Hematopoietic stem cells (HSCs) are a rare population of somatic stem cells that have the ability to regenerate the entire mature blood system in a hierarchical way for the duration of an adult life. Adult HSCs reside in the bone marrow niche. Different niche cell types and molecules regulate the balance of HSC dormancy and activation as well as HSC behavior in both normal and malignant hematopoiesis. Here, we describe the interplay of HSCs and their niche, in particular the involvement of the Wnt signaling pathway. Although the prevailing notion has been that malignant transformation of HSCs is the main cause of leukemia, evidence is mounting that disruption of niche regulation by transformed hematopoietic cells, which may overexpress Wnt signaling or intrinsic stromal defects in gene expression, is at least a collaborative factor in leukemogenesis. Thus, insights into the normal and altered functions of niche components will help to obtain a better understanding of normal and malignant hematopoiesis and how environmental factors affect these processes.