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Megakaryocytes: Regulators of Bone Mass and Hematopoiesis

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Emerging evidence demonstrates that megakaryocytes (MK) play a key role in regulating skeletal homeostasis and hematopoiesis. Recent reports show that MK reside in close proximity to hematopoietic stem cells (HSC). Genetic depletion of MK resulted in mitotic activation of HSC suggesting that MK maintain HSC quiescence. Other studies demonstrated that following irradiation, surviving MK migrate to endosteal surfaces where osteoblast (OB) lineage cells dramatically increase and promote engraftment of transplanted HSC.

Here we investigated if MK directly impact hematopoiesis or whether they indirectly support HSC function through their interaction with OB-lineage cells. Our data suggests that LSK (Lin-Sca+CD117+, an enriched HSC population) co-cultured with MK and OB generate significantly higher numbers of colony forming cells (HSC function) compared to LSK co-cultured with either MK or OB alone. The functionality of this *in vitro* data was confirmed *in vivo* with transplantation studies which showed increased engraftment in mice transplanted with LSK cells co-cultured with OB and MK compared to LSK cells co-cultured with OB alone. To test if loss of MK negatively impacts osteoblastogenesis, we generated conditional knockout mice where cMpl, the receptor for the main MK growth factor, thrombopoietin (TPO), was deleted in MK ($cMpl^{fl/fl}$ x PF4Cre). Unexpectedly, these mice exhibited a 10-fold increase in platelet numbers, megakaryocytosis, a dramatic expansion of phenotypically defined hematopoietic precursors, and a remarkable 20-fold increase in the bone volume fraction.

Collectively, these data indicate that while MK modulate HSC function, this activity is in part mediated through interactions with OB and suggest a complex role for TPO and MK in HSC regulation. While work is needed to further elucidate mechanisms, understanding the coordinated interaction between MK, OB, HSC, and TPO/Mpl should inform the development of novel treatments to enhance HSC recovery following myelosuppressive injuries, as well as bone loss diseases, such as osteoporosis.