CD82/KAI1 Maintains the Dormancy of Long-Term Hematopoietic Stem Cells through Interaction with DARC-Expressing Macrophages

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Hematopoiesis is regulated by crosstalk between long-term repopulating hematopoietic stem cells (LT-HSCs) and supporting niche cells in the bone marrow (BM). Here, we examine the role of CD82/KAI1 in niche-mediated LT-HSC maintenance. We found that CD82/KAI1 is expressed predominantly on LT-HSCs and rarely on other hematopoietic stem-progenitor cells (HSPCs). In $Cd82^{-/-}$ mice, LT-HSCs were selectively lost as they exited from quiescence and differentiated. Mechanistically, CD82-based TGF-β1/Smad3 signaling leads to induction of CDK inhibitors and cell-cycle inhibition. The CD82 binding partner DARC/CD234 is expressed on macrophages and stabilizes CD82 on LT-HSCs, promoting their quiescence. When $DARC^{+}$ BM macrophages were ablated, the level of surface CD82 on LT-HSCs decreased, leading to cell-cycle entry, proliferation, and differentiation. A similar interaction appears to be relevant for human HSPCs. Thus, CD82 is a functional surface marker of LT-HSCs that maintains quiescence through interaction with DARC-expressing macrophages in the BM stem cell niche