Thrombopoietin: Role in Fracture Healing and Pain

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Background and Hypothesis:

The megakaryocyte (MK) growth factor, thrombopoietin (TPO), improves bone healing in mice, rats, and pigs. Here we explore the role of MK-secreted platelet-derived growth factor-BB (PDGF–BB) in TPO's mechanism of improving fracture healing. Interestingly, PDGF has neuroprotective effects, and neuronal PDGF receptors (PDGFRs) are primarily stimulated by PDGF–BB. Additionally, fibroblast growth factor 2 (FGF2) is secreted by osteoblasts (OBs), and MKs stimulate OB proliferation; therefore, MKs may regulate FGF2 expression which also promotes nerve regeneration. Importantly, neuropathic pain caused by fractures can be prevented by neuroprotective therapies. We hypothesize that increases in fracture-related neuropathic pain observed with age are due to reductions in: MK-secreted PDGF-BB and MK-stimulated, OB-secreted FGF2.

Experimental Design or Project Methods:

Dorsal root ganglia (DRG) and MKs from bone marrow and spleens were isolated from 3-4 month-old (young) and 22-24 month-old (old) mice. MKs were also isolated from E13-15 fetal livers of mice and OBs were isolated from the calvaria of neonatal mice. OBs were cultured alone or in the presence of MKs for 4 days. Real-time PCR was completed to examine the expression of PDGF-BB in MKs, FGF2 in OBs, and PDGFR in DRG.

Results:

Old MKs exhibit a 63% reduction in PDGF–BB expression and old DRG exhibit a 68% reduction in PDGFR expression. OBs cultured with MKs show a 1.78 fold increase in FGF2 expression.

Conclusion and Potential Impact:

Decreased expression of PDGF-BB in old MKs and PDGFR in old neurons, as well as increased FGF2 expression in OBs cultured with MKs present possible mechanisms for both the reduction in bone healing and increased fracture pain observed with age. TPO improves bone healing and may potentially reduce neuropathic pain directly by increasing MK secreted PDGF-BB and indirectly through MK PDGF-BB stimulating FGF2 secretion from OBs.