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The Nature of the Haematopoietic Stem Cell Niche

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Introduction

Haematopoietic stem cells (HSCs) are responsible for regulating the turnover of red blood cells (erythrocytes) and platelets including immune cells by switching between the cellular mechanisms of self-regeneration, quiescence, differentiation, and dormancy[1]. However, self-renewal occurs only within the HSC niche. In this regard, the HSC niche is a specific anatomical location (node) in which HSCs reside and undergo self-regeneration. HSCs anatomically located outside the HSC niche have no microenvironments to support self-regeneration but can undergo cellular differentiation to produce mature erythrocytes and platelets[1,2]. Therefore, HSCs and their associated niches are responsible for haemostatic balance during steady state and in response to cellular injury due to bleeding, hypoxia or infection[1, 3].

The HSC niche has become a central area of study, with studies increasingly focusing on the identification and characterisation of cells making up the HSC niche[2]. There is growing evidence that the HSC niche has important role in the pathogenesis of haematopoietic diseases such as myeloproliferative syndrome (MPS) and other congenital haematological diseases[4]. Therefore, the success of such studies is likely to enhance the development biotherapies targeting stem cells to induce remission of such haematopoietic diseases[4].

This paper critically examines the current state of understanding about HSCs and the nature of the HSC niche.

Endosteal/Osteoblastic niche

There are two types of bone cells based on their functional role, osteoblast cells (bone-forming cells) and osteoclast cells (bone-resorbing cells). They are important for bone modelling and remodelling regulation, which involve some factors production. HSCs have calcium-sensing receptors, which make them closely to endosteal surface. This surface contains a high level of calcium due to the activity of osteoblast and osteoclast cells. Therefore, bone modelling and remodelling have an important role in HSC niche formation[5].

Morphologically, there are two types of osteoblast cells lining the endosteal surface: cuboidal cells and spindle-shaped N-cadherin-positive CD45 cells. OBLs support HSC homeostasis through notch ligand jagged 1. Calcium and angiopoietin 1 (Ang-1) are produced from these cells, which have receptors on HSCs. These factors are important for the expansion of HSCs. Stromal-

derived factor 1, which is also released from mesenchymal cells in additional to OBLs, is the major chemoattractant for haematopoietic progenitors. However, nestin-positive mesenchymal stem cells (MSCs) are evolving in HSCs maintenance but osteopontin inhibits the proliferation of HSCs[5–7].

OCLs play important roles in the HSC niche. They release proteolytic enzymes that are needed in the HSC niche by cleaving various factors. They stimulated by growth factors, proteins and bone minerals, which induces bone resorption and affect the maintenance and mobilisation of HSCs. The bone-marrow (BM) HSC niche is extremely affected by the absence of OCLs, which results in the impairment of progenitor-cell expansion. In metabolic bone diseases such as osteoporosis and Paget's disease, when associated with extra-medullary haematopoiesis, OCLs have a role in the initial formation of HSC niches. Studies analysing mice BM HSCs treated with zoledronic acid (ZA; used in the treatment different types of metabolic bone disease) found that the treatment caused a marked increase in HSC and vessel numbers in addition to an increase bone volume. This suggests that ZA can support HSCs through osteoblastic niches[5, 8].

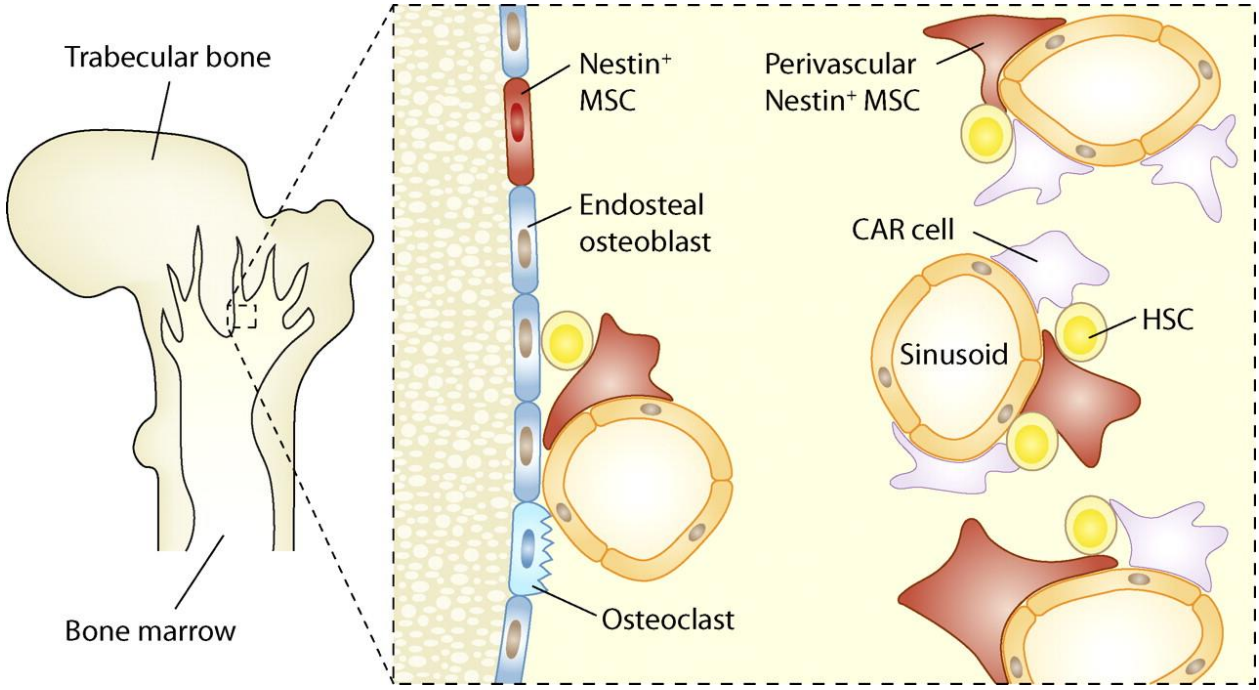

Figure 1. The location of HSCs in bone [9].

Vascular niche

Another type of niche is called a 'vascular niche'. These result from BM sinusoidal walls that are associated with HSCs. 'Sinusoids' are blood vessels with capillaries lined with endothelial cells and covered by reticular cells. Endothelial cells play an important role in HSC maintenance. Some studies have shown that a decreased level of vascular endothelial growth factor receptor 2 results in a decrease in the renewal of endothelial cells, which in turn leads to a reduction in HSC restoration. Reticular cells are found in both vascular and endosteal regions. They are also important for HSC maintenance, as they produce stem cell factor (SCF) and chemokine CXCL 12. CXCL 12 reticular (CAR) cells can differentiate into osteoblasts and adipocyte. Thus, CAR cells depleted result in decreased number of these cells in additional to HSCs affected [7].

Table 1. Regulatory factors in BM niches [6, 10].

Factor	*In vivo* HSC regulation function
Jagged 1	Produced from OBLs and bind with correlates with an increase in notch-1 receptor on HSCs. It is important for HSC expansion
Ang-1	Produced from OBLs and binds to its receptor Tie2 on HSCs to help in maintenance of the HSC niche
Thrombopoietin	Important for maintaining HSC numbers and quiescence. It is released from OBLs
Osteopontin	Released from MSCs to inhibit proliferation of HSCs
SCF	Important in HSC quiescence and adhesion; produced from reticular cells
Chemokine CXCL 12	Released from CAR cells, which have a role in HSC migration and maintenance

Nervous system and adipocytes

The sympathetic nervous system releases adrenaline, which is important for regulating HCS niche migration from BM by regulating the production of CXCL 12 from BM cells. Some studies have shown that the number of HSCs isolated from BM is affected by adipocyte cells. Adipocytes have a negative effect on HSC niches by suppressing the regeneration of haematopoietic cells through secretion of inhibitory mediators such as neuropillin-1, lipocalin-2 and tumour necrosis factor (TNF)-alpha [4,10].

BM micro-environmental defects and haematopoietic abnormalities

Several studies have shown that some haematopoietic diseases released form defect in BM micro-environment. For example, MPS is due to nuclear receptor retinoic acid receptor deficiency, which leads to an increase in granulocytic progenitors and granulocytes in the BM and peripheral blood. This results in changes in the BM micro-environment and reduced maintenance of HSCs. This is mediated by TNF-alpha[4].

Conclusion

BM contains two types of niche: endosteal and vascular. These are important for HSC maintenance, regulation, regeneration and migration to the peripheral blood through regulatory factors secreted by different cell types. Although it is not possible to study HSCs *in vitro* due to their strict niches, new studies are interested in determining the factors for optimal HSC niche functioning. There is growing evidence that the HSC niche has an important role to play in the pathogenesis of haematopoietic diseases. Therefore, the success of such studies is likely to enhance the development biotherapies targeting stem cells to induce remission of these diseases.

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