Targeting Amino Acids to Treat AML

Xuan Zhou, Bei Cao, Juan Li

Phase I Clinical Trials Unit, the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, 210008, China

*Correspondence should be addressed to Bei Cao; cb_cpu@163.com; Juan Li; juanli2003@163.com

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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 reprogramming, 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
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 methyl transferase, 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

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

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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.

**References**

1. De Kouchkovsky I, Abdul-Hay M. ‘Acute myeloid leukemia: a comprehensive review and 2016 update’. Blood Cancer J 2016;6:e441.

2. Estey EH. Acute myeloid leukemia: 2019 update on risk-stratification and management. Am J Hematol 2018;93:1267-91.

3. Li W, Zhong C, Jiao J, Li P, Cui B, Ji C, et al. Characterization of hsa_circ_0004277 as a New Biomarker for Acute Myeloid Leukemia via Circular RNA Profile and Bioinformatics Analysis. Int J Mol Sci 2017;18.

4. Yang X, Yao R, Wang H. Update of ALDH as a Potential Biomarker and Therapeutic Target for AML. Biomed Res Int 2018;2018:9192104.

| 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     |
| NCT03267903 | 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.
5. Rashed WM, Hammad AM, Saad AM, Shohdy KS. MicroRNA as a diagnostic biomarker in childhood acute lymphoblastic leukemia; systematic review, meta-analysis and recommendations. Crit Rev Oncol Hematol 2019;136:70-8.

6. Wang Y, Zhang L, Chen W-L, Wang J-H, Li N, Li J-M, et al. Rapid diagnosis and prognosis of de novo acute myeloid leukemia by serum metabolicomic analysis. J Proteome Res 2013;12:4393-401.

7. Musharraf SG, Siddiqui AJ, Shamsi T, Naz A. SERUM metabolomics of acute lymphoblastic leukemia and acute myeloid leukemia for probing biomarker molecules. Hematol Oncol 2017;35:769-77.

8. Liu Z, Zhou T, Han X, Lang T, Liu S, Zhang P, et al. Mathematical models of amino acid panel for assisting diagnosis of children acute leukemia. J Transl Med 2019;17:38-.

9. You X, Jiang W, Lu W, Zhang H, Yu T, Tian J, et al. Metabolic reprogramming and redox adaptation in sorafenib-resistant leukemia cells: detected by untargeted metabolomics and stable isotope tracing analysis. Cancer Commun (Lond) 2019;39:17.

10. Warburg O. On the origin of cancer cells. Science 1956;123:309-14.

11. Chen W-L, Wang J-H, Zhao A-H, Xu X, Wang Y-H, Chen T-L, et al. A distinct glucose metabolism signature of acute myeloid leukemia with prognostic value. Blood 2014;124:1645-54.

12. Song K, Li M, Xu X, Xuan LI, Huang G, Liu Q. Resistance to chemotherapy is associated with altered glucose metabolism in acute myeloid leukemia. Oncol Lett 2016;12:334-42.

13. Sun LY, Li XJ, Sun YM, Huang W, Fang K, Han C, et al. LncRNA ANRIL regulates AML development through modulating the glucose metabolism pathway of AdipoR1/AMPK/SIRT1. Mol Cancer 2018;17:127.

14. Poulain L, Sujobert P, Zylbersztejn F, Barreau S, Stuani L, Lambert M, et al. High mTORC1 activity drives glycolysis addiction and sensitivity to 6GPD inhibition in acute myeloid leukemia cells. Leukemia 2017;31:2326-35.

15. Cairns RA, Mak TW. An Alternative Sugar Fuels AML. Cancer Cell 2016;30:660-2.

16. Chen WL, Wang YY, Zhao A, Xia L, Xie G, Su M, et al. Enhanced Fruuctose Utilization Mediated by SLC2A5 is a Unique Metabolic Feature of Acute Myeloid Leukemia with Therapeutic Potential. Cancer Cell 2016;30:779-91.

17. More TH, RoyChoudhury S, Christie J, Taunk K, Mane A, Santra MK, et al. Metabolomic alterations in invasive ductal carcinoma of breast: A comprehensive metabolomic study using tissue and serum samples. Oncotarget 2017;9:2678-96.

18. Karlíková R, Široká J, Friedecký D, Faber E, Hrdá M, Mičová K, et al. Metabolite Profiling of the Plasma and Leukocytes of Chronic Myeloid Leukemia Patients. J Proteome Res 2016;15:358-66.

19. Callejón-Leblic B, García-Barrera T, Pereira-Vega A, Gómez-Ariza JL. Metabolic study of serum, urine and bronchoalveolar lavage fluid based on gas chromatography mass spectrometry to delve into the pathology of lung cancer. J Pharm Biomed Anal 2019;163:122-9.

20. Kreitz J, Schönfeld C, Seibert M, Stolp V, Alshamleh I, Oellerich T, et al. Metabolic Plasticity of Acute Myeloid Leukemia. Cells 2019;8.

21. Geck RC, Toker A. Nonessential amino acid metabolism in breast cancer. Adv Biol Regul 2016;62:11-7.

22. Grønningsæter IS, Fredly HK, Gjertsen BT, Hatfield KJ, Bruserud Ø. Systemic Metabolomic Profiling of Acute Myeloid Leukemia Patients before and During Disease-Stabilizing Treatment Based on All-Trans Retinoic Acid, Valproic Acid, and Low-Dose Chemotherapy. Cells 2019;8.

23. Lopez MJ, Mohiuddin SS. Biochemistry, Essential Amino Acids; StatPearls. Treasure Island (FL), StatPearls Publishing Copyright © 2020, StatPearls Publishing LLC., 2020.

24. Yamamoto K, Tsuchisaka A, Yukawa H. Branched-Chain Amino Acids. Adv Biochem Eng Biotechnol 2017;159:103-28.

25. Nie C, He T, Zhang W, Zhang G, Ma X. Branched Chain Amino Acids: Beyond Nutrition Metabolism. Int J Mol Sci 2018;19.

26. Ericksen RE, Lim SL, McDonnell E, Shuen WH, Vadiveloo M, White PJ, et al. Loss of BCAA Catabolism during Carcinogenesis Enhances mTORC1 Activity and Promotes Tumor Development and Progression. Cell Metab 2019;29:1151-65.e6.

27. Hattori A, Tsunoda M, Konuma T, Kobayashi M, Nagy T, Glushka J, et al. Cancer progression by reprogrammed BCAA metabolism in myeloid leukaemia. Nature 2017;545:500-4.

28. Zhou X, Zheng M, Wang Q, Aa J, Cao B, Li J. Metabolomics analysis identifies lysine and taurine as candidate prognostic biomarkers for AML-M2 patients. Int J Hematol 2020;111:761-70.

29. Gao X, Sanderson SM, Dai Z, Reid MA, Cooper DE, Lu M, et al. Dietary methionine influences therapy in mouse
cancer models and alters human metabolism. Nature 2019;572:397-401.

30. Barve A, Vega A, Shah PP, Ghare S, Casson L, Wunderlich M, et al. Perturbation of Methionine/S-adenosylmethionine Metabolism as a Novel Vulnerability in MLL Rearranged Leukemia. Cells 2019;8.

31. Olin-Sandoval V, Yu JSL, Miller-Fleming L, Alam MT, Kamrad S, Correira-Melo C, et al. Lysine harvesting is an antioxidant strategy and triggers underground polyamine metabolism. Nature 2019;572:249-53.

32. Ebrahimi SM, Batheia SZ, Faridi N, Taghikhani M, Nakhjavani M, Faghizadeh S. L-lysine protects C2C12 myotubes and 3T3-L1 adipocytes against high glucose damages and stresses. PLoS One 2019;14:e0225912.

33. Matre P, Velez J, Jacamo R, Qi Y, Su X, Cai T, et al. Inhibiting glutaminase in acute myeloid leukemia: metabolic dependency of selected AML subtypes. Oncotarget 2016;7:7972-35.

34. Gregory MA, Nemkov T, Park HJ, Zaberezhnyy V, Gehrke S, Adane B, et al. Targeting Glutamine Metabolism and Redox State for Leukemia Therapy. Clin Cancer Res 2019;25:4079-90.

35. Gallipoli P, Giotopoulos G, Tzelepis K, Costa ASH, Vohra S, Medina-Perez P, et al. Glutaminolysis is a metabolic dependency in FLT3(ITD) acute myeloid leukemia unmasked by FLT3 tyrosine kinase inhibition. Blood 2018;131:1639-53.

36. Zhou FF, Xie W, Chen SQ, Wang XK, Liu Q, Pan XK, et al. SLC38A1 promotes proliferation and migration of human colorectal cancer cells. J Huazhong Univ Sci Technolog Med Sci 2017;37:30-6.

37. Xie J, Chen Z, Liu L, Li P, Zhu X, Gao H, et al. shRNA-mediated Slc38a1 silencing inhibits migration, but not invasiveness of human pancreatic cancer cells. Chin J Cancer Res 2013;25:514-9.

38. Ni F, Yu W-M, Li Z, Graham DK, Jin L, Kang S, et al. Critical role of ASCT2-mediated amino acid metabolism in promoting leukaemia development and progression. Nature metabolism 2019;1:390-403.

39. Li Y, Shao H, Da Z, Pan J, Fu B. High expression of SLC38A1 predicts poor prognosis in patients with de novo acute myeloid leukemia. J Cell Physiol 2019;234:20322-8.

40. Frezza C. Cancer metabolism: Addicted to serine. Nat Chem Biol 2016;12:389-90.

41. Mattaini KR, Sullivan MR, Vander Heiden MG. The importance of serine metabolism in cancer. J Cell Biol 2016;214:249-57.

42. Newman AC, Maddocks ODK. Serine and Functional Metabolites in Cancer. Trends Cell Biol 2017;27:645-57.

43. Maddocks ODK, Athineos D, Cheung EC, Lee P, Zhang T, van den Broek NJF, et al. Modulating the therapeutic response of tumours to dietary serine and glycine starvation. Nature 2017;544:372-6.

44. Frezza C. Cancer metabolism: Addicted to serine. Nat Chem Biol 2016;12:389-90.

45. Pacold ME, Brimacombe KR, Chan SH, Rohde JM, Lewis CA, Swier LJ, et al. A PHGDH inhibitor reveals coordination of serine synthesis and one-carbon unit fate. Nat Chem Biol 2016;12:452-8.

46. Geiger R, Rieckmann JC, Wolf T, Basso C, Feng Y, Fuhrer T, et al. L-Arginine Modulates T Cell Metabolism and Enhances Survival and Anti-tumor Activity. Cell 2016;167:829-42.e13.

47. Mussai F, De Santo C, Abu-Dayyeh I, Booth S, Quek L, McEwen-Smith RM, et al. Acute myeloid leukemia creates an arginine-dependent immunosuppressive microenvironment. Blood 2013;122:749-58.

48. Mussai F, Wheat R, Sarrou E, Booth S, Stavrou V, Fultang L, et al. Targeting the arginine metabolic brake enhances immunotherapy for leukaemia. Int J Cancer 2019;145:2201-8.

49. Miret JJ, Kirschmeier P, Koyama S, Zhu M, Li YY, Naito Y, et al. Suppression of Myeloid Cell Arginase Activity leads to Therapeutic Response in a NSCLC Mouse Model by Activating Anti-Tumor Immunity. J Immunother Cancer 2019;7:32.

50. Steggerda SM, Bennett MK, Chen J, Emberley E, Huang T, Janes JR, et al. Inhibition of arginase by CB-1158 blocks myeloid cell-mediated immune suppression in the tumor microenvironment. J Immunother Cancer 2017;5:101.

51. Chapuis N, Poulain L, Birsen R, Tamburini J, Bouscary D. Rationale for Targeting Deregulated Metabolic Pathways as a Therapeutic Strategy in Acute Myeloid Leukemia. Front Oncol 2019;9:405.

52. Jones CL, Stevens BM, D’Alessandro A, Reisz JA, Culp-Hill R, Nemkov T, et al. Inhibition of Amino Acid Metabolism Selectively Targets Human Leukemia Stem Cells. Cancer Cell 2018;34:724-40.e4.

53. Guerra VA, DiNardo C, Konopleva M. Venetoclax-based therapies for acute myeloid leukemia. Best Pract Res Clin Haematol 2019;32:145-53.

54. Jordan CT. Can we selectively target AML stem cells? Best Pract Res Clin Haematol 2019;32:101100.

55. Liu X, Zhang F, Zhang Y, Li X, Chen C, Zhou M, et al. PPM1K Regulates Hematopoiesis and Leukemogenesis through CDC20-Mediated Ubiquitination of MEIS1 and
p21. Cell Rep 2018;23:1461-75.

56. Piya S, Mu H, Bhattacharya S, Lorenzi PL, Davis RE, McQueen T, et al. BETP degradation simultaneously targets acute myelogenous leukemia stem cells and the microenvironment. J Clin Invest 2019;129:1878-94.

57. Stuani L, Sarry JE. Help from outside: cysteine to survive in AML. Blood 2019;134:336-8.

58. Jones CL, Stevens BM, D’Alessandro A, Culp-Hill R, Reisz JA, Pei S, et al. Cysteine depletion targets leukemia stem cells through inhibition of electron transport complex II. Blood 2019;134:389-94.