

Targeting metabolic fragility: Heme biosynthesis inhibition as a new therapy in AML

Xintong Deng,¹ Lanxin Zhang,¹ Jianan Zheng,¹ Wanyue Zhou,¹ Chong Chen,^{1,2,*} and Yu Liu^{1,2,*}

¹Department of Hematology and Institute of Hematology, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, China

²State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, China

*Correspondence: yuliuscu@scu.edu.cn (Y.L.); chongchen@scu.edu.cn (C.C.)

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Altered metabolism is a well-recognized hallmark of cancer. Cancer cell–intrinsic metabolic reprogramming not only reshapes the supply of energy and biosynthetic building blocks to meet the demands of rapid proliferation, but also modulates the production of critical cofactors, which can impair the activities of cofactor-dependent enzymes and other proteins.

In normal hematopoiesis, heme acts as a key metabolic rheostat regulating hematopoietic stem and progenitor cell (HSPC) differentiation and mitochondrial fitness. Erythroid differentiation requires robust heme biosynthesis to support hemoglobin production, with disruptions in this pathway (from *ALAS2* to *FECH*) causing maturation arrest. Beyond hemoglobin, heme is essential for mitochondrial respiratory chain complexes and oxidative phosphorylation, supporting energy-intensive HSPC commitment. It also signals via transcription factors like BACH1 to fine-tune genes involved in mitochondrial function and globin synthesis, coupling metabolism to cell fate decisions (Figure 1).

As an iron–porphyrin cofactor, heme enables systemic oxygen transport and serves as a vital prosthetic group for myoglobin, cytochromes, and detoxifying enzymes. It underpins mitochondrial ATP production and contributes to amino acid metabolism and transcriptional regulation. Defects in heme biosynthesis disrupt cellular homeostasis, driving disease pathogenesis. Notably, emerging evidence links dysregulated heme metabolism to therapy resistance in hematological malignancies such as multiple myeloma.

For example, heme—an iron–porphyrin cofactor best known as the oxygen-binding prosthetic group of hemoglobin—binds oxygen reversibly in red blood cells (erythrocytes), enabling hemoglobin to load oxygen in the lungs and unload it in oxygen-poor tissues, thereby facilitating systemic oxygen transport. Besides, heme also serves as an indispensable cofactor for multiple other proteins like myoglobin, cytochromes, peroxidases, and catalases, etc. mediating crucial processes such as cellular metabolism and xenobiotic detoxification.¹ Moreover, as a central constituent of the mitochondrial cytochrome electron transport chain, heme directly underpins ATP production, the primary energy currency for cellular activities. Beyond these roles, heme significantly influences amino acid metabolism, xenobiotic biotransformation, and transcriptional regulation.² Consequently, disruptions in heme biosynthesis pathway can impair cellular and systemic physiological functions, leading to the pathogenesis of various disorders. Notably, emerging evidence implicates heme metabolism in therapy resistance in hematological malignancies such as multiple myeloma.

Lewis et al. recently elucidated a novel role for heme in acute myeloid leukemia (AML), as reported in *Cell*.³ Using a doxycycline-deinducible DNMT3A^{R882H} and constitutive IDH2^{R140Q} and NRAS^{G12D} (DIN)—three of the five most frequently mutated genes in human AML—mouse model, murine Hoxb8 cells, and Beat AML/TCGA patient cohorts, the study observed downregulated heme biosynthesis enzymes (HBEs) expression and reduced intracellular heme levels in AML. In contrast, these reduced HBE and heme phenotypes were absent in normal bone marrow cells and HSPCs. Further, AML cell lines exhibited a strong positive correlation between HBE expression and heme level, while ten of the 12 primary AML samples analyzed had reduced heme compared to normal bone marrow controls. Collectively, these findings demonstrate that reduced HBE expression and low heme levels are common features of AML, driven by key AML driver mutations such as DNMT3A^{R882H} and RUNX1 alterations. The study elucidates the molecular mechanism underlying the importance of heme levels in AML. On one hand, low heme levels maintain the malignant state of AML by regulating downstream gene

expression through the transcription factor BACH1. On the other hand, further inhibition of HBEs exerts anti-leukemic effects by triggering mitochondrial complex disassembly and cuproptosis. The group integrates multi-modal research approaches, including gene editing, systems biology, high-throughput screening, and artificial intelligence, to comprehensively evaluate the function and potential therapeutic value of heme and its synthesis pathway in AML.

First, using immortalized HSPCs expressing the AML-associated DNMT3A^{R882H} mutation, the group observed increased protein levels and chromatin binding of the transcription factor BACH1, which can bind with heme, and subsequently promotes its polyubiquitination and degradation. Heme binds BACH1, promoting its displacement from chromatin and degradation via the ubiquitin proteasome system. When HBEs were inhibited, BACH1 binding sites were enriched in the promoter regions of genes related to metabolism and cell fate. This was accompanied by the upregulation of stem cell signature genes and downregulation of differentiation-related genes. Furthermore, as heme is associated with intracellular ferrous ion concentration, its downregulation leads to ferrous ion accumulation. Lewis et al. further demonstrated that DNMT3A^{R882H} cells exhibited increased sensitivity to mitochondrial complex I inhibitors, ferroptosis inducers, and iron chelators. This sensitivity could be partially reversed by treatment with the exogenous heme analog hemin, suggesting that further inhibition of HBEs might have therapeutic potential. Analysis of AML patient data also supported that low HBE expression correlated with enrichment of stem cell signatures and inflammatory pathways, while high HBE expression was associated with high mitochondrial activity and differentiation features. Inhibiting HBEs in AML cell lines recapitulated some of these transcriptional features. These data indicate that heme levels regulate AML cells through molecules like BACH1, maintaining a malignant stem-like state, while the low heme state also confers therapeutic vulnerabilities to AML.

Building on this, Lewis et al. investigated whether targeting heme synthesis could serve as a therapeutic strategy in AML. Analysis of the Cancer Dependency Map confirmed that the heme biosynthesis pathway is among the most selectively essential pathways in AML cell lines, particularly in those with low basal HBE expression. In various AML models, both genetic knockout and pharmacological inhibition of HBEs significantly suppressed leukemia cell proliferation and extended survival in mice. More importantly, the normal hematopoietic system exhibited a relatively high tolerance to HBE inhibition. These results support the concept that reduced heme synthesis sensitizes AML cells to heme starvation and reveals a potential therapeutic window for targeting this pathway.

Second, to elucidate the pathway through which HBE inhibition induces cell death, and considering that metabolic dependencies may differ significantly, the researchers conducted a CRISPR screen targeting metabolism-related genes. The results showed that sgRNAs targeting genes in the lipoic acid synthesis pathway (such as *LIAS*) or components of the lipoylated protein complex significantly protected cells from HBE inhibitor-induced killing. Lipoic acid synthesis is a key determinant of cuproptosis—a copper-dependent form of cell death reported by Tsvetkov et al. in 2022⁴—knockout of relevant pathway genes conferred resistance to both HBE inhibition and copper supplementation. Mechanistically, HBE inhibition leads to excess copper ions binding to and inducing oligomerization of DLAT, a lipoylated protein in mitochondria, ultimately triggering cuproptosis. Adding cuproptosis inhibitors significantly alleviated HBE inhibition-induced death. This evidence indicates

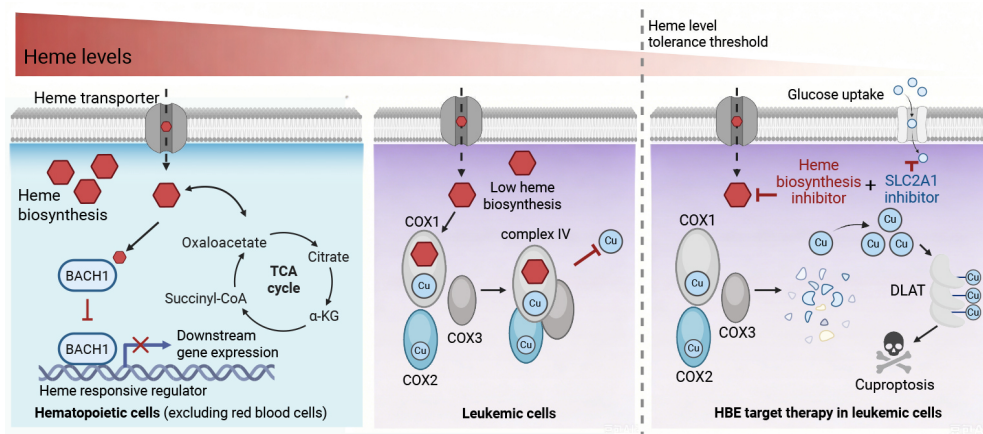


Figure 1. In normal hematopoietic cells, heme synthesis requires the TCA cycle intermediate succinyl-CoA as a precursor substrate Heme, serving as the essential cofactor for cytochromes, promotes oxidative phosphorylation and the TCA cycle upon its increased production. It primarily functions as a key component of mitochondrial electron transport chain cytochromes. Furthermore, heme can bind to and inhibit transcriptional regulators such as BACH1, thereby modulating gene expression. In leukemic cells, heme biosynthesis is often downregulated. As a crucial factor for respiratory chain Complex IV (CIV) assembly, heme cooperates with copper ions to stabilize this complex. Inhibition of heme biosynthesis leads to CIV disassembly and an increase in free copper ions, which then bind to DLAT protein and trigger cuproptosis. Co-targeting heme biosynthesis and glucose import (via SLC2A1 inhibition) synergistically disrupts metabolic and survival pathways, resulting in lethal effects in leukemic cells.

that heme starvation triggers copper-dependent cell death. These experiments are the first to reveal heme depletion as a trigger for cuproptosis, confirming cuproptosis as a cell death pathway existing under pathological conditions and potentially playing a role in AML.

The assembly and function of mitochondrial Complex IV (CIV) depend on both heme and copper. Further investigation revealed that HBE knockout severely disrupted CIV assembly and activity, leading to reduced mature CIV and its supercomplexes, and accumulation of CIV intermediates. Knockout of copper chaperone proteins required for CIV assembly or the heme-binding protein COA7 mimicked the phenotype of HBE inhibition, inducing DLAT oligomerization and inhibiting cell proliferation. This effect could be rescued by the inhibition of cuproptosis mediated by *LIAS* knockout. These results provide a complete mechanistic description of HBE inhibition-induced cuproptosis, heme depletion leads to CIV assembly failure, causing copper ions to accumulate due to ineffective utilization, ultimately inducing cuproptosis.⁵ This finding deepens the understanding of heme metabolic reprogramming and its function in AML.

Finally, to apply these discoveries to AML therapy, the authors performed a CRISPR screen to identify pathways exhibiting synthetic lethality with heme biosynthesis. The results revealed that loss of glycolysis pathway genes enhanced cellular sensitivity to HBE inhibition. While HBE inhibition reduced mitochondrial respiration, it simultaneously increased cellular glucose uptake, indicating adaptive metabolic reprogramming. Both genetic knockout and pharmacological inhibition experiments confirmed that the SLC2A1 inhibitor BAY-876 exhibited synergistic killing effects with HBE inhibitors in AML cell lines. Analysis of patient data suggested that the low heme state might be related to low SLC2A1 expression in AML, limiting the ability of AML cells to enhance glycolysis under energetic stress. The study further explored a novel combination therapy, the combination of HBE inhibitors with glycolysis inhibitors (such as BAY-876) demonstrates potent synergistic killing effects in AML. Key considerations include the limited bioavailability of HBE inhibitors and the potential toxicity to normal erythropoiesis, necessitating dose optimization. AML is heavily dependent on glycolysis (the Warburg effect), and prior validation of combinations involving NOX2 and glycolysis inhibitors supports their potential for clinical translation. This study further explored a

novel combination therapy strategy, the combination of HBE inhibitors with glycolysis inhibitors (such as BAY-876) demonstrates potent synergistic killing effects in AML, highlighting its potential for clinical translation.

In summary, this study establishes that AML cells in a low-heme state are uniquely sensitive to HBE inhibition—a vulnerability potentially common across cancers where anemia occurs. The work mechanistically links heme depletion to mitochondrial CIV disassembly and cuproptosis induction. Given that low heme synthesis enhances AML cell dependence on BCL-2 for survival, co-targeting these two pathways by combining an HBE inhibitor with Venetoclax may yield synergistic lethality for AML. While pharmacological challenges remain, these findings define a new metabolic-targeting paradigm and offer a biomarker-guided path for therapeutic translation in AML and beyond.

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AUTHOR CONTRIBUTIONS

X.D., L.Z., J.Z., and W.Z. wrote the original draft; X.D. and Y.L. reviewed and edited the manuscript; C.C. and Y.L. supervised, conceptualized, and reviewed the manuscript. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.