Dickkopf-1 promotes hematopoietic regeneration via direct and niche-mediated mechanisms.

Journal: Nat Med

Publication Year: 2017

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PubMed link: 27918563

Funding Grants: Niche-Focused Research: Discovery & Development of Hematopoietic Regenerative Factors

Public Summary:
Blood stem cells depend on signals from the bone marrow microenvironment or "niche" for their survival. In clinical practice, hundreds of thousands of patients annually receive chemotherapy or radiation therapy in the treatment of cancer. Such therapies cause damage and death to blood stem cells and also damage the niche wherein stem cells reside. Stem cell regeneration is required for reconstitution of the blood and immune system following chemotherapy, radiation therapy or bone marrow transplantation. However, little is understood regarding the mechanisms that regulate blood stem cell regeneration. We hypothesized that bone progenitor cells regulate the regeneration of blood stem cells following injury. We found that bone progenitor cells secrete a protein called Dickkopf-1 (Dkk1) that promotes blood stem cell regeneration after irradiation. In mice, deletion of the Dkk1 gene in bone progenitor cells caused a significant delay in stem cell recovery and blood recovery after irradiation. Furthermore, treatment of irradiated mice with Dkk1 significantly accelerated stem cell regeneration and blood recovery after irradiation. Dkk1 promoted stem cell regeneration directly via inhibition of Wnt signaling in stem cells and suppression of ROS generation. Interestingly, Dkk1 also promoted stem cell regeneration indirectly by inducing the secretion of epidermal growth factor by bone marrow vascular endothelial cells. Taken together, these studies suggest that systemic administration of Dkk1 has therapeutic potential to accelerate blood and immune system recovery in patients receiving chemotherapy, radiation therapy or undergoing stem cell transplantation.

Scientific Abstract:
The role of osteolineage cells in regulating hematopoietic stem cell (HSC) regeneration following myelosuppression is not well understood. Here we show that deletion of the pro-apoptotic genes Bak and Bax in osterix (Osx, also known as Sp7 transcription factor 7)-expressing cells in mice promotes HSC regeneration and hematopoietic radioprotection following total body irradiation. These mice showed increased bone marrow (BM) levels of the protein dickkopf-1 (Dkk1), which was produced in Osx-expressing BM cells. Treatment of irradiated HSCs with Dkk1 in vitro increased the recovery of both long-term repopulating HSCs and progenitor cells, and systemic administration of Dkk1 to irradiated mice increased hematopoietic recovery and improved survival. Conversely, inducible deletion of one allele of Dkk1 in Osx-expressing cells in adult mice inhibited the recovery of BM stem and progenitor cells and of complete blood counts following irradiation. Dkk1 promoted hematopoietic regeneration via both direct effects on HSCs, in which treatment with Dkk1 decreased the levels of mitochondrial reactive oxygen species and suppressed senescence, and indirect effects on BM endothelial cells, in which treatment with Dkk1 induced epidermal growth factor (EGF) secretion. Accordingly, blockade of the EGF receptor partially abrogated Dkk1-mediated hematopoietic recovery. These data identify Dkk1 as a regulator of hematopoietic regeneration and demonstrate paracrine cross-talk between BM osteolineage cells and endothelial cells in regulating hematopoietic reconstitution following injury.

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