

TGF-beta bioavailability is increased by a new interaction between megakaryocytes and fibrocytes activated in the Gata 1 low mouse

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Primary myelofibrosis is the most severe of the Philadelphia-negative myeloproliferative neoplasms and is associated with progressive TGF- β 1-dependent scarring of the hematopoietic microenvironment which causes hematopoietic failure in the spleen. Nevertheless, the pathogenetic role of TGF- β is still unclear because of the modest (2-fold) increases in its plasma levels, both in patients and in animal models. Transmission electron-microscopy (TEM) observations identified that spleen from PMF patients and Gata1low mice contained megakaryocytes with abnormally high levels of TGF- β and collagen fibres embedded in their cytoplasm. Additional immuno-TEM observations of spleen from Gata1low mice revealed the presence of numerous activated fibrocytes establishing with their protrusions a novel cellular interaction, defined as peripolexis, with megakaryocytes. These protrusions infiltrated the megakaryocyte cytoplasm releasing collagen that was eventually detected in its mature polymerized form. Megakaryocytes, engulfed with mature collagen fibres, acquired the morphology of parapoietic cells and, in the most advanced cases, were recognized as polylobated heterochromatic nuclei surrounded by collagen fibres strictly associated with TGF- β . These areas contained concentrations of TGF- β -gold particles ~1000-fold greater than normal and numerous myofibroblasts, an indication that TGF- β was bioactive. Loss-of-function studies indicated that peripolexis between megakaryocytes and fibrocytes required both TGF- β , possibly for inducing fibrocyte activation, and P-selectin, possibly for mediating interaction between the two cell types. Loss-of-function of TGF- β and P-selectin also prevented fibrosis. These observations identify that myelofibrosis is associated with pathological increases of TGF- β bioavailability and suggest a novel megakaryocyte-mediated mechanism that may increase TGF- β bioavailability in chronic inflammation.

References

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Keywords

Megakaryocytes; activated fibrocytes; neutrophils; TGF- β ; P-selectin; myelofibrosis.