Secreted frizzled-related protein 1 extrinsically regulates cycling activity and maintenance of hematopoietic stem cells.

Secreted frizzled-related protein 1 (Sfrp1) is highly expressed by stromal cells maintaining hematopoietic stem cells (HSCs). Sfrp1 loss in stromal cells increases production of hematopoietic progenitors, and in knockout mice, dysregulates hemostasis and increases Flk2-Cd34-Lin-Sca1+ Kit+ (LSK) cell numbers in bone marrow. Also, LSK and multipotent progenitors (MPPs) resided mainly in the G0/G1 phase of cell cycle, with an accompanying decrease in intracellular beta-catenin levels. Gene-expression studies showed a concomitant decrease Ccnd1 and Dkk1 in Cd34- LSK cells and increased expression of Pparg, Hes1, and Runx1 in MPP. Transplantation experiments showed no intrinsic effect of Sfrp1 loss on the number of HSCs or their ability to engraft irradiated recipients. In contrast, serial transplantations of wild-type HSCs into Sfrp1(-/-) mice show a progressive decrease of wild-type LSK and MPP numbers. Our results demonstrate that Sfrp1 is required to maintain HSC homeostasis through extrinsic regulation of beta-catenin.