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Fibrinogen and leukemic-cell trafficking: possible implications for hyperleukocytosis and differentiation syndrome. Comment on: "Fibrinogen promotes acute myelogenous leukemia progression *via* miR-486/GPR153 axis"

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Fibrinogen and leukemic-cell trafficking: possible implications for hyperleukocytosis and differentiation syndrome. Comment on: "Fibrinogen promotes acute myelogenous leukemia progression *via* miR-486/*GPR153* axis"

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Yang *et al.* provided compelling evidence that fibrinogen (Fg), beyond its established role in coagulation, may actively contribute to acute myeloid leukemia (AML) biology. The authors demonstrate that Fg promotes AML cell proliferation and migration through upregulation of miR-486-5p, suppression of GPR153, and subsequent activation of the mTORC2/AKT pathway.[1] Importantly, the migratory effect was also observed in primary AML cells, suggesting potential clinical relevance of this mechanism.

These findings are particularly intriguing when considered in the context of AML presenting with hyperleukocytosis (HL) and even leukostasis. We recently reported our 20-year single-center experience with therapeutic leukocytapheresis in 65 patients with newly diagnosed AML.[2] The median white blood cell (WBC) count before leukocytapheresis was 176×10^9/L (range, 44–434×10^9/L). Interestingly, despite the severity of the disease and frequent thrombocytopenia, fibrinogen was generally preserved, with a median concentration of 3.10 g/L and values reaching 8.18 g/L.[2]

HL is traditionally viewed predominantly as a consequence of rapid leukemic proliferation. However, the mechanisms determining the distribution of leukemic cells between bone marrow, peripheral blood and extramedullary tissues are considerably more complex. The observations by Yang *et al.* raise the intriguing possibility that Fg-mediated migration may contribute to leukemic cell trafficking, thereby promoting the development of HL and potentially increasing the risk of leukostasis.

Our observations cannot establish such a relationship. Fg is an acute-phase reactant, and its elevation in patients with hyperproliferative AML may simply reflect systemic inflammation or other disease-related processes. Nevertheless, the preservation or elevation of Fg in a population characterized by an exceptionally high circulating leukemic burden is noteworthy in light of the mechanistic findings reported by Yang *et al.* Prospective studies correlating Fg concentrations with peripheral blood blast counts, bone marrow disease burden and patterns of extramedullary involvement could clarify whether Fg is merely a biomarker of aggressive disease or an active contributor to leukemic cell trafficking. Importantly, acute promyelocytic leukemia (APL) should be considered separately in this context. Differentiation syndrome is well recognized in APL treated with differentiation-inducing therapy despite the frequent presence of hypofibrinogenemia as part of its characteristic coagulopathy.

This question may acquire additional clinical relevance with the introduction of differentiation syndrome-inducing therapies, particularly menin and IDH1/2 inhibitors. Revumenib and other menin inhibitors have demonstrated substantial activity in *KMT2A*-rearranged and *NPM1*-mutated acute leukemias.[3] Differentiation syndrome represents a characteristic toxicity of these agents and may be accompanied by rapid leukocytosis, and even possibly leading to leukostasis. In the first clinical study

of revumenib, differentiation syndrome occurred in 16% of patients, and leukocytosis requiring hydroxyurea was observed in several affected patients.[3] Fg levels are not routinely reported in clinical trials or real-world studies.[3-6]

Notably, the molecular subgroups targeted by menin inhibition substantially overlap with AML phenotypes prone to HL. In our cohort of patients, *NPM1* mutations were detected in 17/43 (39.5 %) tested patients and *KMT2A* rearrangements in 5/57 (8.8 %).[2] Thus, patients with a biological predisposition toward a high circulating leukemic burden may increasingly become candidates for therapies that themselves induce profound changes in leukemic cell differentiation and trafficking.

We do not suggest that elevated Fg contributes directly to differentiation syndrome, for which there is currently no clinical evidence. However, the demonstration that Fg can actively promote AML cell migration raises an important question: Could fibrinogen-mediated leukemic cell migration also enhance leukemic cell trafficking during differentiation-inducing therapy and thereby contribute to differentiation syndrome in non-APL AML? This may be particularly relevant in patients presenting with marked HL or high baseline Fg concentrations.

The elegant mechanistic observations of Yang *et al.* therefore deserve consideration beyond the identification of another signaling pathway involved in AML progression. They suggest that Fg may represent part of the microenvironment regulating the movement of leukemic cells between anatomical compartments. In the era of menin and IDH1/2 inhibition, prospective assessment of Fg together with WBC kinetics and clinical manifestations of differentiation syndrome could determine whether this readily available laboratory parameter carries biological or clinical information.

Until such data become available, particular vigilance appears warranted when initiating differentiation-inducing therapy in patients with a pre-existing hyperproliferative phenotype. Understanding the interaction between leukemic-cell intrinsic biology and extracellular regulators such as Fg may ultimately help identify patients at greatest risk of clinically significant leukemic redistribution and differentiation syndrome.

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