The identification of hematopoietic stem cell niche.

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Hematopietic stem cells (HSC) in adult mouse bone marrow are quiescent, while mobilized HSCs are cycling rapidly following depletion of mature and progenitor cells by bleeding, infection, cytotoxic reagents or irradiation. Although interaction between microenvironments and HSCs contributes to maintenance of quiescence of HSCs resulting in the long-term self-renewal, mechanisms are not understood. In this study, we demonstrate that side population (SP), based on FACS analysis with Hoechst33342, in c-kit+ Sca-1+ Lin-(KSL) cells represents a population of quiescent HSC. Cell cycle analysis with BrdU labeling showed that SP were slowly cycling in G0 phase. HSCs mobilized in peripheral blood from a bone marrow niche by G-CSF or 5-FU treatment were cycling and those cycling HSCs were not in SP. HSCs in developing mice, which were cycling and expanding, were also in main population (MP). SP cells in KSL fraction were resistant to myelosuppressive stress including X-ray and 5-FU treatment which depletes cycling hematopoietic cells. Histological examination revealed that the 5-FU resistant HSCs were surrounded by bone-lining osteoblast-like cells on the surface of the bone. These data indicate that the osteoblastic zone is a niche for quiescent HSCs in bone marrow. FACS, RT-PCR and histological examination showed that the expression of Tie2, a receptor tyrosine kinase, was limited to the HSCs in a niche. Angiopoietin-1 (Ang-1), a ligand for Tie2, increased the number of LTC-IC and mixed CFC, accompanied with enhanced adhesion of hematopoietic cells to stroma cells in vitro. Furthermore, Ang-1 induced SP phenotype in HSC in vivo. These data suggest that Ang-1/Tie2 plays a key role for recruitment of stem cells to a niche, and remains cells in quiescent state, resulting in stem cell maintenance.