Kindlin-3-mediated integrin adhesion is dispensable for quiescent but essential for activated hematopoietic stem cells.

Hematopoietic stem cells (HSCs) generate highly dividing hematopoietic progenitor cells (HPCs), which produce all blood cell lineages. HSCs are usually quiescent, retained by integrins in specific niches, and become activated when the pools of HPCs decrease. We report that Kindlin-3-mediated integrin activation controls homing of HSCs to the bone marrow (BM) and the retention of activated HSCs and HPCs but not of quiescent HSCs in their BM niches. Consequently, Kindlin-3-deficient HSCs enter quiescence and remain in the BM when cotransplanted with wild-type hematopoietic stem and progenitor cells (HSPCs), whereas they are hyperactivated and lost in the circulation when wild-type HSPCs are absent, leading to their exhaustion and reduced survival of recipients. The accumulation of HSPCs in the circulation of leukocyte adhesion deficiency type III patients, who lack Kindlin-3, underlines the conserved functions of Kindlin-3 in man and the importance of our findings for human disease.