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Response to Comment on: "SLC25A1 reprograms mitochondrial and fatty acid metabolism to promote the progression of acute myeloid leukemia"

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Response to Comment on: “SLC25A1 reprograms mitochondrial and fatty acid metabolism to promote the progression of acute myeloid leukemia”

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To the Editor,

We thank Li and colleagues for their interest in our study[1] and for raising several important issues regarding metabolic plasticity, venetoclax resistance, and the preclinical safety evaluation of SLC25A1 inhibition. We appreciate the opportunity to clarify the scope and interpretation of our findings. While we agree that the questions raised are relevant to future translational development, we respectfully do not agree that they undermine the central conclusions of our work.

Microenvironmental lipid rescue

Li and colleagues suggest that adipocyte-derived lipid uptake may bypass the need for de novo lipogenesis during SLC25A1 inhibition. This is an important concept in AML biology, but it does not fully capture the mechanism addressed in our study. Our central finding was not simply that SLC25A1 supplies cytosolic acetyl-CoA for fatty acid synthesis. Rather, SLC25A1 inhibition disrupted mitochondrial function, increased ROS-mediated apoptosis, reduced oxygen consumption, altered TCA-cycle metabolites, and suppressed both fatty acid synthesis-related and fatty acid oxidation-related programs[2].

Our data also directly acknowledge metabolic compensation. Palmitic acid partially rescued impaired proliferation and mitochondrial respiration after SLC25A1 knockdown, and lipidomic analysis showed increased phosphoglycerides and triglycerides together with DGAT1 upregulation. The synergy between CTPI2 and DGAT1 inhibition further supports the idea that lipid droplet storage is a compensatory response to SLC25A1 blockade. Thus, rather than ignoring lipid plasticity, our study provides experimental evidence that AML cells attempt to mount such compensation after SLC25A1 inhibition.

We agree that adipocyte-conditioned media, lipid-replete culture systems, and CD36- or FABP4-directed cotargeting would be useful next steps. However, the absence of these additional systems does not invalidate our results in mouse models or AML cells, that SLC25A1 is a therapeutically relevant metabolic node in AML.

Venetoclax sensitization and resistance

The correspondence also argues that validation in bona fide venetoclax-resistant PDX models is necessary before considering CTPI3 for venetoclax-resistant AML. We agree that resistant PDX models would provide valuable translational evidence and should be pursued. Nevertheless, our claim was based on mechanistic and preclinical sensitization data, not on an assertion of proven clinical efficacy in relapsed or refractory AML. Moreover, according to our results, Kasumi-1 and THP1 are both venetoclax-resistent cell lines, which is consistent with previous conclusions in other studies.

In our study, SLC25A1 knockdown increased sensitivity to venetoclax, CTPI2 combined with venetoclax synergistically suppressed AML cell growth and enhanced apoptosis, and CTPI3 combined with venetoclax reduced proliferation, mitochondrial ATP production, TCA intermediates, fatty acid-related metabolites, and CPT1A/CPT1C expression. These findings are consistent with prior evidence that mitochondrial metabolism and fatty acid oxidation contribute to venetoclax response and resistance in AML. Therefore, we believe it is reasonable to propose SLC25A1 inhibition as a promising strategy to improve venetoclax sensitivity, while recognizing that dedicated resistant models are required before clinical translation.

Safety and toxicology

We also appreciate the caution regarding systemic toxicity. However, germline Slc25a1 loss during embryogenesis is not equivalent to partial pharmacological inhibition in adult leukemia models. Developmental lethality or congenital cardiac phenotypes from constitutive genetic disruption cannot be directly extrapolated to the therapeutic window of a small-molecule inhibitor administered to adult subjects.

Within the scope of our study, CTPI3 showed lower toxicity toward healthy mononuclear cells than AML cells, prolonged survival in two murine AML models, reduced leukemia burden, maintained body weight, and did not produce obvious histological toxicity in the liver, kidney, or brain under the tested conditions. We do not present these data as a complete toxicology package. Rather, they provide an initial safety signal that supports further development. We agree that extended dosing, cardiac assessment, pharmacokinetic/pharmacodynamic characterization, and formal toxicology studies will be essential before clinical application.

Conclusion

In summary, the issues raised by Li and colleagues are valuable considerations for future work, but they should be viewed as next translational steps rather than evidence against the validity of the present study. Our data support SLC25A1 as a metabolic vulnerability in AML and identify CTPI3 as a promising preclinical compound that warrants additional evaluation in lipid-microenvironment models, venetoclax-resistant systems, and longer-term safety studies.

References

1. Li R, Liu Z, Wu X. Overcoming metabolic plasticity and microenvironmental rescue when targeting SLC25A1 in acute myeloid leukemia. Comment on: "SLC25A1 reprograms mitochondrial and fatty acid metabolism to promote the progression of acute myeloid leukemia". Haematologica. xxx

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