haematologica
Journal of the Ferrata Storti Foundation

Overcoming metabolic plasticity and microenvironmental rescue when targeting SLC25A1 in acute myeloid leukemia. Comment on: "SLC25A1 reprograms mitochondrial and fatty acid metabolism to promote the progression of acute myeloid leukemia"

by Ruijie Li, Zhenghe Liu and Xuan Wu

Received: April 29, 2026.
Accepted: May 12, 2026.

Citation: Ruijie Li, Zhenghe Liu and Xuan Wu. Overcoming metabolic plasticity and microenvironmental rescue when targeting SLC25A1 in acute myeloid leukemia. Comment on: "SLC25A1 reprograms mitochondrial and fatty acid metabolism to promote the progression of acute myeloid leukemia". Haematologica. 2026 May 21. doi: 10.3324/haematol.2026.301161 [Epub ahead of print]

Overcoming metabolic plasticity and microenvironmental rescue when targeting SLC25A1 in acute myeloid leukemia. Comment on: "SLC25A1 reprograms mitochondrial and fatty acid metabolism to promote the progression of acute myeloid leukemia"

Ruijie Li, Zhenghe Liu, Xuan Wu [#]

Department of Medical Oncology, Henan Provincial Chest Hospital, Chest Hospital of Zhengzhou University, Zhengzhou, China

[#]**Correspondence to:** Xuan Wu, MD. Department of Medical Oncology, Henan Provincial Chest Hospital, Chest Hospital of Zhengzhou University, No. 1, Weiwu Street, Jinshui District, Zhengzhou 450008, Henan, China. E-mail: wuxuan@zzu.edu.cn.

Authors' contributions

Conception and design: X.W., Z.L. and R.L. Manuscript Writing: R.L. and X.W. Manuscript revision: Z.L. and R.L. Research supervision: R.L. All authors contributed to the article and approved the submitted version.

Disclosure

The authors declare no conflict of interest.

To the Editor,

We read with great interest the article by Chen et al. recently published in Haematologica, which elegantly demonstrates that the mitochondrial citrate transporter SLC25A1 is a key metabolic vulnerability in acute myeloid leukemia (AML) [1]. The authors developed a novel inhibitor, CTPI3, showing that blocking SLC25A1 disrupts de novo lipogenesis, induces mitochondrial dysfunction, and synergizes with venetoclax. While these findings present a compelling therapeutic strategy, translating metabolic inhibitors into the clinic requires addressing the profound metabolic plasticity of AML cells—particularly within the bone marrow microenvironment.

The central premise of targeting SLC25A1 rests on starving AML cells of cytosolic acetyl-CoA, thereby crippling endogenous fatty acid synthesis. However, AML stem cells predominantly reside in an adipocyte-rich bone marrow niche. Seminal work has shown that under metabolic stress or pharmacological blockade of lipid synthesis, leukemic cells rapidly adapt by upregulating fatty acid transporters such as CD36 and FABP4, scavenging exogenous free fatty acids directly from surrounding adipocytes[2, 3]. This extrinsic lipid uptake can fully bypass the requirement for de novo lipogenesis. The authors' experiments were conducted in standard lipid-restricted culture media; whether CTPI3 retains efficacy in lipid-replete conditions—or in the presence of adipocyte-derived lipids—remains an open question. Evaluating CTPI3 in adipocyte-conditioned media or in combination with CD36 blockade would clarify whether microenvironmental lipid salvage represents a clinically relevant escape route.

Equally important is the proposed synergy with venetoclax. The authors suggest CTPI3 as a

strategy for venetoclax-resistant patients, yet all experiments were performed in venetoclax-sensitive cell lines (Kasumi-1, THP1). Venetoclax resistance in AML is driven by compensatory upregulation of MCL-1 and a stringent reliance on fatty acid oxidation (FAO) [4, 5]. While CTPI3 impairs overall fatty acid metabolism, it remains unknown whether this inhibition can overcome the specific metabolic rewiring of venetoclax-resistant cells. Validation in bona fide venetoclax-resistant patient-derived xenograft (PDX) models is necessary before claiming efficacy in the relapsed/refractory setting.

Finally, a note of caution regarding systemic toxicity is warranted. Germline Slc25a1 knockout in mice results in perinatal lethality with severe cardiac malformations, and haploinsufficiency causes congenital heart defects within the 22q11.2 deletion syndrome spectrum[6, 7]. The short-term organ histology presented by the authors is reassuring but insufficient to exclude cardiac or developmental toxicity with prolonged dosing. The translational history of mitochondrial inhibitors—including the clinical failures of CPI-613 and IACS-010759 due to dose-limiting neurotoxicity—underscores the narrow therapeutic index of systemic metabolic blockade [8].

In summary, CTPI3 represents an exciting chemical probe and a promising lead compound. Addressing the potential for microenvironmental lipid scavenging to bypass SLC25A1 inhibition, validating efficacy in venetoclax-resistant models, and conducting rigorous long-term toxicology will be essential steps toward realizing the therapeutic promise of this target.

References

1. Chen M, Li W, Tao Y, et al. SLC25A1 reprograms mitochondrial and fatty acid metabolism to promote the progression of acute myeloid leukemia. Haematologica. 2026;111(4):1220-1234.

2. Ye H, Adane B, Khan N, et al. Leukemic Stem Cells Evade Chemotherapy by Metabolic Adaptation to an Adipose Tissue Niche. Cell Stem Cell. 2016;19(1):23-37.

3. Stevens BM, Jones CL, Pollyea DA, et al. Fatty acid metabolism underlies venetoclax resistance in acute myeloid leukemia stem cells. Nat Cancer. 2020;1(12):1176-1187.

4. Pollyea DA, Stevens BM, Jones CL, et al. Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in patients with acute myeloid leukemia. Nat Med. 2018;24(12):1859-1866.

5. Guièze R, Liu VM, Rosebrock D, et al. Mitochondrial Reprogramming Underlies Resistance to BCL-2 Inhibition in Lymphoid Malignancies. Cancer Cell. 2019;36(4):369-84.e13.

6. Kasprzyk-Pawelec A, Tan M, Rahhal R, et al. Inactivation of the SLC25A1 gene during embryogenesis induces a unique senescence program controlled by p53. Cell Death Differ. 2025;32(5):818-836.

7. Ohanele C, Peoples JN, Karlstaedt A, et al. The mitochondrial citrate carrier SLC25A1 regulates metabolic reprogramming and morphogenesis in the developing heart. Commun Biol. 2024;7(1):1422.

8. Molina JR, Sun Y, Protopopova M, et al. An inhibitor of oxidative phosphorylation exploits cancer vulnerability. Nat Med. 2018;24(7):1036-1046.