Robo4 cooperates with CXCR4 to specify hematopoietic stem cell localization to bone marrow niches.

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Public Summary:
Through our research, we want to understand how environmental cues control the blood stem cell, with the hope of designing better blood stem cell transplantation therapies for the treatment of immune deficiency and cancer. In collaboration with Dr. Camilla Forsberg, an assistant professor of biomolecular engineering in the Baskin School of Engineering at UC Santa Cruz, we have demonstrated that hematopoietic stem cells use a molecule called Robo4 to anchor themselves in the bone marrow. Robo4 acts as an adhesion molecule, interacting with other components of the bone marrow to bind the stem cells into their proper niche. Moreover, another molecule called Cxcr4, cooperates with Robo4 to retain hematopoietic stem cells in the bone marrow. However both molecules appear to act through different molecular mechanisms. Their inhibition would be a good way to achieve efficient mobilization of hematopoietic stem cells. We consider these findings may lead to improvements in the safety and efficiency of bone marrow transplants.

Scientific Abstract:
Specific bone marrow (BM) niches are critical for hematopoietic stem cell (HSC) function during both normal hematopoiesis and in stem cell transplantation therapy. We demonstrate that the guidance molecule Robo4 functions to specifically anchor HSCs to BM niches. Robo4-deficient HSCs displayed poor localization to BM niches and drastically reduced long-term reconstitution capability while retaining multilineage potential. Cxcr4, a critical regulator of HSC location, is upregulated in Robo4(-/-) HSCs to compensate for Robo4 loss. Robo4 deletion led to altered HSC mobilization efficiency, revealing that inhibition of both Cxcr4- and Robo4-mediated niche interactions are necessary for efficient HSC mobilization. Surprisingly, we found that WT HSCs express very low levels of Cxcr4 and respond poorly to Cxcr4 manipulation relative to other hematopoietic cells. We conclude that Robo4 cooperates with Cxcr4 to endow HSCs with competitive access to limited stem cell niches, and we propose Robo4 as a therapeutic target in HSC transplantation therapy.