Role of Rap1 GTPases in Growth, Differentiation, and Migration of Myeloid Cells

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Background:
Rap1 is a Ras-like small-molecular-weight GTP-binding protein involved in signal transduction cascades. It cycles between a GDP-bound inactive and a GTP-bound active form. This switching is regulated by specific GEFs and GAPs. Rap1 exists in two isoforms - Rap1a and Rap1b. While Rap1 has been implicated in regulating several hematologic disorders, including chronic lymphocytic leukemia, its role in the development and function of hematopoietic stem cells and progenitors (HSC/Ps) has not been investigated. Macrophages play an essential role in the retention of hematopoietic cells in the mesenchymal niche. Resident macrophages in the spleen retain HSCs through VCAM1 adhesion. Previous studies have shown that loss of both isoforms of Rap1 in mice results in enhanced peripheral blood leukocyte counts and mobilization of primitive hematopoietic stem cells (Lin-KIT^{+}Sca1^{+}) into peripheral blood circulation. Given this loss of retention of primitive hematopoietic cells in the bone marrow, *we hypothesized* that perhaps Rap1 plays an essential role in adhesive interactions of HSC/Ps in the bone marrow.

Methods:
To test this hypothesis, we derived macrophages from the bone marrow of wild-type (WT) and *Rap1a/b* double knockout (DKO) mice and compared their growth, survival and differentiation using proliferation and adhesion assays, as well as flow cytometry to assess apoptosis, macrophage differentiation, MCSF receptor expression, and expression of integrins.

Results:
Our studies show that macrophages derived from *Rap1* DKO mouse bone marrow show impaired growth, survival and differentiation along with impaired adhesion in response to extracellular matrix components including fibronectin.

Future Directions:
In the future, we hope to study macrophage adhesive interactions in response to SDF1, collagen, and other extracellular matrix proteins in myeloid-specific deletion of Rap1 in mice, and to study the role of Rap1 in different lineages of hematopoietic cells using different CRE drivers.