH production by blocking GLN metabolism and indirectly preventing ROS production is a novel therapeutic strategy for ALL.

7 GLN causes cellular ferroptosis in an indirect way

In clinical settings, radiotherapy remains the mainstay treatment for leukemia, although GLN-targeting agents (e.g., CB-839) have been developed to indirectly induce ROS production [8]. It is well known that ROS production and lipid peroxidation is a key feature and an important step in iron death, and the generation of ROS promotes lipid peroxidation, which in turn triggers iron death. However, the mechanism of iron death involves a variety of factors, including antioxidant system factors, such as GSH and GPX4, which are important mechanisms of iron death [86, 87]; iron metabolism factors, such as Fe^{2+} which promotes the production of ROS through the Fenton reaction and so on, which in turn promotes lipid peroxidation [88]; lipid metabolism-related factors, such as lipoxygenase enzymes (LOXs), which can directly oxidize unsaturated fatty acids on biological membranes (PUFAs) and PUFA-containing lipids on biological membranes, which may induce iron death [87]; signaling pathway factors, such as cystathionine-glutamate transporter receptor (system Xc -), p53, and other pathways can regulate iron death. The mechanism underlying the role of GLN in leukemia remains unclear, and its use in clinical practice is relatively rare. Notably, p53-dependent activation of GLS-2 expression correlates with ROS, while elevated ROS levels lead to p53 stabilization and activation [89]. Sawako et al. demonstrated that GLS-2 reduces cellular sensitivity to ROS-related apoptosis [19]. Increased mitochondrial production of ROS and lipid peroxidation, along with decreased expression of GSH and GPX4, lead to ferroptosis [90, 91]. The accumulation of intracellular iron during ferroptosis is important in leukemic cells. GLN metabolism enhances ROS production in the TCA cycle [92–94]. GLN catabolism inhibits intracellular GSH depletion and subsequent ROS generation [49, 95], as well as affecting the TCA cycle [96]. The accumulation of lipid ROS can lead to ferroptosis [96]. Notably, GLS-2 is present on the cell surface of human neutrophils [97], which promotes lipid ROS production and enhances ferroptosis by catalyzing the generation of α-KG from glutamate [98, 99]. GLN increases α-KG levels and can activate amino acid sensor kinases, leading to formation of mTORC1 [100, 101], which then regulates ferroptosis sensitivity [102, 103]. In conclusion, increasing ROS levels through GLN metabolism promotes ferroptosis by blocking GSH synthesis (Fig. 3), which may provide new therapeutic guidelines for ferroptosis-based clinical treatment.

8 Discussion

GLN and its metabolites have significant antileukemic effects. Because of the close association between GLN and leukemia prognosis, we have summarized the latest developments on GLN and leukemia-related drugs or other studies by publication date (in no particular order), category, and content (Table 1).

There are multiple pathways involving GLN in leukemia, along with multiple factors that regulate and interfere with each pathway. GLN metabolic pathway: Supplies carbon for TCA cycle intermediates and nitrogen for nucleotide and amino acid biosynthesis, and plays an important role in hematopoietic tumors and hematologic neoplasms [116]; Bypass

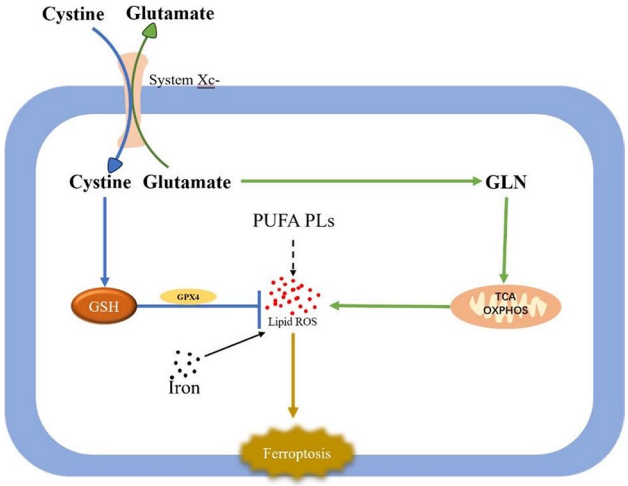

Fig. 3 Glutamine induces ferroptosis. α-KG, α-ketoglutarate; ASCT2, alanine-serine-cysteine transporter protein 2; GLS, glutaminase; GPX4, glutathione peroxidase 4; GSH, glutathione; OXPHOS, oxidative phosphorylation; PLs, phospholipids; PUFA, polyunsaturated fatty acids; ROS, reactive oxygen species; TCA, tricarboxylic acid; XCT, cystine/glutamate transporter

pathway: when leukemia cells are deprived of Gln, the serine pathway upregulates the key serine enzymes phosphoglycerate dehydrogenase (PHGDH) and phosphoribosyltransferase (PSAT), leading to an increased demand for serine and exacerbation of serine dependence in leukemia cells [117]; Lipid-related metabolism: AML cells are dependent on OXPHOS [118–120], AML cells obtain free fatty acids from bone marrow adipocytes and utilize fatty acid oxidation (FAO) and OXPHOS to maintain AML cell survival and growth [121–123]. However, OXPHOS-deficient cells accelerate the utilization of GLN, and GLN depletion promotes the accumulation of ROS [124]. We also note that targeting GLN and GLN metabolism (or parts of it) may have a limited impact on leukemia therapy. For example, ASCT2 is not the sole transporter for GLN [125]. This suggests that GLN influences the development and progression of leukemia. Therefore, future studies related to GLN should focus on the inhibition of multiple metabolic pathways for the effective treatment of leukemia.

Research on human leukemia therapy and GLN continues. The body's immune cells are also the focus of our interference with GLN, both in terms of the dependence of cancer cells on GLN and as a component of the TCA cycle. For example, immune cells use GLN to grow rapidly and gain immunity [126]. Reprogrammed GLN metabolism plays an important role in the antitumor immune response of immune cells, such as T cells, B cells, macrophages, and natural killer cells [127]. Parenteral GLN supplements may be relevant in the anti-tumor immune response, as they enhance neutrophil phagocytosis and maintain the nutritional status [128]. Inhibition of GLN metabolism can lead to immune escape for cancer cells, as observed with the GLN inhibitor V-9302 in human breast cancer cells [129]. Therefore, further experiments should be conducted to determine whether GLN inhibitors and related drugs disrupt the anticancer effects of immune cells in the bone marrow microenvironment during diagnosis and treatment. Targeting GLN metabolism in cancer cells without interfering with the immune response is a major challenge for future research.

Table 1 GLN and leukemia-related drug development and other sustainability studies

Published	Category	Drugs and other substances
2021	Glutamine uptake inhibitors	V-9302 [104, 105]
2019	Glutamine transporter	SLC38A1 [106]
2019	Glutamine uptake inhibitors	GPNA [106, 107]
2018	Asparaginase	Erwinaze [108]
2019–2023	Glutaminase inhibitors	CB-839 [65, 109, 110]
2019	Glutaminase antagonists	DON [111]
2019	Glutaminase antagonists	JHU-083 [112]
2021	Glutaminase inhibitors	Gilteritinib [109]
2021	Asparaginase	Pegcrisantaspase [113]
2019	Asparaginase	ASNase [114]
1982	Glutaminase inhibitors	L-glutamine antagonist [115]

Owing to the limitations of GLN-related drugs and inhibitors of GLN metabolism in clinical trials, they should be used with caution in clinical settings

9 Conclusion

Existing evidence points to the attractiveness of GLN as a new target for the treatment of leukemia. This strategy is already exemplified by CB-839 and V-9302, but includes also mTOR signaling and apoptosis in AML cells. Expression of an abnormal gene (FLT3) can cause GLN metabolic disorders. In addition, GLN plays an important role in CLL and ALL. The key enzyme in GLN metabolism is the GLS-2 isoform, which acts as a tumor suppressor. It activates and promotes hepatic glutamine catabolism and triggers the activation of mTORC1, a signal that also controls ferroptosis.

Inhibitors of GLN metabolism have also some limitations in the treatment of leukemia. First, a clear framework for clinical care has not been established, and there is a lack of additional empirical support for the use of GLN inhibitors to improve the prognosis of leukemia. More experimental studies are needed to provide better empirical data to improve the prognostic gap in GLN treatment of leukemia. Second, numerous studies have been conducted on AML, while relatively few have considered other types of leukemia (including, but not limited to, leukemia with rare genotypes and phenotypes). Such studies could determine whether the mechanism of action is the same in AML as in other types of leukemia.

In conclusion, available studies suggest that GLN is an attractive new strategy for the treatment of leukemia.

10 Future directions

The study of GLN in leukemia is in its preliminary stages, and its mechanism of action and clinical applications need further investigation. Future studies can focus on the following aspects: (1) the regulatory effect of GLN on various functional molecules in leukemia cells, (2) the regulatory mechanism of GLN on the relevant functional molecules in leukemia cells, (3) the application of GLN in leukemia treatment, (4) the effects of GLN on leukemia cell functions, such as cellular energy supply mechanisms, essential molecules, intracellular redox homeostasis mechanisms, and related signaling pathways for survival and proliferation, and (5) the effect of GLN on the prognosis of leukemia patients. The accrued knowledge will provide a new perspective for the effective clinical treatment of different types of leukemia.

Acknowledgements We thank Editage (www.editage.com) for their editing support on this manuscript.

Author contributions W.Z. wrote and structured the paper; W.Z. analyzed literature data and wrote the paper; Y.Q. and L.M. reviewed the literature; all authors have read and agreed to the published version of the manuscript.

Funding No funding was received to assist with the preparation of this manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Competing interests The authors declare no competing interests.

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