Blood Science

An old player, the right niche

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The cellular and molecular components of the niche for hematopoietic stem cells (HSCs) are still not well defined. Angiopoietin-like proteins (Angptls) are a group of secreted glycoproteins that have been reported to play various roles, including the regulation of HSC activity.[1] Specifically, Angptl2, a member of the Angptl family, was demonstrated to support HSC stemness through binding to inhibitory receptors.[2] Angptl2 has also been shown to support HSC activity in exosomes.[3] However, whether and how Angptl2 regulates HSC activities in the HSC niche were still unknown.

Yu et al used an elegant approach to study these questions.[1] Based on the expression pattern of Angptl2 in bone marrow, several conditional knockout (KO) mice were generated to deplete Angptl2 from endothelial, mesenchymal stromal cells, megakaryocytes, and HSCs. Using a number of functional assays, including reconstitution analysis, flow cytometry, and immunofluorescence microscopy, the authors discovered that only endothelial cell-derived Angptl2 but not Angptl2 from other niche cell types supported the repopulation capacity, quiescent status, and niche localization of HSCs. They further demonstrated that Angptl2 enhances peroxisome-proliferator-activated receptor D expression to transactivate G0s2 and sustain the perinuclear localization of nucleolin that prevents HSCs from entering the cell cycle.

This study has clarified sustained questions about the physiological role of Angptl2 in regulating HSC activity. It suggests that Angptl2 is indeed a molecular component in the endothelial niche of HSCs that inhibits differentiation and preserves the stemness of stem cells.

This study also elicits additional questions. The obvious follow-up questions include what is the detailed mechanism by which the extracellular Angptl2 regulates HSC activity and why does Angptl2, a hormone that can circulate in blood, need to be in the endothelial niche to regulate HSC activities? In addition, since Angptl2 can be expressed by cells in the mouse bone marrow other than endothelial cells, what are the functions of Angptl2 expressed by these other cells? What are the roles of other members of the Angptl family in mouse bone marrow and the human HSC niche? What are the functions of bone marrow Angptls and receptors such as LILRB2 in other physiological and pathological processes?

Overall, the study suggests that one molecule, when expressed by different types of cells, may play different roles by regulating different functions. Since Angptl2 and other Angptls were reported to play additional roles such as the regulation of lipid metabolism, angiogenesis, inflammation, and cancer development, further investigations are warranted to understand the diverse functions of Angptls in different types of cells.

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REFERENCES

[1] Yu Z, Yang W, He X, et al. Endothelial cell-derived angiopoietin-like protein 2 supports hematopoietic stem cell activities in bone marrow niches. *Blood* 2021 blood.2021011644. doi: 10.1182/blood.2021011644.

[2] Zheng J, Umikawa M, Cui C, et al. Inhibitory receptors bind ANGPTLs and support blood stem cells and leukaemia development. *Nature* 2012;485 (7400):656–660.

[3] Gu H, Chen C, Hao X, et al. Sorting protein VPS33B regulates exosomal autocrine signaling to mediate hematopoiesis and leukemogenesis. *J Clin Invest* 2016;126 (12):4537–4553.

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