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Breaking the classic niche model: HSC quantity dually constrained by systemic and local factors

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Hematopoiesis ensures a continuous supply of blood cells and plays a vital role in sustaining life and health. This process relies on a limited number of hematopoietic stem cells (HSCs), which possess the ability to self-renew and differentiate into all blood cell types. For a long time, it has been believed that the number of HSCs is primarily regulated by the HSC niche,[1] which is a functional unit composed of various cellular components and cytokines. The HSC niche could provide a suitable microenvironment that supports HSCs in maintaining self-renewal, long-term survival, and quiescence.

The HSC niche is composed of various cell types, including mesenchymal stem cells (MSCs), endothelial cells (ECs), osteoblasts, adipolineage cells, sympathetic nervous system nerves, and others. Among these, MSCs and their differentiated stromal cells are important regulators of HSC activity. They secrete cytokines such as CXCL12 and SCF, which mediate the directional migration and anchorage retention of HSCs, and directly support the survival and self-renewal of HSCs. It is reported that conditional knockout of nestin$^+$ MSCs in mice leads to a reduction in HSCs and progenitor cells in the bone marrow. ECs also play a regulatory role in HSC proliferation and lineage commitment through the expression of key signaling molecules like CXCL12, SCF and Notch ligands. Conditional knockout of *Cxcl12* in ECs leads to a reduction in HSC numbers. Moreover, endothelial-specific ablation of *Scf* results in a significant reduction of the bone marrow HSC pool.[2] Osteoblasts secrete CXCL12 as well, and *Cxcl12* deficiency in osteoblasts results in a decrease in early lymphoid progenitors, but does not affect HSC populations. Similarly, conditional knockout of *Scf* in osteoblasts shows no obvious impact on HSC frequency or function, implying that cytokines originating from distinct niche cell types have distinct contributions to the maintenance of HSCs. Osteoblasts also secrete angiopoietin-1, which promotes adhesion and quiescence of HSCs by interacting with the receptor tyrosine kinase Tie2.

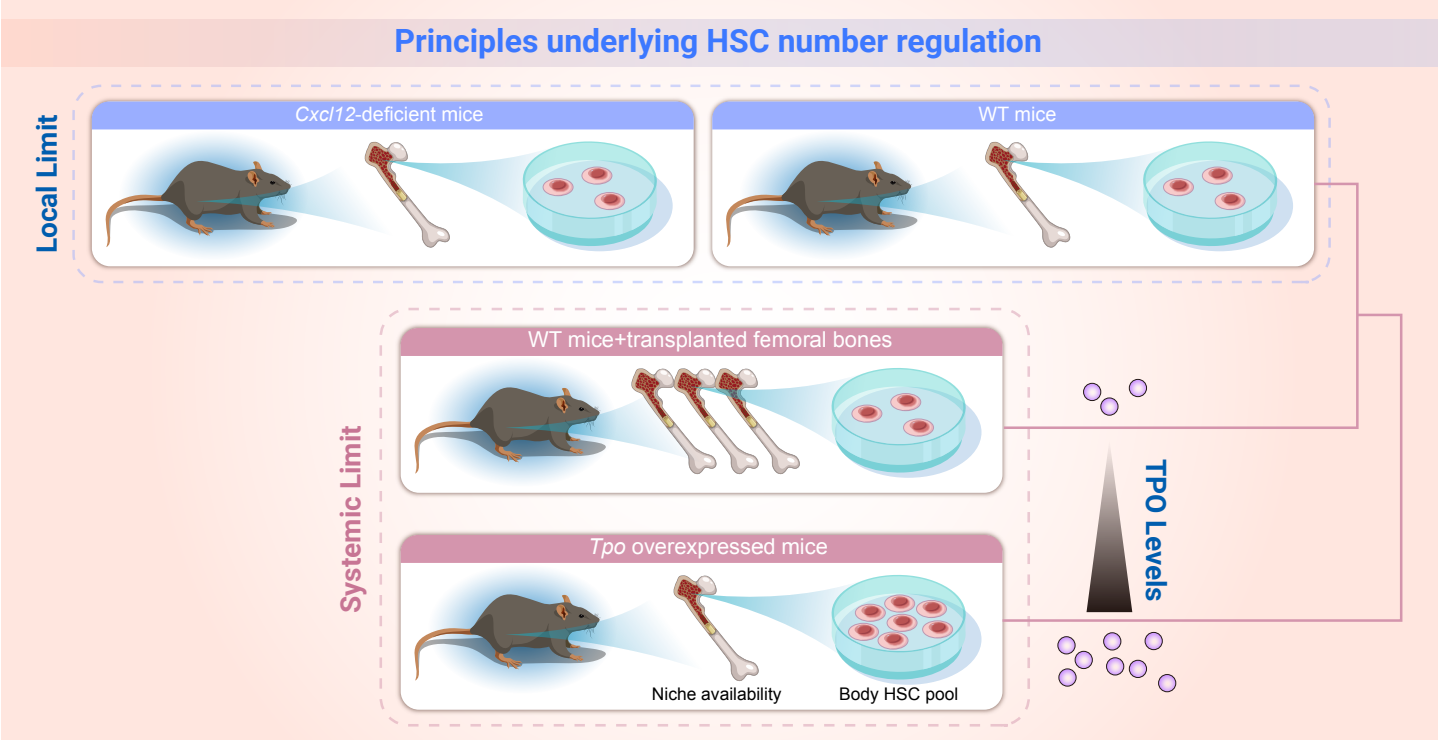

Figure 1. HSC numbers are restricted at both the systemic and local levels HSC numbers are controlled by two separate mechanisms: one acts systemically to limit the overall population, whereas the other acts locally to restrict it within the bone marrow. Localized irradiation and femur transplantation into *Cxcl12* deficient mice demonstrate a local constraint on HSC numbers within each intact niche. Femoral bone transplantation experiments revealed that the total HSC number in the body does not exceed the systemic threshold even when niche availability increases. Mice with aberrant TPO expression demonstrated that TPO levels determine systemic HSC numbers.

Furthermore, studies have revealed that activation of PTH/PTHrP receptors in the osteoblast population leads to an increase in osteoblast numbers, producing elevated levels of Notch ligand Jag1.[3] Jag1 drives the expansion of the HSC population through the activation of Notch signaling.[3] Bone morphogenetic protein signaling governs HSC numbers by modulating niche size through the BMPRIA receptor.

The aforementioned studies demonstrate that the HSC numbers are regulated by multiple cellular and cytokine components within the niche. Beyond these factors, metabolic pathways also play a critical role in controlling HSC numbers. For example, HSCs cultured in serine/glycine-deficient media show compromised homeostasis and a marked decline in population.[4] Protein homeostasis also influences HSC numbers. In *Fancd2* (a Fanconi anemia-associated gene) knockout mice, misfolded proteins accumulate in fetal liver HSCs, inducing endoplasmic reticulum stress and ultimately decreasing HSC

numbers during mid-gestation. Collectively, the mechanisms governing HSC numbers extend beyond the constraints of the HSC niche.

The long-standing paradigm posited that endogenous HSC expansion was constrained by niche availability, with new HSC engraftment possible only following the creation of a vacancy by the loss of a resident HSC. However, this concept was challenged by a study in which purified HSCs were transplanted into non-myeloablated, normal mice. The donor HSCs did not replace the host HSCs but instead engrafted in niches that were distant from the host niches, leading to increased HSC numbers. Nevertheless, the exact regulatory mechanisms underlying HSC numbers remain unknown.

Recently, a study published in *Nature* by Ulrich Steidl, Shoichiro Takeishi, and colleagues from the Albert Einstein College of Medicine revealed the core principles of HSC number regulation (Figure 1).[5] To analyze the impact of niche capacity expansion on HSC numbers, the authors developed a femoral bone transplantation model. A femur from a wild-type (WT) mouse is entirely transplanted under the skin of another recipient mouse. The transplanted femur can reconstruct a functional HSC niche, allowing HSCs from the recipient mouse to home and engraft within it while maintaining normal hematopoietic differentiation capacity. Thus, this transplantation model provides the mouse with an additional HSC niche. Besides, this femur transplantation system has potential applications for investigating the bone marrow microenvironment, as subcutaneously implanted femurs successfully revascularized and established a functional ectopic niche. Based on this model, the authors transplanted six WT femurs simultaneously into a WT mouse. Although the number of HSCs decreased in each individual bone, the total HSC count in the recipient mouse—now carrying six additional femurs—did not exceed the level observed in control mice. This indicates that the total number of HSCs in a mouse is not determined by the capacity of the HSC niche.

Subsequently, the authors utilized *Cxcl12* knockout mice to investigate local regulatory mechanism of HSC numbers. In *Cxcl12*-deficient mice, bone marrow HSCs are mobilized into the peripheral circulation. However, the number of HSCs in the transplanted femurs did not increase despite the elevated HSC count in the blood. The total HSC count in the transplanted bones still did not exceed the normal physiological level. Furthermore, researchers found that irradiation-induced reduction of HSCs in limb bone marrow was not accompanied by compensatory expansion in unirradiated bones. This demonstrates that each HSC niche operates under its own local constraints. This indicates that the HSC population within each niche is locally constrained.

Using *Kitl* conditional knockout mice with severely depleted HSCs, the authors assessed potential recovery mechanisms. Notably, the HSC pool could not be reconstituted through transplantation of extra femurs, G-CSF-mediated mobilization, or splenectomy. Only partial recovery was achieved via exogenous HSPC infusion, demonstrating that endogenous HSC numbers are under strict regulation.

Finally, studies in mice with aberrant TPO expression revealed that TPO acts as a critical systemic factor determining the upper limit of total body HSC numbers. Previous research had already established that TPO promotes HSC self-renewal and expansion following bone marrow transplantation. Beyond this, it is worth considering whether additional factors operate at the systemic level to regulate HSC abundance. Furthermore, the molecular mechanisms underlying abnormal HSC numbers in hematological pathologies remain an open question. This study, through well-designed mouse models, has clearly elucidated the regulatory mechanisms controlling HSC numbers at both systemic and local levels, paving the way for refined bone marrow transplantation therapies. The findings from this study could have significant implications in several research areas and diseases. In hematological malignancies, understanding the restrictions on HSC numbers could lead to novel therapeutic strategies aimed at preventing leukemogenesis by maintaining HSC numbers within safe limits. Additionally, in bone marrow transplantation and regenerative medicine, insights into niche availability and HSC homeostasis may improve transplantation outcomes and recovery processes. This research might also impact the treatment of conditions like aplastic anemia or other bone marrow failure syndromes, where enhancing HSC replenishment and function is crucial. Overall, these shifts in perspective could pave the way for more targeted and effective clinical interventions across a range of hematological and regenerative medicine applications.

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DECLARATION OF INTERESTS

The authors declare no competing interests.