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Targeting Amino Acids to Treat AML

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Acute myeloid leukemia (AML), a life-threatening disease, is a malignant disorder of the bone marrow characterized by the clonal expansion and differentiation arrest of myeloid progenitor cells [1]. It is a highly heterogeneous disease and shows differential prognosis ranging from death within a few days of beginning treatment to complete remission. Systems biology approaches such as genomics and proteomics have already greatly facilitated the leukemia typing and prognosis stratification, which boosted the personalized medicine [2]. However, the actual clinical outcome of patients is not always inconsistent with the current AML-stratification system. Moreover, AML subtypes especially relapse or refractory AML. AML in the old and secondary AML are still hard to cure. Ongoing efforts were made to identify new biomarkers or drug targets which could promote individualized therapy and precision medicine [3-5]. Researchers have discovered that metabolic reprograming, an emerging hallmark, is closely related to the diagnosis, treatment and prognosis of AML patients [6-9], which also provide potential therapeutic target for drug discovery. It has been over half a century since Otto Warburg described increased aerobic glycolysis in cancer cells, which is termed the "Warburg Effect [10]". In recent years, the most well-studied field is glucose metabolism, the altered abundance of metabolites which demonstrate prognostic value in AML patients without cytogenetic abnormality [11-14]. Leukemia cells rely on glycolysis for energy supply and anabolic function. Fructose is also utilized by leukemia cells to compensate for glucose deficiency. Chen et al. observed an up-regulation of fructose transporter GLUT5 in the condition of low glucose [15,16], suggesting it a potential therapeutic target.

Currently, emerging evidence showed that the alterations of amino acids metabolism have been deeply involved in various tumor cells, including leukemia [7,17-19]. Researchers demonstrate that amino acids participate in synthesis and metabolism pathways in most of the cell activities. It has been proved some of the amino acids are taken up and fed in tricarboxylic acid (TCA) cycle to compensate for glucose metabolism deficiency [20]. A large number of researches have shown that targeting the amino acid metabolism which tumor cells depend on can effectively inhibit tumor growth. Metabolic starvation therapy is thus proposed as an interesting theory based on the metabolomics changes in AML [21]. Usually leukemia cells are more dependent on nutrients from outside microenvironment. This approach limits the uptake of a specific metabolite such as particular amino acid, aiming to disturb the proliferation of leukemia cells, which is likely to be a promising strategy due to the low toxicity to normal cells. In addition, amino acid metabolites change a lot when patients receive chemotherapies, and this alteration is often related to disease aggressiveness [22]. Quite a few amino acids have been studied for anti-leukemia treatment and some progress was achieved.

Essential Amino Acids

Essential amino acids (EAAs), defined as amino acids whose carbon skeletons are not synthesized *de novo* or insufficiently synthesized *de novo* by animal cells relative to metabolic needs, are obligatory demand by most tumor cells [23]. EAAs include lysine, tryptophan, phenylalanine, methionine, threonine and so on. Particularly, accumulated evidence demonstrates that as the most abundant of EAAs, branched chain amino acids (BCAAs) valine, leucine and isoleucine are not only raw materials providing carbon and nitrogen sources for protein synthesis or energy metabolism in maintaining the growth of cells including leukemia, they also play critical roles in regulating various biological processes involved in cancer via special signaling network, especially PI3K/AKT/mTOR signal pathway [24,25]. It is revealed that the accumulation of BCAAs promotes the development of tumors by enhancing the activity of mTORC1 [26]. BCAAs are transferred into cells by branched-chain amino transferase 1 (BCAT1). *BCAT1* gene is reported to be overexpressed in AML which has the

ability to predict the prognosis of patients. BCAT1 protein can activate the metabolism of BCAAs and promote the growth of cancer cells. On the other hand, blocking BCAT1 can promote the differentiation of rapidly changing cells, thus down regulating the growth of cancer cells in blood samples from people and mice with leukemia. It is suggested that the invasiveness of leukemia is reversed after blocking the BCAT1 pathway [27].

Methionine, an essential sulphur-containing amino acid, is involved in protein synthesis, regulation of protein function and methylation reactions. Metabolomics profiling identified altered methionine abundance in AML patients compared with healthy donors [28]. It was found in previous studies that methionine had an effect to enhance the growth of cancer cells in a mouse cancer model [29]. It is demonstrated that perturbed methionine metabolism by methionine deprivation reduced overall cellular methylation potential and induced apoptosis in several leukemia cell lines [30]. Thus, targeting methionine is expected to become a powerful assistant in cancer treatment.

Lysine may regulate AML cells' survival by triggering redox metabolism reprogramming. It is reported that a large amount of lysine is taken up in yeast. NADPH is channeled into glutathione metabolism, which leads to increase of glutathione and decrease of reactive oxygen species [31]. The increased oxidant tolerance triggered by lysine also plays a protective role in high glucose-induced toxicity [32]. Until recently, there is rare study in this area. Recent work by Zhou et al. suggested lysine as a new candidate prognostic biomarker in patients with AML [28]. Aplenty of lysine is needed for cell proliferation, especially leukemia cells. Further research shows that the lysine transporter hCAT1 is highly expressed in bone marrow mononuclear cells in AML patients, suggesting a large demand for lysine. In addition, attenuated proliferation of leukemia cells is observed when cultured in medium lacking lysine. Thus, the reduction of lysine uptake has the potential to inhibit leukemia blasts survival.

Nonessential Amino Acids

Nonessential amino acids can be produced by normal cells. However, they are needed urgently in many tumor cells for proliferation and cell activity. Thus, targeting nonessential amino acids is promising in treating tumor cells while it has little influence in normal cells.

Glutamine is the most abundant amino acid in plasma. It is normally produced in cells by their own synthesis which however cannot meet the needs of rapid proliferation of tumor cells. As a result, it is necessary to utilize glutamine from the outside of cells through the membrane transporter or enhance the expression and activity of key metabolic enzymes in the glutamine metabolic pathway to maintain the needs of cell proliferation. The pleiotropic effects of glutamine in cell function include energy synthesis, macromolecular synthesis, mTOR activation and active oxygen balance.

Glutaminase (GLS) is the first enzyme in glutamine metabolism, which is responsible for the conversion of glutamine to glutamate. The expression of GLS is increased in several AML cell lines [33]. Targeting glutamine metabolism as a treatment strategy shows encouraging progress. CB-839, a glutaminase inhibitor, blocks glutamine metabolism and shows anti-leukemic activity by decreasing glutathione production and increasing the level of reactive oxygen species and apoptosis [34]. CB-839 combined with other drugs is proved to effectively erase AML or ALL cells *in vitro* and *in vivo*. FLT3 tyrosine kinase inhibitors (TKI) have been used in treating AML patients with FLT3 internal tandem duplication (FLT3-ITD) and achieved promising results. However, some patients become resistant to this therapy because of metabolic adaptation. Leukemia cells utilize glutamine to support TCA cycle in response to reduced glucose uptake and glycolysis caused by TKI treatment. Researchers indicate the depletion of GLS is a strong synthetic lethal effect in FLT3-ITD AML receiving TKI treatment [35].

Besides targeting GLS, researchers also attempt to block glutamine metabolism by directly inhibiting the glutamine uptake. Previous studies have shown that glutamine depletion caused by SLC38A1 or SLC1A5 knockdown reduce the proliferation of various cancer cells [36-38]. The high expression level of SLC38A1, the glutamine transporter, is associated with a shorter overall survival in AML patients [39].

It is reported that cancer cells are also addicted to serine, and serine biosynthesis enzyme is overexpressed in various types of cancer [40-42]. Recently, it was reported that removing serine and glycine from the diet of mice can slow down the development of lymphoma and colorectal cancer [43]. In many cases, extracellular serine alone is enough to support the proliferation of cancer cells, while some cancer cells will increase the synthesis of serine in glucose, and even in the presence of a large amount of extracellular serine, it is necessary to synthesize serine from scratch. The change of serine biosynthesis pathway (SSP) is a common phenomenon in cancer cells. Phosphoglycerate dehydrogenase (PHGDH) regulates serine production. The expression of PHGDH in triple-negative breast cancer and melanoma cells increased significantly, and inhibition of PHGDH expression can lead to a significant decrease in the proliferation rate of tumor cells [44,45]. To find inhibitors of key enzymes in serine metabolism is a new direction of cancer treatment. Exogenous serine is transformed into glycine by serine hydroxy methyltransferase, which provides a carbon unit to participate in a carbon cycle for nucleotide biosynthesis.

Arginine plays an important role in tumor microenvironment. The abundance of arginine directly

impacts the survival capacity of T cells. It is demonstrated that increased L-arginine enhances anti-tumor activity of T cells through regulating several metabolic pathways [46]. Aberrant arginine metabolism is often reported in leukemia cells. Arginine is consumed by AML blasts through arginase II and iNOS, which is accompanied with T cell dysfunction [47]. Inhibition of arginine metabolism helps to restore T cell function and this phenomenon suggests targeting arginine metabolism may enhance T cells immunotherapy responses [48,49]. Clinical trials (i.e. NCT02903914) are in progress aiming to determine the effects of arginase inhibitor CB-1158 in several kinds of tumors and has come out with encouraging results [50].

Leukemia stem cells (LSCs) play pivotal roles in AML as they have the ability of producing all the leukemia cells. Targeting LSCs is suggested to be a possible curative therapy for AML patients. However, traditional therapy does not have much effects on LSCs because of chemoresistance. Inhibition of amino acids metabolism shows encouraging potential in eradicating LSCs which has been discussed in several articles [51,52]. As BCL-2 inhibitor, venetoclax alone or in combination with other common chemotherapies shows encouraging effects in treating elderly AML patients. The mechanism involves perturbing amino acids metabolism which causes down-regulation of LSCs [53,54].

BCAT1 is also overexpressed in the leukemia cell group which is rich in LSCs. BCAT1 supports LSCs survival via providing BCAAs. It has been pointed out that the overexpression of BCAT1 also plays an important role in the pathogenesis of chronic myeloid leukemia. PPM1K, a rate limiting enzyme for the degradation of BCAAs, is reported to accelerate the development of leukemia. Knockout of PPM1K results in dysfunction of hematopoietic stem cells through accumulation of BCAAs in the cytoplasm [55].

It is reported that leukemia stem cells (LSCs) may rely on cysteine metabolism for survival. Glutathione is synthesized from glutamine, cysteine/cystine, and glycine. Blocking any of these amino acids results in inhibition of glutathione anabolism and subsequently increasing of oxidative stress [56]. The depletion of cysteine results in impaired glutathione and inhibition of electron transport complex II, which blocks energy supply to LSCs. The application of cysteine-degrading enzyme selectively eliminates LSCs but not normal hematopoietic stem/progenitor cells, indicating cysteine to be a potential therapeutic target [57,58].

Overall, targeting amino acids shows broad application prospects. Up to date, some anti-leukemic drugs targeting amino acid metabolism have been developed and are under clinical trials (Table 1). It is indicated that metabolic starvation therapy may become an important part in assisting AML treatment.

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Identifier	Start date	Status	Drug	Target	Disease	Phase
NCT01251809	2010	Terminated	PEG-rASNase	Asparagine	ALL	1,2
NCT02875093	2016	Terminated	ADI-PEG 20	Arginine	AML	1
NCT03267030	2017	Recruiting	GRASPA	Asparagine	ALL	2
NCT02071927	2017	Completed	CB-839	Glutamine	AML, ALL	1
NCT03641794	2018	Recruiting	DN1406131	Tryptophan	Advanced solid tumors	1
NCT03455140	2018	Recruiting	PEG-BCT-100	Arginine	Pediatric AML/ALL	1,2
NCT03435250	2018	Recruiting	AG-270	Methionine	Lymphoma	1
NCT03792750	2019	Active, not recruiting	BMS-986205	Tryptophan	Advanced cancer	1,2

Table 1: Recent clinical trials on drugs targeting amino acid metabolism.

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