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The thrombopoietin/MPL axis is activated in the *Gata1low* mouse model of myelofibrosis and is associated with a defective RPS14 signature

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Myelofibrosis is characterized by hyperactivation of thrombopoietin signaling which induces a RPS14 deficiency that de-regulates GATA1 in megakaryocytes by hampering its mRNA translation. Since mice carrying the hypomorphic Gata1low mutation, which reduces the levels of Gata1 mRNA in megakaryocytes, develop myelofibrosis[1] (Zingariello M. et al. 2015), we investigated whether the thrombopoietin axis is hyperactive in this model. Gata1low mice contained 2-times more Tpo mRNA in liver and TPO in plasma than wild-type littermates. Furthermore, Gata1low LSKs expressed levels of Mpl mRNA (5-times greater than normal) and protein (2-times lower than normal) similar to those expressed by LSKs from TPO-treated wild-type mice. Gata1low marrow and spleen contained more JAK2/STAT5 than wild-type tissues, an indication that these organs were reach of TPO-responsive cells. Moreover, treatment of Gata1low mice with the JAK inhibitor ruxolitinib reduced their splenomegaly. Also in Gata1low mice activation of the thrombopoietin/MPL axis was associated with a RSP14 deficiency and a discordant microarray ribosome signature (reduced RPS24, RPS26 and SBDS expression). Finally electron microscopy revealed that Gata1low megakaryocytes contained poorly developed endoplasmic reticulum with rare polysomes. In summary, Gata1low mice are a bona-fide model of myelofibrosis which recapitulates the hyperactivation of the TPO/MPL/JAK2 axis observed in megakaryocytes from myelofibrotic patients.

[1] A novel interaction betweenmegakariocytes and activated fibrocytes increased TGF-beta bioavaibility in the GATA 1 low mouse model of mielofibrosys. Am J blood Res 2015 Dec 25; 5 (2): 34-61

Keywords

MPL, Thrombopoietin (TPO), JAK2, GATA1, megakaryocytes

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