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Guest editorial: hematopoietic regulators in the marrow: new players in inter-organ communication

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Hematopoietic stem/progenitor cells (HSCs/HPCs) possess the ability to maintain the entire population of blood cells throughout life and to replenish the hematopoietic system after transplantation into marrow-ablated recipients. Bone marrow is the primary organ for hematopoiesis, in which HSCs/HPCs reside in microenvironments adapted to supporting their activity. Such a specialized microenvironment is called a "niche".

The skeletal and the hematopoietic systems are two different research lines now being united through the definition of a new function of bone-forming osteoblasts as a regulatory niche for HSCs/HPCs in 2003. Since that time, the specific cell types that harbor niche function continue expanding in the perivascular area, such as CXCL12-abundant reticular cells, nestin$^+$ mesenchymal stem cells (MSCs), endothelial cells, perivascular leptin receptor$^+$ stromal cells, and α SMA$^+$ macrophages. HSCs are located adjacent to these supporting cells. Depletion of these supporting cells or factors produced by these cells results in the decrease of HSCs/HPCs or deregulation of their behavior.

In addition to the accumulation of knowledge about niche cells themselves, novel findings about cells regulating niche function (niche modulators) have also recently emerged. In this issue, four excellent and informative review articles by young investigators (Asada, Casanova-Acebes, Yamazaki, and Kunisaki) cover recently identified novel niches and niche modulators in the bone marrow (Fig. 1).

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The endosteal microenvironment has been extensively characterized, as the osteoblast is the first niche cell type to be identified and functionally characterized. In addition to osteoclast, which has been reported as modulating the HSC/HPC niche, the third player in the bone metabolism is the osteocyte, the terminally differentiated osteoblast-lineage cell. It is now well known in the research field of bone metabolism that osteocytes are major conductors of bone homeostasis, which they achieve by regulating the balance between osteoblast and osteoclast. Asada summarizes the importance of this cell type for the regulation of endosteal microenvironment in association with sympathetic nervous system (SNS) and macrophages [1].

The circadian rhythm of the number of circulating HSCs/HPCs in steady state was first reported to be regulated by SNS. It is also known that terminally differentiated descendent "neutrophils" demonstrate circadian rhythmic activity in association with their senescence. This indicates potential synchronization between mature and immature hematopoietic cells. Casanova-Acebes has discovered that this phenomenon appears to be orchestrated by bone marrow macrophages that communicate with the HSC/HPC niche. In her review, she summarizes the general functions of macrophages in the homeostasis of hematopoietic system [2].

Although it has been known that bone marrow is a highly innervated organ, the exact roles of the nervous system in hematopoiesis have only emerged recently. The maintenance of HSC quiescence is critical for avoiding hematopoietic cell exhaustion. Yamazaki reported that the key factor for HSC quiescence is transforming growth factor-β, and he summarizes a novel role for the nervous system as a major producer of this hibernation factor in the bone marrow [3].

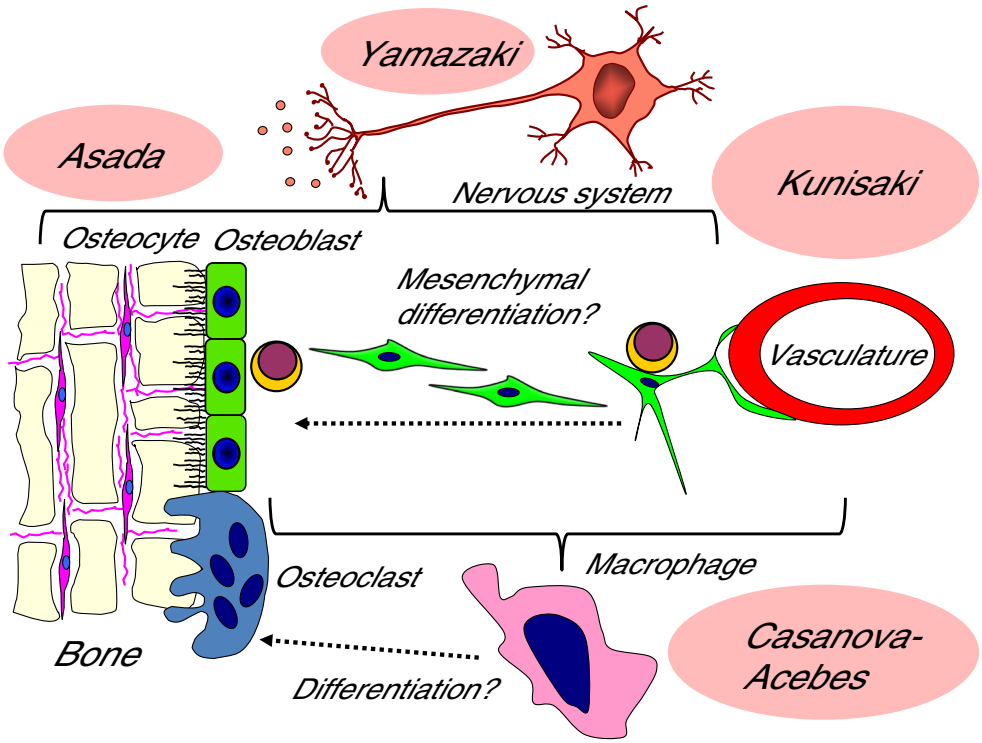

Fig. 1 Hematopoietic microenvironment and niche-modulators. Inter-communication of bone metabolism, innate immunity, nervous system, and vascular networks makes the bone marrow functional (summarized in this Progress In Hematology review series)

Nestin^{+} MSC has been intensively characterized by the Frenette lab as a vascular HSC niche that interacts with SNS and macrophages. They recently found that a population among nestin^{+} MSCs is arteriole-associated pericyte. Kunisaki summarizes spatially and functionally distinct vascular niches [4].

This series of progress in hematology review articles will help us understand more deeply how communication between bone metabolism, innate immunity, nervous system, and vascular networks makes the bone marrow such a highly functional and sophisticated organ.

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