Cell Cycle 13:10, 1511–1512; May 15, 2014; © 2014 Landes Bioscience

Driving human–mouse avatars to understand the HSC niche

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Adult stem cells hold immediate clinical applications, where hematopoietic stem cell (HSC) are the best-characterized somatic stem cell and are currently used in bone marrow (BM) transplantation (BMT). Human BMT, however, is still constrained by inefficiencies of achieving long-term hematopoietic reconstitution, which is thought to arise from an inability to expand HSCs ex vivo,[1] and by the difficulty in obtaining larger numbers of donor HSCs.[2] Thus, a shift in research focus has mounted to understand the molecular and cellular mechanisms that control HSC's regenerative function in vivo that includes interaction with specialized BM microenvironment called "niche."[3] The concept of the niche was originally proposed to capture and define spatial structure within the supportive BM in which HSCs are housed and maintained during homeostasis, but grew rapidly in complexity to encompass the dynamic turnover between self-renewal, differentiation, quiescence, and dormancy during steady-state or in response to injury.[4] These regulatory processes are primarily dependent on the cellular composition of the HSC niche characterized in mouse studies[5] that include bone-lining osteoblasts, vascular cells, osteoprogenitors, stromal cells, osteoclasts, adipocytes, and neurons. In the human, precise characterization of the human BM niche remains unclear, and future studies are hindered by the absence of model systems that validate human HSC niche regulators beyond observational data obtained during BMT in the clinic.

Putative human HSCs have been identified and enriched based upon their ability to reconstitute multilineage hematopoiesis in immunodeficient NOD/SCID mice, and thus are functionally defined as SCID repopulating cells (SRC).[6] The SRC assay, therefore, includes unique features, allowing infused human HSC to grow, self-renew, and differentiate within mouse BM, providing a real-time measurement of HSC regeneration in vivo.[6] Aside from the physiological and anatomical boundaries between human and mouse, the current consensus about the SRC assay is that the human xeno-engrafted hematopoietic cells should represent a biological phenocopy of the original HSC source in humans. The underlying assumption is that the human SRC assay could serve as more than a surrogate readout of HSC transplantation, but may also serve as an "avatar" to study dynamic interactions of human HSC with cells comprising the BM niche or influences of administered drugs.

To this point, we have recently compared the HSC–BM microenvironment between mouse–human xenografted bones and human bone trephine biopsy. Both revealed similar anatomical structures, with a dichotomy between enriched cortical bone or trabecular area (TBA) and fewer/sparse long bone area (LBA), and enrichment of human HSCs within the osteoblastic endosteal BM niche tightly interconnected to osteoprogenitors cells and vasculature.[7] Importantly, LBA and TBA immunophenotypic similarities (frequencies and total number of cells) were observed in humans vs. human–mouse xenografts for putative human HSCs ($CD34^+$ $CD38^-$), HSCs subsets ($CD49f^+$ and $CD49^-$), as well as late progenitors ($CD34^+$ $CD38^+$), representing the first in situ identification of the anatomical position of human HSCs in the BM space.[7] Functionally, both de novo (human BM biopsies) and engrafted human engrafted HSCs (xenotransplants) showed superior TBA vs. LBA hematopoietic progenitors potential, and HSCs from the TBA displayed superior long-term reconstitution activity and self-renewal capacity when infused in secondary recipients.[7]

As this dynamic distribution between TBA and LBA regions of the BM develop shortly after the transplantation of human HSCs, its seems that HSC heterogeneity from humans is more likely not cell-autonomously dependent, and is governed by specific interactions with different specialized BM niches. This idea was corroborated by the gene expression profiling of both functionally validated SRC isolated fractions from the TBA vs. LBA matched interacting endosteal niche cell subsets and showed prevalence of Notch signaling (through contact with osteoblasts) known to be directly involved in human HSC function.[8] We further illustrated the presence of a Notch receptor–ligand axis in TBA endosteal niche by the disruption of human HSCs anatomical location and their functional regenerative capacity in recipient mice following in vivo administration of Notch inhibitors.[7] Corroborating these observations with an independent approach, isolation of Jagged1-binding human HSCs showed superior hematopoietic regenerative capacity upon transplantation. We propose the concept of "extended phenotype" to functionally define human HSCs that

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Submitted: 03/04/2014; Accepted: 03/10/2014; Published Online: 04/22/2014
http://dx.doi.org/10.4161/cc.28958
Comment on: Guezguez B, et al. Cell Stem Cell 2013; 13:175-89; PMID:23910084; http://dx.doi.org/10.1016/j.stem.2013.06.015

incorporates HSCs as an independent cellular entity, together with complex BM architecture that ultimately equates to desired HSCs properties used in BMT clinically.

Ultimately, despite a number of caveats and uncertainty still to be optimized in future studies, we have been able to demonstrate that in vivo reconstitution of human SRC is able to model human HSC–BM niche interactions that recapitulate anatomical location and functional properties in human patients. As this extends beyond the use of the SRC assay as a surrogate readout alone, we believe these new insights will serve as an appealing tool to test novel approaches for manipulating human HSCs to enhance engraftment of normal stem cells and perhaps prevent leukemia relapse in clinical settings as a unifying goal of BM niche regulation.

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