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Intimacy of the Niche: Perivascular Remodeling Cuddles Incoming HSCs

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Abstract

Stem cells reside in “niches,” which provide signaling cues necessary for self-renewal. In a recent issue of Cell, Tamplin et al. (2015) perform live imaging of hematopoietic stem and progenitor cells (HSPCs) and find dynamic remodeling of endothelial cells is triggered upon arrival of HSPCs at the caudal hematopoietic tissue.

Tissue stem cells underlie the development and homeostasis of each major organ system. They reside in unique microenvironments known as “niches,” which are necessary to maintain stem cell survival and self-renewal over the lifetime of the organism. Over the last decade, we have gained a better understanding of the cell types and signals necessary for stem cell retention in a tissue. Many features are conserved across diverse organs and organisms, and paradigms of how stem cell niches operate have emerged (reviewed in Morrison and Spradling, 2008). However, we currently lack a detailed understanding of the cellular interactions and steps required for hematopoietic stem and progenitor cell (HSPC) niche formation and function, in part due to the difficulty of live cell imaging in vivo. Recent advances in imaging approaches have opened new avenues of inquiry into the in vivo behavior of murine HSPCs (Lo Celso et al., 2009; reviewed in Joseph et al., 2013). Similarly, in a recent issue of *Cell*, Tamplin et al., (2015) have exploited the transparency of the zebrafish embryo to perform high-resolution imaging of HSPC interactions with cells in the caudal hematopoietic tissue (CHT), where nascent HSPCs first establish residency. They discover a stereotyped cellular behavior that is triggered in endothelial cells of the CHT upon HSPC arrival. Importantly, this behavior appears to be conserved over evolution, as Tamplin and colleagues observe similar interactions between nascent HSPCs and their vascular niche in the murine fetal liver ex vivo.

HSPCs give rise to all adult blood cell types, including the myeloid, lymphoid, and erythroid lineages. Vertebrates share a high degree of conservation in the molecular and cellular processes required for the genesis, maturation and maintenance of HSPCs (reviewed in Clements and Traver, 2013). After specification in the floor of the dorsal aorta, HSPCs migrate through transitory niche sites, which include the fetal liver and spleen in mammals and the CHT in teleosts. In these transient tissues, HSPCs expand and mature before colonizing their adult niche sites. Live imaging has significantly enhanced our understanding

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of biological processes, providing information that would be unattainable through still images. Here, Tamplin et al. (2015) use the translucent zebrafish embryo to obtain high-speed, high-resolution images and gain a better understanding of the complex cellular interactions that occur between the stem cell and its endothelial niche.

Tamplin and colleagues first generate a highly specific marker for HSPCs. They establish a transgenic zebrafish line with the well-characterized murine Runx1 +23 enhancer element (Bee et al., 2009), which drives the expression of a reporter EGFP or mcherry (*Runx:EGFP*, *Runx: mcherry*) fluorophore. Importantly, serial dilution transplantation assays demonstrate the ability of runx:EGFP+ cells to reconstitute the adult marrow of recipients. This demonstrates that Runx+ HSPCs possess the hallmarks of HSCs, namely self-renewal and multipotency. These functional studies represent an important advance in the study of HSCs in the zebrafish embryo, something that has previously been lacking.

To directly image the cellular interactions between Runx:EGFP+ HSPCs and the transient niche in the CHT, time-lapse imaging using spinning disk confocal microscopy was performed. HSPCs are observed to exit from circulation and lodge upon the outer wall of the endothelium. Within minutes, a small group of endothelial cells remodel their membranes to surround a single HSPC and form a pouch, which the authors refer to as “endothelial cuddling” (Figure 1).

Next, because perivascular cells have been demonstrated to be key niche elements in mammalian bone marrow (Méndez-Ferrer et al., 2010; Ding et al., 2012), the authors make use of a *cxcl112a:DsRed2* transgenic zebrafish, which labels mesenchymal stromal cells in the CHT. *Cxcl12:DsRed2+* cells appear similar to the “fibroblastic reticular cells” previously observed in the CHT (Murayama et al., 2006). The authors observe close association between *cxcl12a: DsRed*+ and endothelial cells in the CHT. Furthermore, when co-imaged with Runx+ cells, they observe that many HSPCs are in direct contact with them. Interestingly, the division plane of HSPCs within the vascular niche may be dictated by the orientation of HSPCs relative to their stromal neighbors. It may thus be possible to address whether or not the stromal niche instructs asymmetric stem cell division, a demonstrated feature of the stem cell niche in other systems, including the germline of *Drosophila melanogaster* (reviewed in Morrison and Spradling, 2008).

Finally, the authors perform a high-throughput chemical screen to identify compounds that modulate HSPC seeding of the CHT. 147 bioactive compounds (out of 2400), were found to modulate hematopoietic marker expression in the CHT. From these, they identify an interesting compound, Lycorine, which is currently being studied for its anti-cancer and anti-inflammatory properties (Kang et al., 2012). The authors find that embryos treated with Lycorine during niche colonization have increased in HSPC numbers in the CHT. Strikingly, transient administration of Lycorine during embryogenesis led to sustained increases in Runx+ HSPC number 3 months later in the adult kidney. By performing gene expression analysis of HSPCs and endothelial niche cells following Lycorine treatment, the authors identify significant changes in the expression of genes involved in cell adhesion, including CXCR4. Future work should determine the specific pathways through which Lycorine acts, as it has a potential use in the treatment of hematopoietic disease.

Together, the current work describes a novel niche for emerging HSPCs and highlights the utility of live cell imaging to understand the stepwise progression of niche formation. However, many questions still remain. What is the molecular basis for HSPC/niche recognition, remodeling, and retention? Of the several cell types that make contact with HSPCs, which are key in maintaining HSC fate? Are the molecular networks utilized in the CHT niche maintained in the subsequent niche of the kidney? Are the functions of these identified stromal elements conserved with their counterparts described in murine bone marrow? These studies set the stage for continued live cell imaging to better understand how different signaling pathways integrate to control stem cell fate decisions during homeostasis and disease. It will be important to create new fluorescent reporter lines to better delineate HSCs from their progeny and to more precisely follow HSCs as they shift from niche to niche during development. The findings of Tamplin et al. (2015) position the zebrafish for the elucidation of these issues and provide the framework for continued high-resolution imaging of stem cell-niche interactions.

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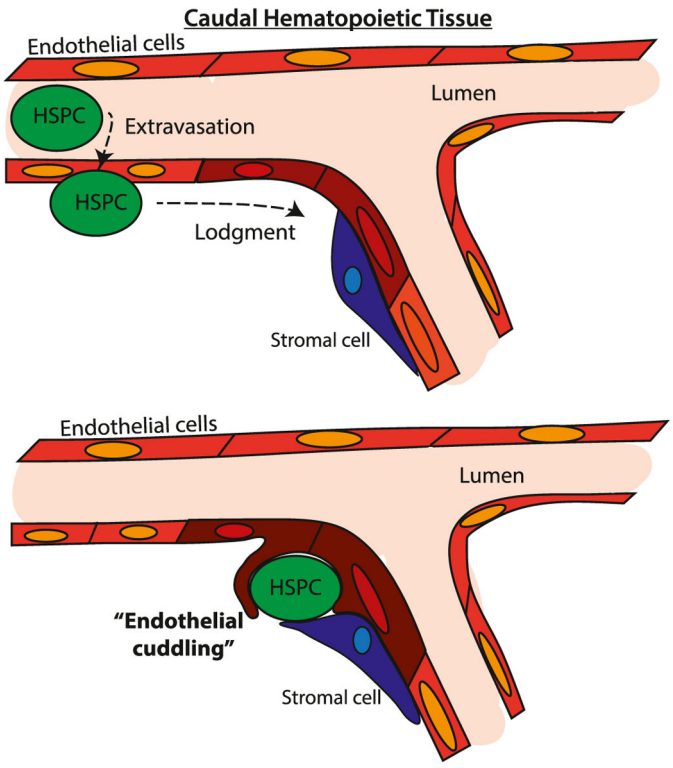

Figure 1. Remodeling of the Endothelial Niche Cells in the CHT

HSPCs (green) arrive to the CHT via circulation, extravasate, and lodge at the outer wall of the endothelium. A small group of endothelial cells (red), different from those that make initial contact, undergo "endothelial cuddling," remodeling their membranes around a single HSPC. Stromal cells (blue) are located adjacent to the HSPC. Previous work has shown that perivascular stromal cells are necessary for HSPC maintenance in mouse bone marrow (Ding et al., 2012).