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Vitamin D receptor: a critical regulator of inter-organ communication between skeletal and hematopoietic systems

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Abstract

The functions of vitamin D receptor (VDR) have been extensively studied, for example, in the bone biology field. It is widely known that VDR knockout mice display the characteristic features of rickets type II. However, the contribution of VDR signaling to bone marrow (BM) hematopoiesis in association with the phenomena observed in clinical hematology has not been evaluated thoroughly. Hematopoietic stem cells (HSCs) can be mobilized from the BM into and harvested from peripheral blood as a BM transplantation source for the curable treatment of hematologic malignancies. This HSC mobilization can be achieved by the administration of cytokine granulocyte colony-stimulating factor (G-CSF) for several consecutive days. We have reported that, using the murine model, G-CSF induces the high sympathetic tone in the BM and a β_2-adrenergic signal into osteoblasts induces a rapid and drastic increase of VDR, which is critical for the subsequent cascade for HSC mobilization. This is an example of the transient deviation of the inter-organ communication in three different systems (nervous, skeletal, and hematopoietic) bridged by VDR in osteoblasts. It would be important to reconsider VDR as a pivotal molecule that mediates inter-organ communication to broaden the application of vitamin D signal modulators.

Keywords:

vitamin D receptor, hematopoietic stem cells, sympathetic nervous system, osteoblasts, mobilization

In clinical hematology, hematopoietic stem cell transplantation is an important therapeutic option for intractable blood diseases, such as leukemia and lymphoma. Bone marrow (BM) used to be the only source for transplantation. However, cytokine granulocyte colony-stimulating factor (G-CSF) has been identified as a strong mobilizer of hematopoietic stem/progenitor cells (HSCs/HPCs) from the BM to peripheral blood, and now the majority of transplantation source has been replaced by the G-CSF-mobilized peripheral blood instead of BM. In spite of the worldwide clinical utilization of peripheral blood stem cell transplantation, the mechanism of how G-CSF induces the mobilization of HSCs/HPCs from the BM to circulation is unclear. Several phenomena in the BM during G-CSF-treatment are thought to be associated with mobilization such as the strong down-regulation of chemokine CXCL12, which are produced by osteolineage cells and anchors HSCs/HPCs in the BM,[1-3] and the suppression and decrease of bone forming osteolineage cells which are utilized as the microenvironment for HSCs/HPCs.[4,5] However, precise signaling relay from G-CSF to these microenvironmental defects has not been elucidated.

In this mini-review, the studies about the interaction between bone forming and blood forming systems for HSC/HPC trafficking and the essential role of vitamin D receptor (VDR) in the regulation of this communication will be introduced.

Endosteal microenvironment for bone metabolism and hematopoiesis

In the endosteal region, bone-forming osteoblasts and bone-resorbing osteoclasts cooperate to keep the homeostasis of bone metabolism. Moreover, the matrix-embedded osteocytes regulate this balance and control the status of the bone tissue.[6] In addition, macrophages located near the endosteum, called “OsteoMac”, are reported to be critical supporters of osteoblasts.[7] The deletion of macrophages leads to the rapid disappearance of osteoblasts.[8,9] Furthermore, we recently reported that BM neutrophils also support osteoblast function by producing prostaglandin E_2 by the stimulation of the sympathetic nervous system (SNS).[10] Our previous studies showed that signals from the SNS in the

BM triggered by G-CSF suppress the activity of osteoblasts and osteocytes, leading to the HSC/HPC release from the BM (mobilization) by the loss of functions as their supporting microenvironment.[5,11] Thus, several kinds of myeloid lineage hematopoietic cells differentiated from HSCs (osteoclasts, macrophages, and neutrophils) and osteolineage cells differentiated from mesenchymal stem cells (osteoblasts and osteocytes) tightly cooperate to form bone tissue and many of these players are regulated by the nervous system (Figure 1).[12,13]

VDR in the regulation of the endosteal microenvironment for HSCs/HPCs

As mentioned before, the exogenous administration of cytokine G-CSF induces HSC/HPC mobilization from the BM to circulation. The detailed mechanisms are as follows. Sympathetic nerves express functional G-CSF receptor and the stimulation of this receptor directly inhibits the reuptake of neurotransmitters released in the synapse.[14] Thus, G-CSF administration for several consecutive days induces high catecholaminergic state in the BM. Osteoblasts express β_2-adrenergic receptor (AR) and the stimulation of this receptor by the high catecholaminergic tone strongly inhibits osteoblast activity. As a consequence, HSCs/HPCs that use osteoblasts as a part of their microenvironment are released from the BM.[5] However, the downstream signal of β_2-AR in osteoblasts during G-CSF-induced HSC/HPC mobilization is unclear. Because calcium regulation is critical for bone metabolism, we hypothesized that a crosstalk between sympathetic stimulation and a signal by a major calcium-regulating hormone vitamin D might exist in the regulation of HSC/HPC mobilization by G-CSF. To approach this hypothesis, we used VDR-deficient ($VDR^{-/-}$) mice.[15]

$VDR^{-/-}$ mice are well known to display the characteristic features of rickets type II.[16] We first examined the BM hematopoietic parameters in these mice and found that the numbers of HSCs/HPCs were comparable to $VDR^{+/+}$ littermates in the steady state. Surprisingly, G-CSF almost completely failed to mobilize HSCs/HPCs from the BM to peripheral blood. Similar results were obtained also from $VDR^{-/-}$ mice fed with high calcium diet to correct the rickets

type II phenotype. We next generated chimeric mice that harbored $VDR^{-/-}$ BM hematopoiesis with normal ($VDR^{+/+}$) microenvironment by BM transplantation and found that the mobilization was normal in these mice. On the contrary, chimeric mice that harbored $VDR^{+/+}$ BM hematopoiesis with $VDR^{-/-}$ microenvironment showed strongly impaired mobilization. Thus, VDR in the BM microenvironment was critical for G-CSF-induced mobilization.

The morphological assessment revealed that the impaired mobilization in $VDR^{-/-}$ mice was due to the lack of suppression/reduction of mature osteoblasts after G-CSF administration. Then, we tried to figure out the relationship between β_2-AR and VDR in osteoblasts. We first administered a single dose of pan β-AR agonist isoproterenol into wild-type mice and checked the alteration of several genes related to bone metabolism in the BM. Surprisingly, we found that VDR mRNA selectively showed a sharp increase. In addition to this in vivo study, both VDR mRNA and protein were drastically increased (approximately 10 times increase at the mRNA level assessed by real-time polymerase chain reaction) in both MC3T3-E1 osteoblastic cells and primary calvarial osteoblasts in a short period (2 h) after stimulation by the β_2-AR specific agonist clenbuterol. To confirm the functional up-regulation of the β_2-AR-induced VDR, a luciferase reporter-gene assay using plasmid-containing vitamin D-responsive elements (VDRE) of the human 24-hydroxylase gene was carried out in MC3T3-E1 cells. In the presence of $1,25(OH)_2D_3$, pretreatment with clenbuterol enhanced the transcriptional activity in transfected MC3T3-E1 cells, which suggested that VDR function stimulated by the SNS was, at least partially, a genomic action. Furthermore, even if the clenbuteral stimulation was transient, the complex of enhanced VDR and $1,25(OH)_2D_3$ led to the long-lasting stimulation of downstream signal such as the mRNA enhancement of RANKL (receptor activator of nuclear factor kappa-B ligand), which may stimulate bone-resorbing osteoclasts that secret proteolytic enzymes to degrade anchoring proteins for HSCs/HPCs including CXCL12 presented by osteolineage cells.[17]

Collectively, after G-CSF administration, β_2-AR signals emerging from the SNS lead to the suppression of HSC/HPC microenvironment via functionally

up-regulated VDR by the transcriptional control of its target genes in osteoblasts (Figure 2).[15]

As mentioned above, the inter-organ communication between skeletal and hematopoietic systems is essential in the homeostasis in both organs and a transient distortion of this network explains how HSCs/HPCs can be mobilized from the BM to circulation. VDR plays a central role in this signaling relay and bridges multiple systems (nervous, skeletal, and hematopoietic). We are currently working on the potential role of VDR in an irreversible distortion of the inter-organ network, which leads to the hematologic disorders. It would be important to reconsider VDR as a pivotal molecule that mediates inter-organ communication to broaden the application of vitamin D signal modulators.

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The author has no competing interests to declare.

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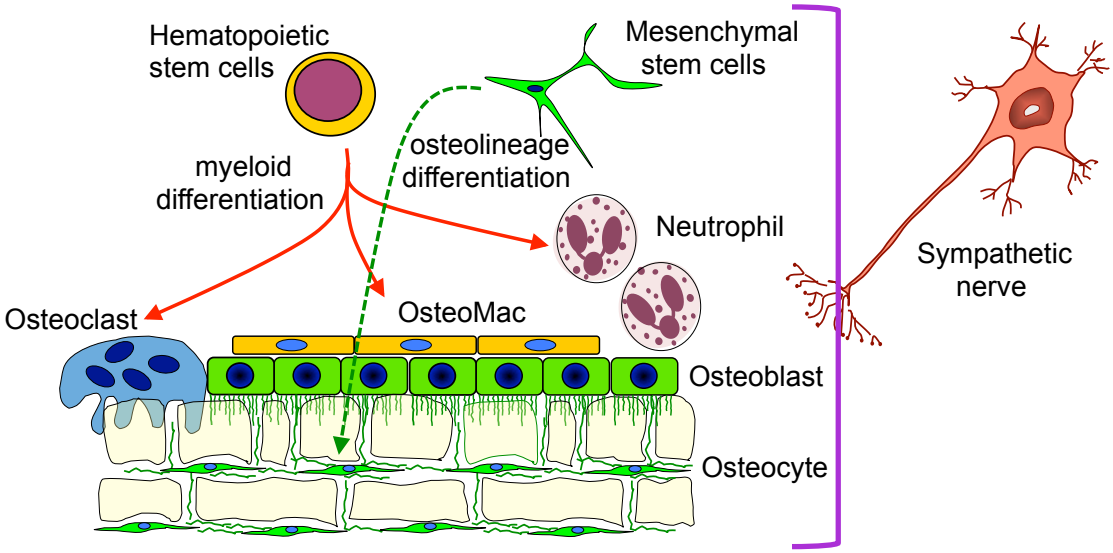

Figure 1. Inter-organ communication between skeletal and hematopoietic systems

In the endosteal region, mesenchymal stem cells and hematopoietic stem cells cooperate to precisely establish the bone tissue. Osteoclast is a classical hematopoietic component to adsorb bone tissue. OsteoMac (bone associated macrophage) critically supports osteoblast activity. Neutrophil also supports osteoblast via prostaglandin E_2 production upon sympathetic stimulation. The activity of mesenchymal lineage cells (mesenchymal stem cells, osteoblasts, and osteocytes) is negatively regulated by the sympathetic nervous system.

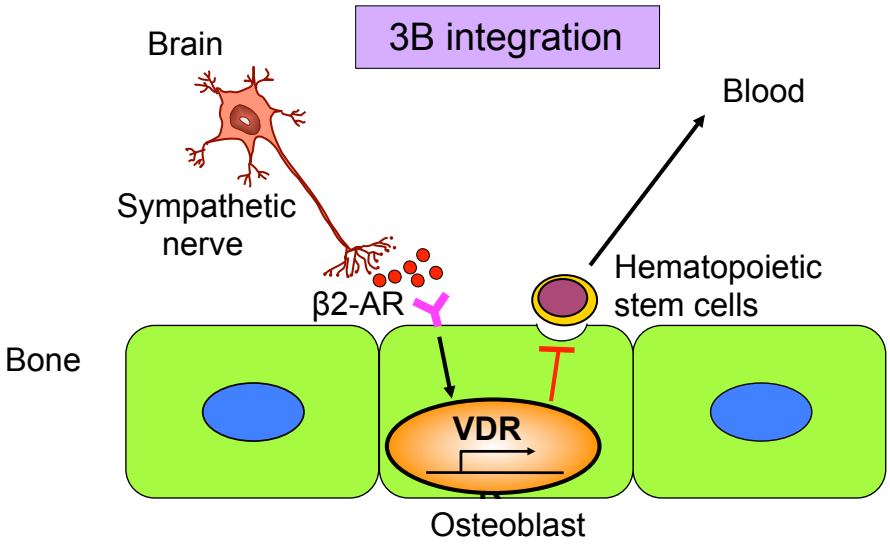

Figure 2. 3B (brain-bone-blood) integration bridged by VDR

In osteoblasts, VDR is drastically up-regulated by the high sympathetic tone via β_2-adrenergic receptor (AR) and maintains the long-lasting downstream signals for hematopoietic stem cell mobilization. This is a novel function of VDR as a critical regulator of the neuronal control for osteoblastic microenvironment for hematopoietic stem/progenitor cells. Even if the concentration of ligand (active vitamin D) is stable, VDR signal can be strongly enhanced by the sympathetic tone.