RESEARCH HIGHLIGHT

Niche-generated taurine is leukemic fuel

Christina Mayerhofer[1,2,3] and David T. Scadden[1,2,3]✉

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A new study by Sharma et al. shows that taurine supplied by osteolineage cells in the bone marrow niche, is hijacked by myeloid leukemia to fuel mTOR-driven glycolysis and resist BCL-2 inhibition. Inhibiting taurine uptake or synthesis in niche cells prevents leukemia progression supporting the idea of a niche-directed therapeutic approach.

The bone marrow niche consists of heterogeneous cell types required to support blood production.[1,2] Hematopoiesis is regulated to match physiological demands, yet sustained overproduction can enable clonal expansion that results in blood malignancies. Selective pressure of leukemia progression in turn alters bone marrow stromal cell populations. Defining these leukemia-driven changes may uncover stromal targets to improve clinical outcomes.

Using single-cell RNA sequencing of murine bone marrow, Sharma et al. [3] captured how non-hematopoietic stromal populations change from health to incipient, evolving and end-stage myeloid leukemia in non-conditioned recipients. Conditioning is relevant because many published studies use sub-lethal irradiation for improved leukemia engraftment, which perturbs niche cells. To build an interactome of the leukemic bone marrow niche, their stroma dataset was integrated with transcriptomic data of human leukemia stem cells (LSCs).[3] This interactome identified receptor–ligand pairs relevant to the maintenance of LSCs in the remodeled microenvironment. The authors found that osteoblast lineage cells expressing cysteine dioxygenase 1 (Cdo1), an enzyme driving taurine biosynthesis, expanded in leukemic animals.[3] Importantly, and confirming the data in mice, CDO1 expression increased in stroma cells of patients who progressed to secondary acute myeloid leukemia (AML), and those with AML relapse.[3] Conditional *Cdo1* deletion in osteolineage cells blunted leukemia expansion and prolonged mouse survival, directly linking a niche-contained metabolite to blood cancer progression[3] (Fig. 1).

The idea that bone marrow supplies myeloid cells with crucial molecules is intriguing given the high likelihood of bone marrow relapses of myeloid malignancies. This exchange can be in several forms. For example, direct transfer of processed tRNAs or eIF4a in extracellular vesicles or mitochondria via tunneling nanotubes from osteoblastic or other stromal cells to myeloid progenitors has been revealed[4–6] and metabolites like aspartate from stromal cells have been shown to support pyrimidine synthesis in chemoresistant leukemia cells.[7] These studies support the idea of coordinated leukemia–stroma interactions contributing to disease biology and potentially providing targetable vulnerabilities for leukemia therapy.

Sharma et al. substantially advanced that concept and provided a path forward for development. They conducted a CRISPR dropout screen in LSCs that identified SLC6A6 — better known as the taurine transporter (TAUT) — as a top dependency.[3] TAUT loss in AML LSCs impaired leukemogenesis in vivo, whereas non-malignant hematopoietic progenitors tolerated taurine deprivation.[3] It is striking that taurine, an atypical amino-sulfonic acid never incorporated into proteins, was found to be locally supplied by osteogenic stromal cells and serve as an exogenous driver of leukemia progression.

Molecular dissection placed taurine upstream of the RAG-GTPase-mTORC1 axis. When taurine import was inhibited by knocking out the transporter in AML, mTORC1 activity, glycolytic gene expression and glucose flux all dropped.[3] The work therefore positions taurine as an exogenous "on switch" that lets LSCs maintain rapid growth through mTOR activation and the resultant high-throughput, Warburg-like glycolysis needed for macromolecule generation. Venetoclax, a selective BCL-2 inhibitor, has reshaped AML therapy but faces resistance in monocytic or NRAS-mutant subclones.[8] Sharma et al. report that venetoclax-resistant clones express the highest TAUT levels.[3] Combining TAUT blockade with venetoclax decreased colony formation from primary patient samples and extended xenograft survival beyond either agent alone.[3] Mechanistically, taurine withdrawal dampened BCL-2 expression, providing a rationale for the synergy.[3]

This important study demonstrates metabolic cross-talk in the leukemic bone marrow niche by combining single-cell profiling, multi-omic analyses of leukemic blasts, and functional validation. Niche-driven metabolite addictions are established for asparagine in pediatric ALL (acute lymphoblastic leukemia) and some metabolites in solid tumors; the present work extends the concept to taurine, itself a metabolic modifier, in AML. Taurine, here seems to be serving as a trigger for enhancing anabolic activity through mTORC1 though as a sulfur-containing product of cysteine metabolism, it also has antioxidant effects and can alter mitochondrial gene translation.[9] It is widely consumed in supplements, meat, and energy drinks and linked to increased murine lifespan.[10] As taurine is a potentially targetable, exogenous dependency, blockade of taurine import and dietary restriction of

[1]Krantz Family Center for Cancer Research, Massachusetts General Hospital, Boston, MA, USA. [2]Harvard Stem Cell Institute, Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, USA. [3]Broad Institute of the Massachusetts Institute of Technology and Harvard University, Cambridge, MA, USA.
✉email: david_scadden@harvard.edu

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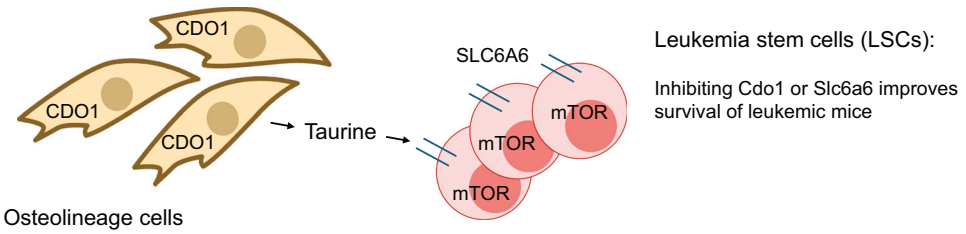

Fig. 1 Role of taurine in the leukemic bone marrow niche. Deletion of the taurine synthesis enzyme *Cdo1* in osteolineage cells or deletion of the taurine transporter *Slc6a6* slowed leukemia growth. Taurine activates mTOR in LSCs to drive glycolysis and cell growth.

taurine-rich products may be a testable addition to leukemia therapies.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to David T. Scadden.