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Hierarchical organization of fetal and adult hematopoietic stem cells

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Abstract

Mammalian hematopoiesis is a hierarchically organized process in which all types of mature blood cells are continuously generated from more primitive cells that lack any morphological evidence of differentiation. However, it is now accepted that this morphologically homogeneous precursor population consists of multiple distinct subsets of cells. The most primitive of these are defined by their ability to produce similarly undifferentiated progeny through many cell divisions, in addition to generating cells with activated differentiation programs. The term hematopoietic stem cell (HSC) is now conventionally restricted to cells with this long-term self-sustaining ability. Nevertheless, clonal tracking studies have revealed significant heterogeneity in the behavior of such stringently defined HSCs. Moreover, superimposed on the heterogeneous behavior that can be elicited from the HSCs present at any given time during development are additional differences that distinguish HSCs at different times both before and after birth. The latter include changes in the representation of HSCs that display specific differentiation programs, as well as changes in their turnover and self-renewal control. Here, we summarize recent studies characterizing these developmental changes, some of the mechanisms that control them, and their potential relevance to understanding age-associated differences in leukemia as well as normal hematopoiesis.