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Defining the Role of Malignant Megakaryocytes on Clonal Hematopoiesis

Myeloproliferative neoplasms (MPNs) occur when a hematopoietic stem cell (HSC) acquires a driver mutation, often decades before disease presents. Over time the mutant HSC exhibits a fitness advantage, allowing a single clone to outcompete wild-type (WT) counterparts, termed clonal hematopoiesis (CH). Elucidating how CH occurs may allow us to prevent mutant HSCs from acquiring a fitness advantage, representing a potential therapeutic target. HSCs reside in the bone marrow (BM) stem cell niche and their function is directly altered by nearby cells. Megakaryocyte (Mk) cells live proximally to HSCs and drive HSC behavior in both homeostasis and stress. However, MPNs are defined by aberrant Mk signaling and morphology. We seek to determine if mutant Mk directly alter MPN niche function to favor mutant HSCs over WT HSCs.

To distinguish the differences between mutant and WT HSC fitness in MPNs, we are conducting competitive transplantations of lethally irradiated CD45.1 mice with congenic CD45.2 donor whole BM cells harboring the most common MPN driver mutation, JAK2V617F, or WT JAK2 (JAK2WT). Measuring CD45.2 chimerism in HSCs and red blood cells from engrafted mice revealed that CD45.2 cells harboring JAK2V617F disproportionally contributed to the myeloid lineage. JAK2V617F HSCs display increased fitness relative to their JAK2WT counterparts during myeloproliferation. To determine if mutant Mk are responsible for this increased JAK2V617F HSC fitness, we are cloning a lentiviral construct which will specifically ablate JAK2V617F Mk from the MPN niche.

To identify the key transcriptomic differences between JAK2V617F and JAK2WT Mk, we are developing strains of mice which fluorescently report JAK2V617F expression. These tools will allow us to specifically sort JAK2V617F and JAK2WT Mk and elucidate how they alter the HSC niche. Because the specific contributions of Mk to MPN pathogenesis remain unclear, this work is essential to determining the specific role of Mk in CH.