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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 *Gata1^{low}* mutation that induces megakaryocyte abnormalities that recapitulate those observed in PMF. *P-sel^{null}Gata1^{low}* mice survived splenectomy and lived three months longer than *P-sel^{WT}Gata1^{low}* 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 *Gata1^{low}* 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 *Gata1^{low}* mice contained numerous cKIT^{pos} activated fibrocytes, probably of dendritic cell origin, whose membrane protrusions interacted with megakaryocytes establishing niches hosting immature cKIT^{pos} hematopoietic cells. These activated fibrocytes were not detected in spleens from *P-sel^{null}Gata1^{low}* or TGF-β-inhibited *Gata1^{low}* littermates and were observed in spleen, but not in marrow, from PMF patients. Therefore in *Gata1^{low}* 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

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Keywords

Myelofibrosis; Megakaryocytes; P-Selectin.

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