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Haematopoietic stem cells and their niches

Comment on: Miftakhova R, et al. Cyclin A1 regulates the interactions between mouse haematopoietic stem and progenitor cells and their niches. Cell Cycle 2015; 14(12):1948-60; PMID:25785996; http://doi.dx.org/10.1080/15384101.2015.1026513

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In adult bone marrow, the fate of haematopoietic stem and progenitor cells (HSPC) is regulated by multiple intrinsic cellular pathways, and is also dependent on the tissue microenvironment termed niches. At least 2 anatomical niches have been identified in the bone marrow: an endosteal niche near the bone surface and a perivascular niche adjacent to the endothelial sinuses.[1,2] The perivascular niches in part constitute of endothelial cells, mesenchymal stromal cells, which play an essential role in regulating stem cell self-renewal and differentiation.[2] HSPC are responsible for hematopoiesis, whereas their niches are required for the composition and structure of the bone marrow.[3] However, the cellular mechanisms underlying the interaction between HSPC and their niches are poorly understood. A recent study from Dr. Jenny L Persson's group at Lund University in Sweden, published in Cell Cycle issue [4] (2015 Mar 18:0. [Epub ahead of print]), suggests that there is a reciprocal relationship between HSPC and their niches. Cyclin A1, a cell cycle regulator, and vascular endothelial growth factor receptor 1 (VEGFR1) are involved in facilitating the interaction of HSPC with their niches in the bone marrow. In the absence of gene encoding for cyclin A1, the absolute number and frequency of HSPC are significantly increased in the BM, and the ability of HSPC to home and migrate to the endosteal and perivascular niche zones is impaired. Loss of cyclin A1 function in endothelial cells also results in increased microvessel density and altered structure of perivascular niches, leading to a reduced ability of the niches to engraft HSPC after bone marrow transplantation. These data suggest that loss of cyclin A1 impaired the proper physiological connection of HSPC with the endosteal and perivascular niches, thus disrupted proliferation and self-renewal of stem cells. Thus cyclin A1 is an important factor that contributes to the physiological interaction between HSPC and their niches (**Fig. 1**).

The authors further show that VEGFR1 expression is significantly increased in HSPC and endothelial cells of the bone marrow that lack *Ccna1* alleles of cyclin A1. Blockage of VEGFR1 production in the endothelial niche cells results into a decrease in HSPC numbers from cyclin A1-deficient bone marrow. This suggests that cyclin A1 regulates interactions of HSPC with their perivascular niches via VEGFR1-dependent signaling. Because circulating soluble VEGFR1 and VEGFR2 may have impact on VEGF-induced neovascularization,[5,6] the increased VEGFR1 level in cyclin A1-deficient endothelial cells may result in increased vascularization in the bone marrow. This study provides new evidence that VEGFR1 is an important component in perivascular niches which are required for controlling proliferation and

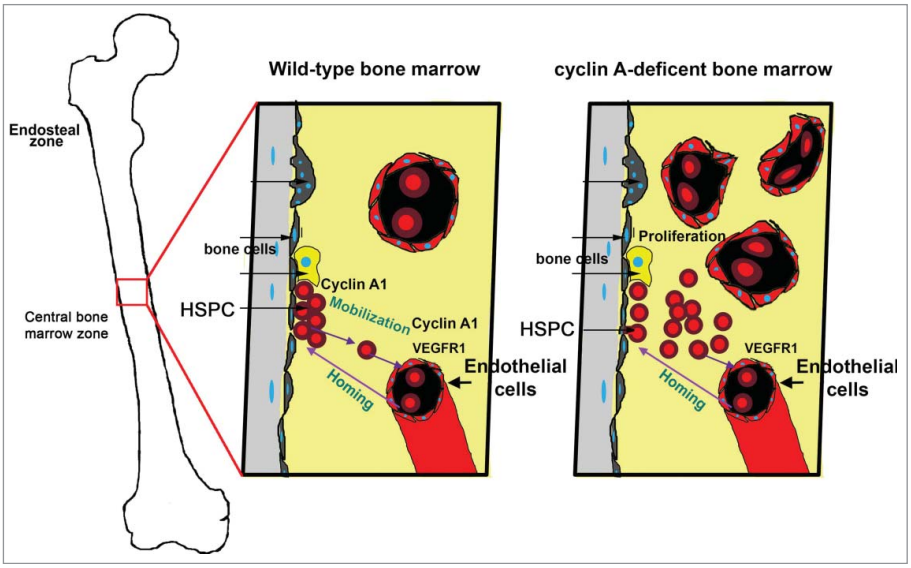

Figure 1. A schematic model to illustrate bone marrow microenvironment from the femur bone of wild-type of mouse vs. cyclin A1-deficient mouse. In the wild-type bone marrow, HSPC are resided in the endosteal niches near the bone surface. HSPC are constantly migrating to the central bone marrow zone where the perivascular niches are located. The endothelial cells may have a dominant and stimulatory influence on proliferation and migration of HSPC under homeostatic conditions. In cyclin Cyclin A1-deficient bone marrow, loss of cyclin A1 impairs the perivascular niches and proliferation of HSPC. There is an increase in HSPC numbers and perivascular vessels, and the process of homing and migration of HSPC is disrupted. The increased VEGFR1 in cyclin A1-deficient endothelial niche cells may be functionally linked to this process.

migration of HSPC (**Fig. 1**). It will be interesting to further investigate the underlying mechanisms on how cyclin A1 is functionally associated with VEGFR1 signaling in haematopoietic system. Thus, understanding the interplay between cyclin A1 and VEGFR1 in HSPC and their niches may provide new insights into therapeutic approaches.

References

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