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Response to Comment on: “Fibrinogen promotes acute myelogenous leukemia progression *via* miR-486/*GPR153* axis”

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We thank Látal for their thoughtful comments on our study¹ and for placing our findings in the clinically relevant context of hyperleukocytosis and differentiation syndrome (DS) in acute myeloid leukemia (AML).

In our study², we demonstrated that fibrinogen (Fg) promotes AML cell proliferation and migration, with the pro-migratory effect also observed in primary AML cells. We therefore agree that it is reasonable to investigate whether Fg may contribute to the trafficking and distribution of AML cells among the bone marrow, peripheral blood, and other tissues.

Látal reported preserved or elevated Fg levels in patients with marked hyperleukocytosis³. This observation suggests that the relationship between Fg and circulating leukemic burden need further investigation. However, the *in vivo* regulation and biological effects of Fg are likely to be considerably more complex than the direct interaction between Fg and leukemic cells examined in our experimental models. Circulating Fg is influenced by inflammatory signaling, hepatic function, and other disease-related factors⁴. Conversely, Fg itself may participate in innate immune responses and modulate inflammatory mediator release⁵, creating potentially bidirectional interactions between Fg, systemic inflammation, and the leukemic microenvironment. Thus, alternative explanations and potential confounding factors should be considered. Although our *in vitro* and *in vivo* findings support a disease-promoting role of Fg in AML, they do not establish whether elevated Fg in patients is a driver of AML progression, a consequence of an inflammatory and hyperproliferative disease state, or both. Moreover, our current findings do not establish that Fg-mediated leukemic cell migration contributes to hyperleukocytosis in patients with AML.

The possible relationship between Fg and DS during treatment with menin or IDH1/2 inhibitors is particularly intriguing. Differentiation-inducing therapies can alter leukemic cell phenotype⁶ and trafficking⁷, but whether extracellular factors such as Fg

modulate these processes remains largely unknown. From a mechanistic perspective, it would be informative to determine whether the Fg-responsive pathway identified in our study is altered during differentiation-inducing therapy. At present, there is no evidence that Fg directly contributes to DS, and our study was not designed to address this question. Nevertheless, serial measurement of circulating Fg before and during menin or IDH1/2 inhibitor treatment, together with leukocyte kinetics, markers of leukemic differentiation, and the clinical manifestations of DS may provide useful insights into this potential relationship.

We appreciate Látal for extending our mechanistic observations to these clinically important questions. Their comments highlight a broader implication of Fg that it may function not only as a coagulation factor or biomarker, but also as a component of the extracellular microenvironment capable of modulating AML cell behavior. Determining whether this mechanism contributes to leukemic cell trafficking in patients, particularly during differentiation-inducing therapy, represents an interesting direction for future investigation.

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