'Selectin' endothelium to protect blood stem cells

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Hematopoietic stem cells (HSC) reside in anatomically defined regions that control their number and fate. These are referred to as the bone marrow niche or microenvironment. The composition of this niche is complex, with ever-increasing reports of different cell types regulating HSC, among them cells of the osteoblastic lineage,[1,2] endothelial cells,[3-5] reticular cells highly expressing Cxcl12,[6] Nestin-expressing mesenchymal cells[7] and non-myelinating Schwann cells.[8] Regardless of possible overlaps between different niche types, it is conceivable that such a plurality of niche cells orchestrate HSC behavior in response to specific needs.

Murine HSC represent a heterogeneous population, likely consisting of dormant cells with the potential of transient 'activation' into a proliferative pool upon hematopoietic stress or injury.[9] The factors regulating this functional switch have not been completely clarified, but distinct niches might facilitate different functional states. In particular, it has been hypothesized that the 'endosteal' ('osteoblastic') niche may govern quiescence[10] while 'endothelial' niches favor activation and proliferation, but this still remains to be defined in experiments.

A recent study by Winkler *et al.* generates novel insights on this topic.[11] The authors identified endothelial cell-derived E-selectin as a new regulator of HSC proliferation. HSC from *Sele*$^{-/-}$ mice showed increased quiescence and this dormancy was shown to be cell-non-autonomous in reciprocal HSC transplantation studies. In the environment, E-selectin was found to be exclusively expressed in endothelial cells and not in stromal subsets. While the proliferative effect of E-selectin on HSC was apparent under homeostatic conditions, its relevance became evident only under conditions of hematopoietic injury. HSC quiescence induced by genetic deficiency or pharmacological antagonism of E-selectin resulted in better survival of HSC after chemotherapy and accelerated recovery of hematopoiesis after irradiation.

While it remains to be determined what underlying mechanisms (either direct or indirect) govern the E-selectin induced proliferation of HSC and confirmation of endothelium-specificity awaits studies of targeted deletion, the paper offers intriguing perspectives for HSC biology and clinical practice.

The data reveal a previously unrecognized *in vivo* contribution of endothelial cells to HSC proliferation, adding further evidence to a functional role of this cell type in regulating HSC. Importantly, the data may also be of clinical relevance. The finding that pharmacological inhibition of E-selectin protected HSC through inhibition of proliferation could lead to the development of endothelium-targeting strategies in which transient blockade of E-selectin attenuates cytotoxicity to HSC and thus limits the duration of cytopenia and the associated clinical risks in patients treated with cell-cycle dependent myelosuppressive agents. It needs to be stated, however, that in the leukemia setting the specificity of these effects on hematopoietic rather than leukemic stem cells (LSC) first needs to be demonstrated, as this niche-targeting strategy could potentially also cause LSC protection from cell cycle-based anti-cancer therapies.

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