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MINIREVIEW

Bone marrow cell death and proliferation: Controlling mechanisms in normal and leukemic state

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Abstract

Bone marrow cell death and proliferation are regulated by multiple factors including genetic and epigenetic alterations of hematopoietic cells, crosstalk of hematopoietic cells with bone marrow mesenchymal cells through direct cell-cell interaction or cytokine/chemokine production, vascularity of the bone marrow, and interactions of sympathetic nerve system with hematopoiesis. Cell proliferation usually predominates over cell death in neoplastic processes such as leukemia and myeloproliferative neoplasms, while apoptotic processes also have a significant role in the pathogenesis of myelodysplastic syndromes. Recently, hematopoietic stem cells (HSCs) and leukemia stem cells (LSCs) have been identified and their characters on self renewal process, differentiation, cell dynamics and drug resistance have been implicated. Although most leukemia cells are initially sensitive to chemo- or radiotherapy, LSCs are resistant and considered to be the basis for disease relapse after initial response. HSCs and LSCs may use similar interactions with bone marrow microenvironment. However, bone marrow microenvironment called niche should influence the normal as well as malignant hematopoiesis in different manners. Recent studies have expanded the number of cell types constituting bone marrow niche and made the issue more complex. Since the majority of excellent and contributing studies on bone marrow niches have been performed in animal models, niches in human tissues are beginning to be localized and characterized. In this article, we summarize the relation of hematopoietic cells with niches and hope to point a hint to the novel strategy for treatment of malignant proliferation of hematopoietic cells.

Key words: Bone marrow; Hematopoietic stem cells; Niche; Apoptosis; Leukemia

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INTRODUCTION

Cell dynamics of hematopoietic cells/leukemic cells may be regulated by multiple factors in the bone marrow. Recently, interactions of hematopoietic stem cells (HSCs) with the bone marrow microenvironment have been extensively studied mainly using animal models with genetic modification. Many signaling pathways such as CXCR4/CXCL12, Jagged/Notch, Wnt, Ang-1/Tie2, SCF, very late antigen-4 (VLA-4), VCAM-1, and TGF have been shown to regulate the self-renewal, differentiation, proliferation, and apoptosis/senescence of HSCs[1-11]. Mechanisms of crosstalk between hematopoietic cells and the bone marrow microenvironment would be closely associated with the pathogenesis of hematologic diseases including malignancies. Although leukemia cells are thought to harbor cell-autonomous mutations, the interaction with the microenvironment should play an important role

in the regulation of leukemia cell dynamics[12]. This article reiterates the importance of mechanisms affecting the functions of the bone marrow microenvironment on the proliferation/apoptosis of hematopoietic/leukemia cells.

HSCS AND THEIR NICHE

The HSCs have two opposing characters - maintenance of an undifferentiated state analogous to pluripotent stem cells, and the execution of tissue-specific hematopoietic functions[13]. In the bone marrow, characters of HSCs are maintained within a special microenvironment called a niche. The concept of niches was proposed in the 1970s; however, the nature and function of these stromal structures remains unclear. HSCs are in contact with bone-lining osteoblastic cells, but only a part of the HSCs seem to be located in this endosteal niche region. Instead, many HSCs are found in association with the sinusoidal endothelium, referred to as the vascular niche. However, osteoblast depletion results in extramedullary hematopoiesis, suggesting that a vascular niche alone is not sufficient to maintain hematopoiesis[14]. Endosteal and vascular niches might regulate different HSC populations, although recent data depicts a more complicated feature, with functional crosstalk between cells in these two regions[2,15,16].

Recently it was suggested that primitive mesenchymal cells, including CXCL12-abundant reticular cells[17-20], nestin-expressing cells with sympathetic nerve system[21-23], nonmyelinating Schwann cells[24] and macrophages[25,26] act as bone marrow niche-associated cells. The interactions between CXCR4 and CXCL12 (SDF-1) are especially important in the localization and retention of HSCs in the bone marrow. Furthermore, chemokine interactions through CXCL12 can cause the up-regulation of vascular cell adhesion molecule-1 and VLA-4 expression[27]. CXCL12 also has an essential role in colonization of the bone marrow by HSCs during early development, because CXCL12-deficient embryos have severely reduced HSC numbers and a disturbed function[28]. Further studies on the interplay of such regulatory forces as "cell fate and localization determinant" will likely shed light on the pathogenesis of hematological diseases.

BONE MARROW NICHES IN HEMATOPOIETIC PATHOLOGY

Recent animal model studies have provided insights into the role of aberrant microenvironment signaling leading to the pathogenesis of hematological diseases. Perturbations in niche signaling in murine models[29] can mimic idiopathic myelofibrosis, leading to enhanced stem cell mobilization and the creation of alternate niches[30]. The deletion of the *Dicer1* gene specifically in mouse osteoblasts (endosteal niches) disrupted the integrity of hematopoiesis. Myelodysplastic syndromes (MDS)-like phenotypes emerged in spite of the fact that hematopoietic cells had an intact *Dicer1*[31]. Therefore, perturbation of specific mesenchymal stromal cells can cause disorder in the differentiation, proliferation, and apoptosis of hematopoietic cells. In this mouse model, acute myeloid leukemia (AML) emerged with several acquired genetic abnormalities, supporting the concept of niche-induced leukemogenesis. Also, in human samples, the impaired expression of *DICER*-associated genes was demonstrated in mesenchymal stromal cells from MDS patients[32].

Concerning the bone marrow cell dynamics in MDS, excessive apoptosis of hematopoietic cells was observed to be induced by the bone marrow microenvironment[33-48]. The apoptosis was mediated by paracrine as well as autocrine factors, implicating both medullary stromal cells and hematopoietic cells in the pathology of the disease. Pro-inflammatory cytokines such as tumor necrosis factor in the bone marrow microenvironment are mainly paracrine mediators of apoptosis. As autocrine stimulation mechanisms, it has recently been shown that the deregulation of ribosome biogenesis can initiate a stress response in hematopoietic cells through the p53-mediated signaling pathway. Thus, both the stromal cells of the bone marrow microenvironment and hematopoietic cells themselves possess a common and characteristic biology in this heterogeneous disease entity.

In human samples, the microenvironment has also been studied in multiple myeloma[49]. Self-renewal pathway activation in the niche (such as the canonical Wnt pathway) has been postulated to result in enhanced myeloma cell survival[50]. Another example of microenvironment-associated disease is the WHIM (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) syndrome. This rare syndrome is known to exhibit congenital neutropenia often caused by mutations in CXCR4 with increased sensitivity to CXCL12[51].

LEUKEMIA STEM CELLS AND NICHES

Like many cancers, AML has been identified as a cell autonomous disorder. Namely, the genetic events leading to transformation of the normal hematopoietic cell are found within leukemia cells and are necessary and sufficient for the generation of leukemia. However, many studies have demonstrated evidence of functional heterogeneity among AML cells. In particular, there seems to be a subpopulation of AML cells referred to as "leukemia stem cells" (LSCs) that alone have long-term repopulating potential and the ability to propagate and maintain the AML phenotype[52]. To understand the difference of LSCs from HSCs, clarification of the crosstalk between LSCs and niches would be very important. Niche-mediated mechanisms promote the engraftment and survival of LSCs. The biology of LSCs has been determined by studies of primary human AML cells transplanted into NOD-SCID or NOD-SCID IL2Rγ^{null} mice[53,54]. In these xenograft models, AML cells have a phenotypic hierarchy, which parallels that of normal hematopoietic stem/progenitor cells[1,55-58]. For example, the CD34$^+$CD38$^-$ AML population could engraft efficiently in NOD-SCID mice, but the more differentiated CD34$^+$CD38$^+$ and CD34$^-$ AML cells were unable to engraft and yield colony-forming progenitors. Human AML cells preferentially engrafted in

the bone marrow endosteal region in NOD-SCID IL2R^{null} mice, and remained adjacent to bone marrow osteoblasts for up to 4 mo following transplantation[54]. Homing to the microenvironment appears important in sustaining the survival of LSCs. Moreover, these cells were highly enriched for quiescent cells and were resistant to cytosine arabinoside chemotherapy[59].

CROSSTALK OF LSCS WITH NICHES

Next, the specific mechanisms of niches regulating LSC fate should be clarified[60]. For example, the interaction between CXCR4 and CXCL12 is known to regulate normal HSC proliferation and survival[61-63]. What is the case in LSCs? Actually, CXCR4 is also expressed on primary leukemic cells, and high-level expression of CXCR4 on AML cells is a negative prognostic factor of relapse-free and overall survival[64,65]. Treatment with the CXCR4 antagonist was shown to inhibit stromal cell-induced proliferative signals in AML cells and to increase the sensitivity to chemotherapy, resulting in the extended survival of AML-transplanted mice compared with treatment with chemotherapy alone[66]. These data suggest that LSCs possess a CXCR4-dependent homing capacity that is analogous to normal hematopoietic cells, and antagonism of the CXCR4/CXCL12 axis is a logical therapeutic strategy for the treatment of acute leukemia.

However LSCs are rather heterogeneous. Even in LSCs, different patterns of interactions with niches were identified[67]. The homing of pre-LSCs was similar to long-term HSCs, while the homing of established LSCs was most similar to that of committed myeloid progenitor and distinct from HSCs.

After homing to the bone marrow niches, leukemia cells are retained in these niches through cellular adhesion molecules such as VLA-4 and LFA-1 integrins[68]. Increased VLA-4 expression has been demonstrated to correlate with increased bone marrow blast counts in AML[69]. Furthermore, VLA-4-highly expressing AML cells show relative resistance to chemotherapy-induced apoptosis, and the administration of VLA-4 neutralizing antibodies inhibits this resistance[70].

On the other hand, the leukemia cells were able to directly modulate the niche at the expense of normal hematopoietic stem and progenitor cells by down-regulating CXCL12 levels in areas of leukemia infiltration[71]. It has been shown that stem cell factor, a niche regulator, was secreted by the leukemia cells, leading to the abnormal retention and engraftment of normal HSCs in the microenvironment with leukemic infiltration. Thus, identifying the mechanisms involved in the generation of various signals by HSCs, LSCs, and niches might provide new insights into the pathogenesis of acute leukemia as well as MDS and myeloproliferative neoplasms.

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