Exploiting metabolic dependencies in acute myeloid leukemia: DHODH inhibition meets lipid and cholesterol metabolism

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Acute myeloid leukemia (AML) is characterized by marked biological heterogeneity and unpredictable therapeutic responses. Although recent advances have expanded treatment options, many patients fail to achieve durable benefit, highlighting the need for new strategies that move beyond genetic stratification alone. One approach that has gained increasing attention is targeting metabolic dependencies that support leukemic cell survival and identity. In this context, inhibition of dihydroorotate dehydrogenase (DHODH), a key enzyme in *de novo* pyrimidine synthesis and mitochondrial metabolism, has emerged as a promising but still incompletely understood therapeutic strategy.[1-4]

In this issue of *Haematologica*, Hogeling *et al.*[5] provide an integrative analysis of DHODH inhibition in AML that offers an important insight into why responses vary and how therapeutic efficacy might be improved. By combining *ex vivo* drug sensitivity profiling of primary AML samples with proteomic and lipidomic analyses, the authors identify cholesterol and lipid metabolism as central features associated with sensitivity to the DHODH inhibitor JNJ-74856665. Their work supports a model in which metabolic state, rather than genetic subtype, shapes response to DHODH inhibition and highlights lipid regulatory pathways as actionable points of vulnerability.

A central observation of the study is the substantial heterogeneity in responses to DHODH inhibition across primary AML samples. While some samples show strong suppression of proliferation and viability, others are far less affected. This variability is not explained by mutational status and is only weakly associated with baseline proliferation, underscoring the limitations of using genetic or simple phenotypic features to predict response to metabolic therapies. In addition, differentiation responses occur in only a subset of samples and do not consistently align with cytotoxic effects, reinforcing the idea that DHODH inhibition engages multiple, partially independent biological processes.

To better understand what distinguishes sensitive from resistant AML, the authors integrated quantitative proteomic data with functional drug response. This analysis revealed a clear association between DHODH inhibitor sensitivity and elevated cholesterol and lipid metabolic programs. AML samples most sensitive to DHODH inhibition were enriched for pathways related to lipid synthesis, cholesterol homeostasis, and lipid detoxification, whereas less sensitive samples showed enrichment for transcriptional and translational programs linked to proliferation. Among the proteins most strongly associated with sensitivity was SREBF2, a key transcriptional regulator of cholesterol biosynthesis and lipid metabolism. These findings suggest that AML cells with active lipid metabolic programs may be particularly reliant on DHODH activity, potentially because of increased mitochondrial engagement or a greater need to manage metabolic and oxidative stress.

The functional relevance of these associations is supported by experiments in AML cell line models with distinct metabolic profiles. Although these models differ in their reliance on glycolysis *versus* oxidative phosphorylation, DHODH inhibition in both settings disrupts mitochondrial function, increases oxidative stress, and alters lipid homeostasis. A consistent feature across models is the accumulation of polyunsaturated fatty acids, triglycerides, and lipid droplets, suggesting activation of lipid-buffering mechanisms in response to metabolic stress. Together, these observations support a broader conceptual link between DHODH activity, mitochondrial metabolism, redox balance, and lipid handling in AML cells.

Building on this framework, the authors explore whether interfering with lipid regulatory pathways can enhance the effects of DHODH inhibition. They focus on dipyridamole, a US Food and Drug Administration-approved antiplatelet drug

that inhibits activation of sterol regulatory element-binding proteins (SREBP) and also affects nucleoside transport.[6] While dipyridamole alone has limited activity, its combination with DHODH inhibition results in strong synergy in AML cell lines and primary patient samples, leading to enhanced loss of viability and increased differentiation. Additional combination studies targeting cholesterol synthesis or nucleoside transport further support the idea that AML cells rely on lipid and nucleotide homeostasis to tolerate DHODH inhibition, although the magnitude of these effects varies across models.

Several broader implications emerge from this work. First, it reinforces the concept that metabolic heterogeneity is a major determinant of therapeutic response in AML and that this heterogeneity is not captured by genetic classification alone. Second, it highlights lipid and cholesterol metabolism as active modulators of sensitivity to mitochondrial and nucleotide stress, rather than passive correlates. Third, it provides a clear rationale for combination strategies that exacerbate metabolic stress by limiting the cell's ability to adapt through lipid buffering or metabolic rewiring.

At the same time, important questions remain. The therapeutic potential of combined DHODH and SREBP inhibition has thus far been demonstrated only *in vitro* and *ex vivo*. Given the profound influence of the bone marrow microenvironment on leukemic metabolism, *in vivo* validation in xenograft or patient-derived models will be essential to establish efficacy and a therapeutic window. In addition, whether lipid metabolic signatures or markers of SREBP activity can be developed into predictive biomarkers remains to be determined.

Clinical trials of DHODH inhibitors, including BAY2402234 and JBZ-001, have shown acceptable tolerability but limited efficacy as single agents, emphasizing the need for rational combination approaches. The study by Hogeling *et al*. provides a strong conceptual basis for such strategies and suggests that targeting lipid regulatory pathways may be particularly effective in this setting. More broadly, it illustrates how integrating functional drug response data with metabolic profiling can uncover clinically relevant vulnerabilities that are not apparent from genomic analyses alone.

In summary, this work advances our understanding of DHODH inhibition in AML by placing metabolic context at the center of therapeutic response. By linking DHODH dependency to lipid and cholesterol metabolism, and demonstrating the potential of combination strategies that disrupt these pathways, the authors offer a compelling framework for future translational studies. As efforts continue to refine metabolic therapies in AML, such integrative approaches will be critical for identifying patients most likely to benefit and for guiding the design of next-generation combination trials.

Disclosures

No conflicts of interest to disclose.

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References

1. Sven C, Merz C, Evans L, et al. The novel dihydroorotate dehydrogenase (DHODH) inhibitor BAY 2402234 triggers differentiation and is effective in the treatment of myeloid malignancies. Leukemia. 2019;33(10):2403-2415.
2. Sykes DB, Kfoury YS, Mercier FE, et al. Inhibition of dihydroorotate dehydrogenase overcomes differentiation blockade in acute myeloid leukemia. Cell. 2016;167(1):171-186.e15.
3. Zhou J, Yiying Quah J, Ng Y, et al. ASLAN003, a potent dihydroorotate dehydrogenase inhibitor for differentiation of acute myeloid leukemia. Haematologica. 2019;105(9):2286-2297.
4. Cisar JS, Pietsch C, DeRatt LG, et al. N-heterocyclic 3-pyridyl carboxamide inhibitors of DHODH for the treatment of acute myelogenous leukemia. J Med Chem. 2022;65(16):11241-11256.
5. Hogeling SM, Sternadt D, La Rose N, et al. Potent synergy of DHODH and SREBP inhibition in acute myeloid leukemia via disruption of cholesterol and lipid metabolism. Haematologica. 2026;111(7):2319-2329.
6. Esquejo RM, Roqueta-Rivera M, Shao W, et al. Dipyridamole inhibits lipogenic gene expression by retaining SCAP-SREBP in the endoplasmic reticulum. Cell Chem Biol. 2021;28(2):169-179.e7.