P-Selectin sustains extramedullary hematopoiesis in the Gata1 low model of myelofibrosis

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Splenomegaly is a major manifestation of primary myelofibrosis (PMF) contributing to clinical symptoms and hematologic abnormalities. The spleen from PMF patients contains increased numbers of hematopoietic stem cells (HSC) and megakaryocytes. These megakaryocytes express high levels of P-selectin (P-sel) that, by triggering neutrophil emperipolesis, may cause TGF-β release and disease progression. This hypothesis was tested by deleting the P-sel gene in the myelofibrosis mouse model carrying the hypomorphic Gata1low mutation that induces megakaryocyte abnormalities that recapitulate those observed in PMF. P-selnullGata1low mice survived splenectomy and lived three months longer than P-selWTGata1low littermates and did not express fibrosis and osteosclerosis in the marrow or splenomegaly. Furthermore, deletion of P-sel disrupted megakaryocyte/neutrophil interactions in spleen, reduced TGF-β content and corrected the HSC distribution that in Gata1low mice, as in PMF patients, is abnormally expanded in spleen. Conversely, pharmacological inhibition of TGF-β reduced P-sel expression in megakaryocytes and corrected HSC distribution. Spleens, but not marrow, of Gata1low mice contained numerous cKITpos activated fibrocytes, probably of dendritic cell origin, whose membrane protrusions interacted with megakaryocytes establishing niches hosting immature cKITpos hematopoietic cells. These activated fibrocytes were not detected in spleens from P-selnullGata1low or TGF-β-inhibited Gata1low littermates and were observed in spleen, but not in marrow, from PMF patients. Therefore in Gata1low mice, and possibly in PMF, abnormal P-sel expression in megakaryocytes may mediate the pathological cell interactions that increase TGF-β content in MK and favor establishment of a microenvironment that supports myelofibrosis-related HSC in spleen.

References


Keywords

Myelofibrosis; Megakaryocytes; P-Selectin.