EDITORIAL

Gatekeepers of mitochondrial metabolism: the emerging role of the SLC25 family in leukemia

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In the current issue, Chen *et al.*[1] provide important new insights into the role of Solute Carrier Family 25 Member A1 (SLC25A1) in acute myeloid leukemia (AML). SLC25A1 is a mitochondrial transporter that exports citrate into the cytoplasm, directing the partitioning of this key metabolite between the mitochondrial tricarboxylic acid (TCA) cycle and cytoplasmic processes including lipogenesis and protein acetylation.[2] The authors show that SLC25A1 expression is upregulated in AML cells and that its knockdown (KD) or pharmacological inhibition impair mitochondrial function and reduce leukemic cell proliferation. They further establish the therapeutic potential of SLC25A1 inhibition by demonstrating that CTPI-3, a novel SLC25A1 inhibitor, effectively targets primary AML cells in murine models and acts synergistically with venetoclax.

AML is an aggressive malignancy with a high relapse rates and poor overall survival. Recent advances have highlighted the complex metabolic landscape of AML, where both glycolysis and oxidative phosphorylation (OXPHOS) play critical roles in supporting leukemic cell survival and proliferation. While bulk AML cells often rely on aerobic glycolysis to meet their metabolic needs, leukemia stem cells (LSC) exhibit a distinct metabolic profile characterized by a greater dependence on mitochondrial respiration.[3] This reliance on OXPHOS is fueled by amino acid and fatty acid metabolism, uncovering unique vulnerabilities in LSC. The introduction of venetoclax, a BCL-2 inhibitor, has marked a major therapeutic breakthrough, particularly when combined with hypomethylating agents in older or unfit patients. BCL-2 was shown to regulate mitochondrial metabolism, independently of its anti-apoptotic activity, supporting OXPHOS metabolism specifically in LSC. It preferentially targets LSC by inhibiting amino acid-driven OXPHOS, leading to bioenergetic collapse.[4] However, resistance to venetoclax frequently emerges and is increasingly recognized to involve adaptive rewiring of mitochondrial metabolism. Bypass pathways that restore OXPHOS, such as increased reliance on fatty acid oxidation, upregulation of electron transport chain components, or metabolic plasticity via alternative substrates, enable leukemic cells to evade venetoclax-induced cell death.[5] A better understanding of the key mediators of dysregulated mitochondrial function in leukemia cells can therefore identify novel targets to overcome resistance to venetoclax.

In this context, members of the SLC25 mitochondrial carrier family have gained attention as critical modulators of mitochondrial metabolism and metabolic plasticity, positioning them as promising therapeutic targets. The SLC25 family constitutes the largest group of solute carriers in humans, responsible for transporting a diverse range of substrates across the mitochondrial inner membrane, including fatty acids, amino acids, carboxylic acids, inorganic ions, and other metabolic products.

Abnormal expression and function of SLC25 family transporters are closely linked to tumor initiation and progression, with growing evidence implicating them in leukemia. SLC25A5 is overexpressed in several malignancies, including lung, ovarian, and neuroblastoma cancers, where it mediates ATP/ADP exchange across the mitochondrial inner membrane to sustain high proliferative demands and modulates oxidative stress responses, processes that are also critical for LSC survival. SLC25A12 exports aspartate to the cytosol, supporting nucleotide biosynthesis and redox homeostasis, its inhibition limits aspartate availability.

Beyond energy metabolism, SLC25 transporters regulate metabolites that serve as essential co-factors for chromatin-modifying enzymes, directly linking mitochondrial function to epigenetic regulation in leukemia. SLC25A26 imports S-adenosylmethionine (SAM) into mitochondria, driving mitochondrial DNA hypermethylation and altering mitochondrial gene expression, which can influence differentiation and survival pathways in AML. SLC25A21 modulates α-ketoglutarate (α-KG) availability, a co-factor for DNA and histone demethylases frequently perturbed in AML, possi-

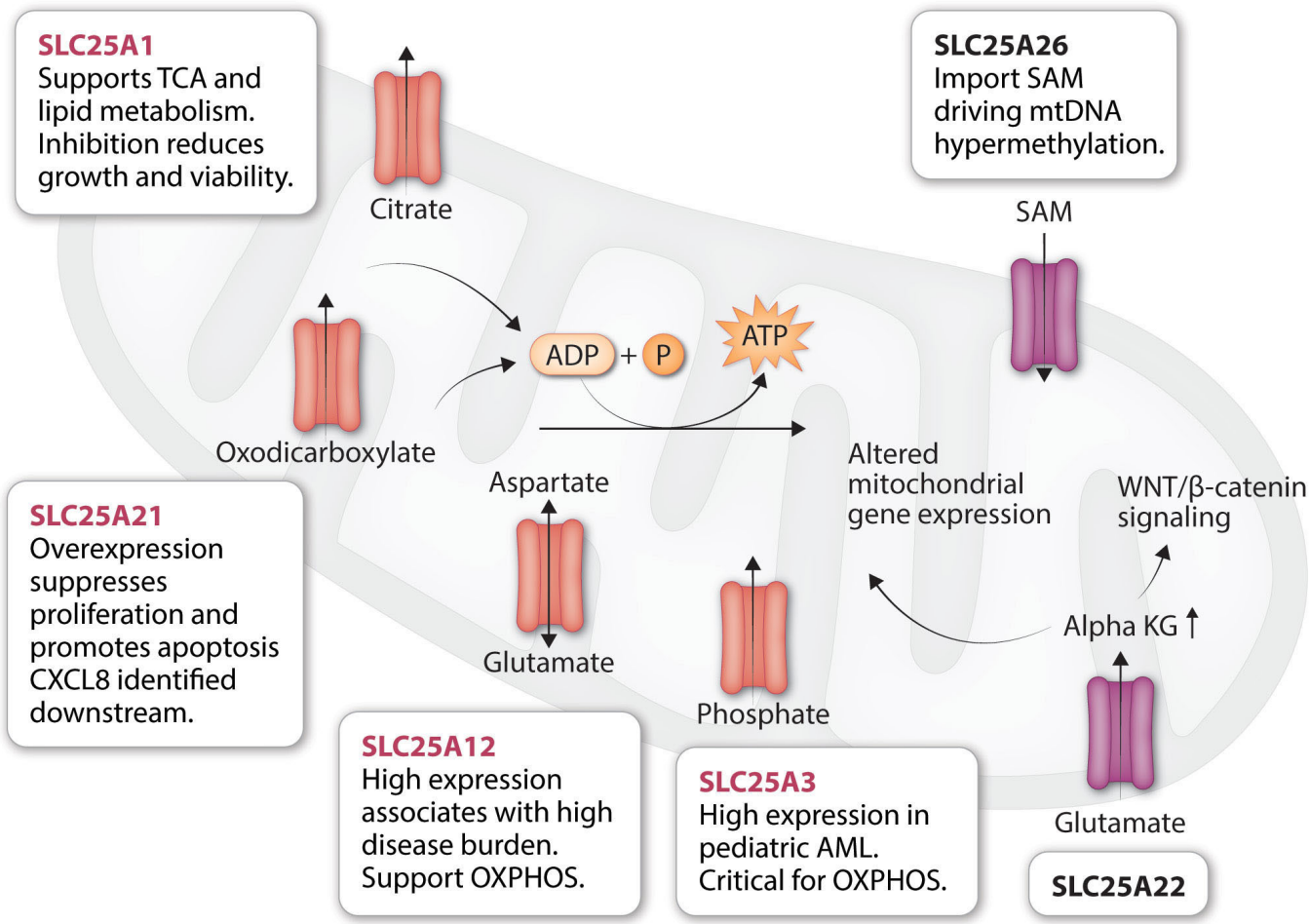

Figure 1. Mitochondrial SLC25 carriers with established and proposed roles in acute myeloid leukemia biology. Pink transporters indicate SLC25 family members with published evidence linking them to acute myeloid leukemia (AML) biology. Purple transporters represent suggested candidates with plausible roles in AML metabolism or signaling, proposed for future investigation. Functional consequences of transporter activity are annotated, including support of tricarboxylic acid (TCA) cycle and lipid metabolism, oxidative phosphorylation (OXPHOS), mitochondrial DNA (mtDNA) methylation, altered mitochondrial gene expression, and modulation of WNT/β-catenin signaling. SAM: S-adenosylmethionine; α-KG: α-ketoglutarate; ADP: adenosine diphosphate; ATP: adenosine triphosphate; P: phosphate; CXCL8: C-X-C motif chemokine ligand 8. Created by BioRender and modified by Somersault18:24 Studio BV.

bly contributing to aberrant methylation. SLC25A1 itself transports citrate to the cytoplasm, directly impacting the cytoplasmic acetyl-CoA pool available for protein (including histone) acetylation. SLC25 members can also impact oncogenic signaling. For instance, SLC25A22, although primarily studied in solid tumors, promotes α-KG accumulation activating WNT/β-catenin signaling, an axis with established relevance to leukemia stemness and treatment resistance.[6]

Several SLC members were studied in AML. SLC25A12 and SLC25A3, both support OXPHOS and were shown to be upregulated in AML.[7,8] Conversely, SLC25A21 (oxodicarboxylate carrier) is downregulated in AML, where low expression predicts poor prognosis. Restoring SLC25A21 restrains leukemic growth via mitochondrial apoptosis pathways and CXCL8 (C-X-C motif chemokine ligand 8) modulation.[9]

SLC25A1 was also shown to be upregulated in AML and linked to worse survival.[10] The current work by Chen *et al.* further adds to our understandings of the role of SLC25A1 in leukemia development. Silencing of SLC25A1 in AML models prolonged mouse survival, with lowered leukemic blast burden in bone marrow, spleen, and peripheral blood. The authors further demonstrated that both genetic silencing and pharmacologic inhibition of SLC25A1 caused mitochondrial structural damage, decreased mitochondrial membrane potential, and suppressed oxygen consumption rates. These mitochondrial defects were accompanied by elevated reactive oxygen species (ROS) levels, which contributed to AML cell death. Notably, SLC25A1 inhibition increased the sensitivity of AML cells to the BCL-2 inhibitor venetoclax, resulting in synergistic growth suppression, higher ROS accumulation, and enhanced apoptosis. Mechanistically, transcriptomic, metabolomic, and lipidomic analyses revealed that SLC25A1 KD downregulated key enzymes involved in fatty acid synthesis (ATP citrate lyase [ACLY], fatty acid synthase [FASN]) and oxidation (carnitine palmitoyltransferase [CPT] 1A and 1C), altered citrate and CoA levels, and reduced palmitic acid production.

Finally, through *in silico* screening and docking optimization, a novel and more potent SLC25A1 inhibitor, CTPI3, was identified. CTPI3 reduced AML cell viability, induced apoptosis, and extended survival in murine AML models. Consistent with the effects observed with SLC25A1 KD, CTPI3 decreased TCA cycle metabolites, impaired fatty acid metabolism, and demonstrated strong synergy with venetoclax, leading to

reduced proliferation, diminished ATP production, and decreased CPT1A/C expression.

In conclusion, the study by Chen *et al.*, together with prior research, underscores the critical role of SLC family mitochondrial carriers in leukemogenic processes, including metabolic reprogramming, epigenetic regulation, and key signal transduction pathways. As our understanding of these transporters deepens, selectively targeting specific SLC proteins, either as monotherapy or in combination with established treatments, may provide a valuable and complementary strategy to enhance current therapeutic approaches in AML.

Disclosures

BN has received consulting fees/honorarium from Medison, BMS and Abbvie. AH has no conflicts of interest to disclose.

Contributions

BN and AH wrote, reviewed and edited the manuscript. Both authors have read and agreed to the published version of the manuscript.

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