Pediatric RESEARCH

IMAGE

Insights image for "Evaluation of angiogenic signaling molecules associated with reactive thrombocytosis in an iron deficient rat model"

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Pediatric Research (2021) 90:492; https://doi.org/10.1038/s41390-021-01575-7

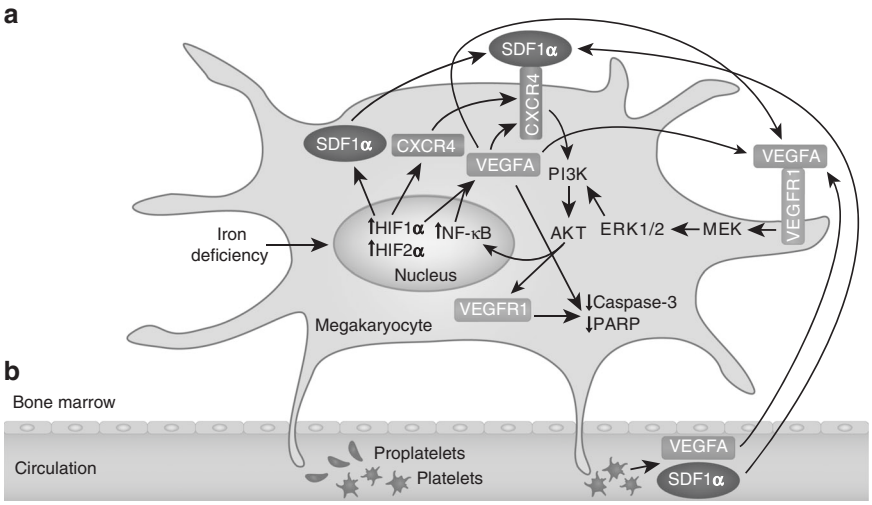

Fig. 1 Under iron-deficient conditions, MK and MKP cells in the hypoxic bone marrow microenvironment increase expression of HIF1α and HIF2α. They in turn activate the expression and secretion of SDF1α and VEGFA in these cells. (**a**) HIF2α increases production of CXCR4, which translocates to the cell membrane where it serves as a receptor for SDF1α. Binding of the secreted SDF1α to CXCR4 triggers a downstream signaling cascade through PI3K/AKT pathway resulting in more VEGFA production. VEGFA can in turn increase CXCR4 expression in MKs resulting in a positive feedback loop. (**b**) On the other hand, secreted VEGFA binds to one of its receptor VEGFR1 resulting in intracellular accumulation of VEGFR1 and VEGF through the MEK/ERK and PI3K/AKT signaling pathways. Intracrine AKT/ERK signaling and downregulation of apoptotic molecules (Caspase 3 and PARP) induced by the interaction of VEGF and VEGFR1 increases survival and proliferation of MKs. Platelets are also known to secrete VEGFA and SDF1α in the bloodstream and this can further play a significant role in activation of these two interlinked pathways. A combination of these pathways can lead to increased megakaryocytes and platelets under iron deficiency. TPO thrombopoietin, MK megakaryocyte, MKP megakaryocyte precursors, HIF1α hypoxia-inducible factor 1 alpha, HIF2α hypoxia-inducible factor 2 alpha, SDF1α stromal-derived factor 1, CXCR4 CXC chemokine receptor 4, VEGFA vascular endothelial growth factor A, VEGFR1 vascular endothelial growth factor receptor 1, PI3K phasphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, AKT AKT serine/threonine kinase 1, ERK extracellular signal-regulated kinase, MEK mitogen-activated protein kinase kinase 1, PARP poly (ADP-ribose) polymerase 1 (ref. [1]).

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

Patient consent: Patient consent was not required for this study.

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REFERENCE

1. Garcia, J., Mankin, P., Gnanamony, M. et al. Evaluation of angiogenic signaling molecules associated with reactive thrombocytosis in an iron-deficient rat model. *Pediatr. Res.* https://doi.org/10.1038/s41390-020-01318-0 (2021).

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Received: 29 April 2021 Accepted: 29 April 2021
Published online: 9 June 2021