Heme starvation triggers cuproptosis

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A recent study published in *Cell* by Lewis and colleagues reveals that acute myeloid leukemia depends on suppressed heme biosynthesis, creating a metabolic vulnerability that triggers copper-dependent cuproptosis. These findings redefine how mitochondrial dysfunction and copper homeostasis govern leukemic cell fate and point to new therapeutic opportunities.

Acute myeloid leukemia (AML) remains one of the most difficult hematologic cancers to treat, as relapse and resistance continue to limit durable remissions despite advances targeting the anti-apoptotic B-cell lymphoma 2 (BCL2) pathway or metabolic vulnerabilities driven by mutant isocitrate dehydrogenase 1 and 2 (IDH1/2)[1,2]. Yet the full metabolic architecture of AML is far from resolved. One area that has long been overlooked is heme biology. Although heme is essential for mitochondrial respiration, iron handling, and diverse signaling processes, it has rarely been viewed as a cancer dependency[3]. A central question has therefore persisted: do AML cells deliberately rewire heme biosynthesis to sustain leukemic self-renewal, and if so, could this create a metabolic vulnerability? A recent study by Lewis and colleagues in *Cell* shows that suppressed *de novo* heme biosynthesis is a recurrent feature of AML and establishes a metabolic state that sensitizes leukemic cells to cuproptosis, a mitochondrial copper-dependent form of cell death[4].

The authors first established that heme biosynthesis enzymes (HBEs) are broadly downregulated across mouse models, AML cell lines, and primary patient samples, leading to reduced intracellular heme levels[4]. This low-heme state is tightly linked to leukemic stem cell biology because heme deficiency stabilizes and activates the heme-sensing transcription factor BTB domain and CNC homolog 1 (BACH1)[5], which enforces stemness-associated transcriptional programs and represses differentiation (Fig. 1). As AML cells already operate near the threshold of heme insufficiency, further disruption of this pathway becomes uniquely lethal: inhibiting HBEs collapses mitochondrial complex IV, perturbs copper handling[4], and ultimately triggers cuproptosis — a form of cell death mechanistically distinct from apoptosis[6]. These findings identified heme biosynthesis as a selective vulnerability that connects metabolic, mitochondrial, and copper-regulatory networks in AML.

The research unfolds through a logical and tightly integrated experimental strategy. Using a reversible DNA methyltransferase 3 alpha (Dnmt3a)^{R882H} mouse model[7], the authors showed that acute removal of the oncogene leads to rapid induction of HBE transcription, implying that leukemic drivers actively repress heme biosynthesis. This observation is echoed across AML patient datasets, where HBE expression is consistently lower than in healthy marrow[4]. To determine whether these transcriptional patterns translate into metabolic changes, they quantified total heme and tested pathway flux using a 5-aminolevulinic acid pulse-chase assay in homeobox B8 (Hoxb8) progenitors engineered to express Dnmt3a^{R882H} or to lose the tumor suppressor RUNX family transcription factor 1 (Runx1). Both manipulations reduced heme synthesis, confirming that AML-associated mutations directly impair heme production[4].

The authors then turned to the mechanistic consequences of low heme on gene expression. Because heme binding destabilizes BACH1, reduced heme allows this factor to accumulate and bind chromatin more broadly. Sequencing analyses revealed BACH1 occupancy at genes governing differentiation, amino acid metabolism, and redox homeostasis. Metabolomics supported these findings by showing depletion of key amino acids, and functional assays revealed that heme-deficient cells become more sensitive to metabolic stresses, including iron overload triggered by ferroptosis inducers and mitochondrial inhibitors, with these effects reversed by hemin supplementation[4]. Although not the primary death pathway in this study, these responses underscore how low heme heightens metabolic vulnerability and primes cells for stress-sensitive states.

Having shown that low heme supports AML biology, the authors next asked whether AML cells require a minimal level of *de novo* heme synthesis for survival. Analyses from the Cancer Dependency Map identified HBE genes, particularly *uroporphyrinogen decarboxylase* (*UROD*) and *ferrochelatase* (*FECH*), as among the most AML-selective essential genes. CRISPR competition assays across multiple murine and human AML models confirmed that disrupting HBE genes severely impairs leukemic growth, especially in heme-low subtypes. Pharmacologic inhibition using succinylacetone or the FECH inhibitor *N*-methylprotoporphyrin recapitulated these effects, with hemin rescue confirming on-target action. Importantly, normal hematopoietic stem and progenitor cells are far less sensitive, highlighting a promising therapeutic window[4].

To determine how heme depletion kills AML cells, the authors performed a metabolism-focused CRISPR screen under heme-starved conditions[4]. The most significant resistance hit cluster in the lipoic-acid synthesis pathway, including lipoyl synthase (LIAS), lipoyltransferase 1 (LIPT1), LIPT2, and mitochondrial trans-2-enoyl-CoA reductase (MECR), mirroring known signatures of cuproptosis resistance[8]. Follow-up experiments validated that cells lacking these enzymes are protected from HBE inhibition but not from apoptosis, necroptosis, or ferroptosis. Additional evidence

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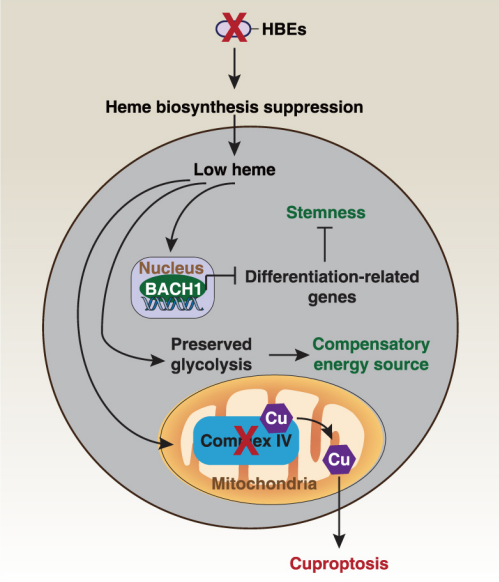

Fig. 1 Consequences of heme biosynthesis suppression on AML cell fate. Reduced activity of HBEs lowers intracellular heme, leading to stabilization of nuclear BACH1, repression of differentiation-associated genes, and reinforcement of leukemic stemness programs. Progressive heme depletion impairs assembly of mitochondrial complex IV, disrupts copper homeostasis, and promotes mitochondrial copper accumulation, culminating in cuproptosis. Despite early mitochondrial dysfunction, glycolytic flux remains preserved and may provide a compensatory energy source during heme starvation.

came from copper accumulation measured by inductively coupled plasma mass spectrometry and the oligomerization of lipoylated dihydrolipoamide S-acetyltransferase (DLAT), a biochemical hallmark of cuproptosis[8]. Together, these data show that heme starvation kills AML cells by triggering copper-dependent proteotoxic stress.

This mechanistic picture was completed by proteomics and mitochondrial assays showing that heme depletion disrupts mitochondrial complex IV assembly, diminishes cytochrome c oxidase (COX) activity, and alters copper chaperone for superoxide dismutase (CCS). Knockout of complex IV assembly factors produced similar copper dysregulation and sensitized cells to heme starvation, linking impaired mitochondrial respiration directly to cuproptosis initiation. The *in vitro* conclusions were strongly supported by *in vivo* experiments using an inducible knockout of *aminolevulinate dehydratase* (*ALAD*), which encodes the second enzyme in the *de novo* heme biosynthesis pathway, in human MV4-11 xenografts. Disrupting *ALAD* effectively blocked heme production in leukemic cells, and its deletion *in vivo* significantly delayed disease progression and prolongs survival[4].

The authors also reported that glycolytic flux remains largely preserved under heme depletion through unknown mechanisms, suggesting that glycolysis may act as a compensatory energy source during early mitochondrial dysfunction. Consistently, dual inhibition of heme biosynthesis and glycolysis produced synergistic effects in AML cells[4].

This study opens several avenues for future investigation. Although heme depletion clearly triggers cuproptosis, the biochemical steps linking complex IV collapse to copper accumulation remain unresolved, and defining how heme availability shapes copper import and buffering will be essential for rational combinations. Another question is why low heme heightens sensitivity to ferroptosis inducers, through altered iron handling, weakened antioxidant capacity, or broader metabolic stress, and how this cross-talk might be exploited[9,10]. Clinically viable inhibitors of heme biosynthesis enzymes are also needed, as current compounds have limited translational potential. Given AML's metabolic heterogeneity, HBE inhibition may synergize with agents targeting BCL2, IDH, or mitochondrial complex I, especially in heme-low subtypes[1]. Finally, because heme deficiency stabilizes BACH1 and reinforces stem cell-like programs, pairing HBE inhibition with differentiation- or stemness-targeting strategies may produce more durable responses.

Overall, this study reveals a hidden metabolic dependency in AML and establishes heme biosynthesis as a central node connecting mitochondrial function, copper homeostasis, and cell-fate regulation, representing a significant advance in our understanding of leukemia metabolism and cell death.

COMPETING INTERESTS

The authors declare no competing interests.

REFERENCES

1. Shimony, S., Stahl, M. & Stone, R.M. *Am. J. Hematol.* **100**, 860–891 (2025).
2. Kantarjian, H. et al. *Blood Cancer J.* **14**, 163 (2024).
3. Yien, Y.Y. & Perfetto, M. *Front. Cell Dev. Biol.* **10**, 895521 (2022).
4. Lewis, A.C. et al. *Cell* https://doi.org/10.1016/j.cell.2025.10.028 (2025).
5. Ogawa, K. et al. *EMBO J.* **20**, 2835–2843 (2001).
6. Tsvetkov, P. et al. *Science* **375**, 1254–1261 (2022).
7. Mohanty, S. & Heuser, M. *Cancers* **13**, 6192 (2021).
8. Tang, D., Kroemer, G. & Kang, R. *Nat. Rev. Clin. Oncol.* **21**, 370–388 (2024).
9. Chen, X., Kang, R., Kroemer, G. & Tang, D. *Nat. Rev. Clin. Oncol.* **18**, 280–296 (2021).
10. Dai, E. et al. *Nat. Cell Biol.* **26**, 1447–1457 (2024).

ADDITIONAL INFORMATION

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