Thrombopoietin-induced genes and pathways for the regeneration and maintenance of hematopoietic stem cells

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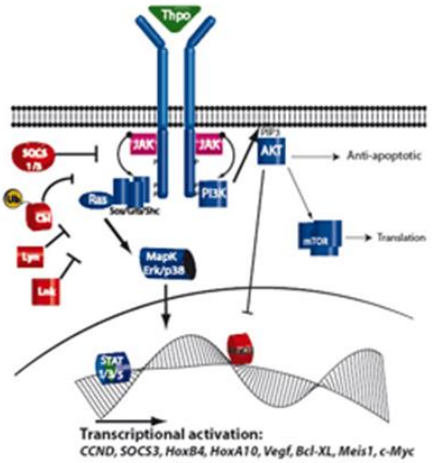

Mpl signaling pathways and negative regulators.
Source: PEI

HSC function is controlled by many factors including cytokines and their receptors, like the thrombopoietin (Thpo) receptor Mpl. Mpl was identified as the cellular homologue of the myeloproliferative leukemia virus oncogene (v-Mpl). Thpo/Mpl-signaling is involved in both, the expansion and the maintenance of HSCs. Furthermore, signaling via Mpl is crucial for megakaryocyte differentiation and platelet formation. Deregulation of MPL signaling causes hematological disorders. Activating mutations of MPL or mutations in downstream mediators of MPL signaling induce myeloproliferative disorders. MPL deficiency leads to thrombocytopenia and aplastic anemia.

We have demonstrated the correction of the Mpl-deficient phenotype in the Mpl knockout mouse model by lentiviral gene transfer. Especially interesting is the regeneration of HSC after Thpo/Mpl signaling was re-established. We analyzed the gene expression profile of regenerated HSC after Mpl gene therapy. Based on these analyses we could identify a Thpo/Mpl specific gene expression signature. Using lentiviral vectors expressing potential Mpl downstream targets in the Mpl-deficient mouse model we are searching for candidates that will allow to expand HSC and/or improve their functionality. Expression of the identified candidate genes may also support HSC that undergo in vitro genetic modifications. Furthermore, we aim for a deeper understanding of how Thpo/Mpl signaling controls HSC self-renewal and quiescence.