

Rap1 is a Potential Therapeutic Target for Non-myeloablative Conditioning

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Myeloablative conditioning regimens used for transplantation of hematopoietic stem cells (HSCs) causes various side effects including gastrointestinal mucositis. Identification of therapeutic targets and determining their role in HSC development and function is important to determine a regimen for non-myeloablative conditioning. Previous studies have shown that GTPases play a critical role in self-renewal, engraftment and retention of HSCs. Rap1, a GTPase, is necessary for migration, adhesion as well as function of mature hematopoietic cells. To study the role of Rap1 in hematopoietic stem and progenitor cells (HSC/Ps), we have generated a mouse model in which the Rap1a and Rap1b isoforms of Rap1 are conditionally deleted in HSC/Ps (*Rap1a/b* *-/-*). Deficiency of Rap1a/b results in increased peripheral blood count as well as increase in HSCs in bone marrow along with a decrease in bone marrow cellularity. Rap1a/b deficient bone marrow HSC/Ps also have reduced adhesion capability *in vitro*. The self-renewal property of HSCs, in conjunction with their ability of multi-lineage reconstitution is important to repopulate the hematopoietic system of irradiated recipients of bone marrow transplant. *Rap1a/b* *-/-* HSCs show a defect in engraftment as well as multi-lineage reconstitution when they are transplanted into lethally irradiated hosts. Rap1 deficient HSCs show decreased homing into bone marrow of lethally irradiated recipients. To determine whether Rap1 can be used as a potential target for non-myeloablative conditioning, we performed bone marrow transplant into WT and *Rap1a/b* *-/-* mice without prior irradiation. Deficiency of Rap1a/b in HSCs resulted in availability of bone marrow niche for exogenously transplanted HSCs to engraft along with subsequent multi-lineage reconstitution. Overall, our study reveals that Rap1a/b are important for homing and retention of hematopoietic cells in bone marrow and deletion of Rap1a/b in HSCs result in engraftment of exogenous HSCs within the bone marrow of non-irradiated recipients.

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