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Review

Hematopoiesis and microenvironment in hematological malignancies

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ABSTRACT

Adult hematopoietic stem cells (HSCs) and progenitors (HPCs) reside in the bone marrow, a highly orchestrated architecture. In the bone marrow, the process of how HSCs exert self-renewal and differentiation is tightly regulated by the surrounding microenvironment, or niche. Recent advances in imaging technologies and numerous knockout or knockin mouse models have greatly improved our understanding of the organization of the bone marrow niche. This niche compartment includes a complex network of mesenchymal stem cells (MSC), osteolineage cells, endothelial cells (arterioles and sinusoids), sympathetic nerves, nonmyelinating Schwann cells and megakaryocytes. In addition, different types of mediators, such as cytokines/chemokines, reactive oxygen species (ROS) and exosomes play a pivotal role in regulating the function of hematopoietic cells. Therefore, the niche components and the hematopoietic system make up an ecological environment that maintains the homeostasis and responds to stress, damage or disease conditions. On the other hand, the niche compartment can become a traitor that can do harm to normal hematopoietic cells under pathological conditions. Studies on the diseased bone marrow niche have only recently begun to appear in the extant literature. In this short review, we discuss the most recent advances regarding the behaviors of normal hematopoietic cells and their niche alterations in hematological malignancies.

1. The suppression of hematopoiesis in malignancy

Normal hematopoietic cells and leukemia cells are considered as competitive populations in that they share the same microenvironment. A co-transplantation model demonstrated that increasing doses of normal hematopoietic cells or hematopoietic stem and progenitor cells (HSPCs) significantly delayed leukemic progression.[1] But how normal hematopoietic cells respond to leukemia attack and why they cannot win the blood feud is still unclear, even though this issue was raised 18 years ago by clinicians.[2] In the past few years, several studies have attempted to critically examine this issue. JAK2V617F^{+} myeloproliferative neoplasm cells secreted lipocalin-2 to induce excessive ROS level in adjacent normal hematopoietic cells, which led to oxidative DNA damage and p53 pathway mediated apoptosis. By contrast, mutant clones were not sensitive to lipocalin-2 induced oxidative stress due to p53 inactivation. Thus they acquired a growth advantage over the normal counterparts.[3] By using two different leukemia models, our group described the detailed kinetics of HSCs and HPCs during leukemic cell expansion.[4,5] Notably, hematopoietic stem cells (HSCs) were forced into a non-cycling state in leukemic marrow, and thus the HSCs differentiation into hematopoietic progenitor cells (HPCs) was blocked. Importantly, HSCs in the bone marrow were significantly reduced only in late stages of the disease. However, the residual normal HSCs reconstituted a new recipient normally when removed from the leukemic environment, indicating that the inhibitory effect of leukemia on HSCs is reversible. Therefore, a state of deep quiescence may be a self-protection mechanism for HSCs (Fig. 1A and B). In line with our study, Miraki-Moud et al. used a xenograft model of acute myeloid leukemia (AML) and AML patient

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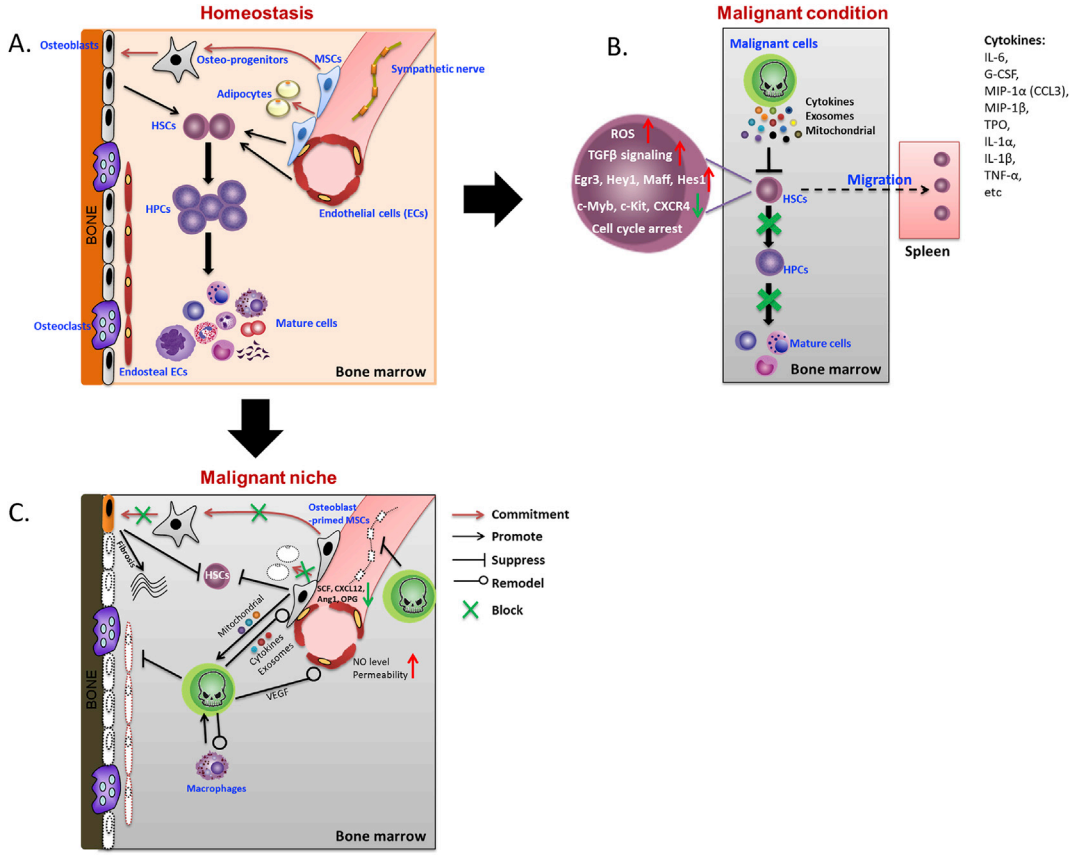

Fig. 1. Mechanisms for the suppression of normal hematopoiesis and niche in malignancies. A. Overview of the main components of the hematopoietic stem cell (HSC) niche in homeostasis. B. In malignant condition, normal HSCs are forced into a more quiescent state, and their differentiation is blocked. Malignant cells secrete soluble factors to suppress HSC function, partially due to several signaling pathways. C. Summaries of niche abnormalities observed in various models. Malignant cells remodel niche cells to create a self-reinforcing leukemic niche, which favors leukemic cell growth while suppressing normal hematopoiesis.

samples to show that AML cells did not deplete normal hematopoietic stem cells but rather impeded their differentiation.[6]

As demonstrated in several studies, leukemic bone marrow plasma could sufficiently suppress HSPC proliferation,[5,7] suggesting the presence of certain factors which can affect the signaling in HSCs. In an acute lymphoblastic leukemia (ALL) model, leukemia cells hijacked normal bone marrow niche and secreted high levels of stem cell factor (SCF) to attract normal $CD34^+$ HSPCs to migrate into the leukemic niche. Thus, $CD34^+$ cells in leukemic mice decreased in number over time and failed to mobilize into the peripheral circulation. Neutralization of SCF normalized $CD34^+$ cell numbers and function.[8] In chronic myelogenous leukemia (CML) mouse model and CML patients, CXCL12 was decreased whereas many negative cytokines for HSC homing, retention and function were elevated in the CML bone marrow, including interleukin (IL)-6, granulocyte colony-stimulating factor (G-CSF), MIP-1α (CCL3), MIP-1β, IL-1α, IL-1β and tumor necrosis factor-alpha (TNF-α)[7,9] (Fig. 1B). Imatinib treatment could partially restore abnormalities in cytokine levels.[7] CCL3 was elevated in the plasma of AML mice and AML patients which inhibited erythroid differentiation of hematopoietic stem cells, common myeloid progenitors and especially megakaryocytic/erythroid progenitors, thus demonstrating that elevated CCL3 in the leukemic environment suppresses erythropoiesis.[10]

The intrinsic mechanism for the suppression or preservation of HSC in leukemia is poorly understood. By using non-irradiated AML model, Egr3 was shown to be highly expressed in HSCs in leukemic bone marrow.[5] Overexpression of Egr3 led to cell cycle arrest and reconstituted defects of HSCs as seen in leukemia. In contrast, Egr3 knockdown promoted proliferation of HSCs as well as their engraftment ability. Notably, Egr3 knockdown could restore the cycling of HSC in leukemic marrow, indicating Egr3's role in suppressing HSCs in leukemia. In contrast to the effect of Egr3, upregulation of MafF and Hey1 were able to enhance the function of HSPCs, indicating their role in preserving HSCs in leukemia[11] (Fig. 1B). By using an ALL model, Hes1-Cdkn1a axis was identified as a mediator for cell cycle alteration of HSCs.[12] Exogenous activation of Hes1 silenced HSPCs, and preserved their function in leukemia (Fig. 1B). Through microarray analysis, other genes (Nr4a2, Egr1) were also found to be involved in the functional suppression of HSCs in leukemia.[13,14] Furthermore, transforming growth factor β (TGFβ) signaling was upregulated in HSCs from bone marrow of AML mice as a result of excessive production of TGFβ1 from megakaryocytes, and hyperactivation of latent TGFβ1 protein[15] (Fig. 1B). SMAD3 directly bound to Egr3 and upregulated its expression to arrest proliferation of HSCs. Taken together, these studies suggest a seesaw paradigm, in which the suppressor and potentiator genes keep in balance in steady-state HSCs, but the balance is biased and the suppressor genes play a dominant role in the leukemic condition. Therefore, further studies regarding how to restore the balance of suppressor and potentiator genes are needed.

2. The niche as a driver for malignancy

Emerging evidence suggests two viewpoints (a chicken-egg debate) of the causal relationship between the niche and malignancy: 1) the niche can be a driver for malignancy, and 2)

malignancy creates an aberrant niche. Several key studies have revealed that genetic alterations in the bone marrow niche cells can promote myeloid proliferation. The retinoic acid receptor-gamma (RARγ) knockout mice had a myeloproliferative phenotype, and an increase in myeloid progenitors and granulocytes in peripheral blood, bone marrow and spleen.[16] Reciprocal transplantation showed that when wild-type hematopoietic cells were transplanted into RARγ knockout mice, the mice also developed myeloproliferation, suggesting that environmental cues cause the malignancy. However, another study showed a different phenomenon. Retinoblastoma (Rb) gene knockout mice had a similar myeloproliferation, but the phenotype could be only observed when Rb deletion occurred in both hematopoietic cells and their niche cells, as deletion in either one alone was not sufficient to induce myeloproliferation.[17] Similarly, myeloproliferation also developed in mice with depletion of mind bomb 1 (Mib1) in niche cells.[18] The mice with specific deletion of the Gsα subunit in osteocytes also developed myeloproliferation.[19] All of these the observations taken together suggest that an altered microenvironment is able to cause hematopoietic dysfunction, specifically myeloproliferation.

The first evidence that demonstrated a specific stromal cellular lineage driving hematological malignancy was reported in 2010 by Scadden and his colleagues. Osteoprogenitor cell-specific deletion of Dicer1 gene led to a myelodysplasia syndrome (MDS), and in some cases, mice developed AML with several genetic abnormalities that had intact Dicer1.[20] Subsequently, another model used Col1-Cre to drive constituent activation of β-catenin in osteoblasts cells, leading to the development of AML.[21] Furthermore, close to 40% of MDS and AML patients had increased β-catenin signaling in their osteoblastic cells as assessed in bone marrow biopsies. Recently, a study reported that Ptpn11 mutations in Nestin$^+$ MSCs and osteoprogenitors, but not in differentiated osteoblasts or endothelial cells, caused excessive production of the chemokine CCL3, which recruited monocytes to the vicinity of HSCs. Consequently, HSCs were hyperactivated by interleukin-1β produced by monocytes, leading to exacerbated myeloproliferative neoplasm (MPN).[19] Taken together, these findings suggest that an altered microenvironment can serve as a cause of malignancy.

3. The niche as an accomplice for malignancy

There is increasing that malignant cells are able to shape the niche, thus creating a malignancy-favorable environment to support their survival at the expense of normal hematopoiesis.

3.1. Mesenchymal stem cells, osteolineage cells and adipocytes

Mesenchymal stem cells (MSCs) are self-renewing precursor cells that mainly commit to bone, fat and cartilage cells of the bone marrow.[22] The deterioration of MSCs is a hallmark of hematological malignancies, with common features such as growth defects, accelerated senescence, dysregulated osteogenic differentiation potential, and compromised capacity to support normal hematopoiesis.[23–25]

In an AML mouse model, Nestin$^+$ MSCs were expanded and primed to osteoblastic differentiation, but they were blocked at the precursor stage and failed to form mature functional osteoblasts, which explained the enhanced osteogenic differentiation of MSCs *in vitro* whereas the reduction of mature osteoblasts in AML bone marrow. Moreover, these Nestin$^+$ MSCs expressed lower levels of HSC-supporting factors, including, SCF, CXCL12 and ANGPT1, further leading to the mobilization of HSCs to peripheral circulation and spleen[26] (Fig. 1C). In AML patients, primitive MSCs were reduced in the bone marrow and showed defective *in vitro* growth and colony-forming capacity, with a greater proportion of senescence compared to normal MSCs. Co-culture with AML-MSCs resulted in attenuated *in vitro* expansion and *in vivo* engraftment of normal HSPCs in irradiated NSG mice, which might be due to the failure to activate Notch signaling in normal HSPCs by AML-MSCs.[24] Adipocytes can promote the regeneration of hematopoiesis by secreting SCF after irradiation.[27] However, in AML mice, the number of adipocytes was significantly reduced[26] (Fig. 1C). Analyses from AML patients revealed that AML cells suppressed bone marrow adipocytes, leading to impaired myelo-erythroid maturation. Administration of peroxisome proliferator-activated receptor gamma (PPARγ) agonists could induce bone marrow adipogenesis, which rescued healthy hematopoietic maturation while limiting leukemia growth.[28]

In CML models, leukemic cells induced bone marrow stromal cells to overproduce placental growth factor, thus in turn promoting leukemia cell proliferation.[29] Furthermore, CML cells could progressively remodel the endosteal bone marrow niche into a self-reinforcing leukemia niche.[30] CML cells stimulate MSCs to overproduce functionally altered osteoblasts with compromised HSC-supportive activity and caused myelofibrosis development, which was induced by TPO, CCL3 and directly cell–cell interactions between CML cells and MSCs (Fig. 1C).

By using an ALL model, our group reported that MSCs isolated from ALL mice had impaired proliferation capacity and differentiation potential due to enhanced senescence. Moreover, the ALL-MSC could not efficiently support the function of HPCs *in vitro*. Osteoprotegerin (OPG) could improve the function of ALL-MSCs and enhance normal HPC output. Therefore, OPG might be a potential target to restore the function of ALL-MSCs.[31]

In a xenograft MDS model, MSCs were shaped to support the reestablishment of a MDS phenotype by upregulating cytokines such as leukemia inhibitory factor (LIF), vascular endothelial growth factor-alpha (VEGF-A), and Insulin-like growth factor-binding protein 2 (IGFBP2). Even the engraftment of lower-risk MDS could be enhanced when co-transplanted with MDS-MSCs.[32] Consequently, normal CD34$^+$ HSPCs from patients showed a significantly larger proportion in the G0 phase compared with healthy controls. This effect could be mimicked by co-culturing healthy HSPCs on MDS-MSCs, indicating MSCs were greatly involved in the suppression of normal hematopoiesis in MDS. Moreover, the cycling of HSPCs from patients of early stage could be activated when co-cultured on healthy MSCs whereas HSPCs from late stage could not. The results suggested that the quiescence of normal HSPCs became a cell-autonomous phenomenon in advanced hematological neoplasms, which might not be rescued by targeting the bone marrow niche.[25]

3.2. Endothelial cells

It has been reported that micro-vessel density is significantly increased in the bone marrow of AML, CML, and MDS patients.[33–36] The increased angiogenesis was associated with shorter overall survival[37] but could be reduced to a normal level after chemotherapy induced complete remission.[34] Conventionally the effects of hematological neoplasms on endothelial cells are thought to be mediated by VEGF. Fiedler et al. nearly 20 years ago reported that a higher level of VEGF was observed in the extracellular fluid of AML patients.[38] Leukemia cells overexpressed VEGF and VEGFR simultaneously to form an autocrine loop to promote their own proliferation.[43] Furthermore, other pro-angiogenic factors such as basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF) and TNF-α were also reported to be incorporated in angiogenesis in hematological malignancies.[36,40] Unfortunately, clinical trials of anti-VEGF inhibitors have not produced encouraging outcomes,[41,42] suggesting that targeting pro-angiogenic factors alone may not be sufficient to

disrupt the interplay between malignant cells and the vascular niche.

Two elegant two-photon imaging studies published recently enhanced your knowledge of vascular niche in leukemia. In the first study, Passaro et al. using a xenograft model reported that AML cells altered vascular architecture and function via increased permeability in bone marrow. Chemotherapy alone failed to correct the abnormal vasculature. Nitric oxide (NO) was increased in the AML bone marrow, and inhibition of NO production could reduce vascular permeability, potentiate normal hematopoietic stem cell function, and improve treatment response.[43] In the second study, Duarte et al. found that AML progressively remodeled endosteal blood vessels coupled to loss of HSCs. Preserving endosteal vessels with deferoxamine (DFO) increased the number of HSCs and improved chemotherapeutic outcome.[44] Taken together, the two studies suggest that restoring the function of the vasculature may improve current treatment for leukemia (Fig. 1C).

3.3. Other cell types

In a non-irradiated AML model, leukemia infiltration led to the destruction of the sympathetic nervous system (SNS) both in the bone marrow and in the spleen[26] (Fig. 1C). Pre-treatment with 6-hydroxydopamine to ablate the SNS accelerated AML progression, suggesting that the neuropathy caused by leukemia was meant to favor their own invasion. The disrupted SNS was mediated by Adrβ2. Nonetheless, an Adrβ2 agonist was not an ideal candidate therapy for AML due to its effect of expanding leukemia cells *in vitro*. In contrast to AML, MPN-induced SNS injury was accompanied by the apoptosis of MSCs and Schwann cells.[45] The deterioration of the bone marrow niche caused by SNS dysregulation was due to an Adrβ3 signaling defect, and an Adrβ3 agonist was able to prevent myelofibrosis and block MPN progression. Besides altering sympathetic nerve fibers, ALL cells could change the distribution and function of macrophages both in bone marrow and spleen.[46] The remodeled macrophage had the capacity to support the migration and proliferation of ALL cells.

4. Raised focus on exosomes and mitochondria

Mediators transfer among malignant cells, niche cells and normal hematopoietic cells are not limited to cytokines or chemokines. Recent studies on exosome transfer from malignant cells to niche cells or HSCs have opened our eyes to new mediators. Exosomes are lipid vesicles or microparticles containing proteins, mRNAs, miRNAs and lipids. AML cells suppressed normal hematopoiesis by releasing exosomes that contain miR-155 targeting c-Myb[47] (Fig. 1B). In addition, AML-derived exosomes also reduced the clonogenicity of HSCs, forcing them to lose CXCR4 and c-Kit expression.[48] Chronic lymphocytic leukemia (CLL)-derived exosomes transferred miRNAs and proteins to bone marrow MSCs and endothelial cells to alter their transcriptome and to induce release of inflammatory cytokines and pro-angiogenic factors.[49] Moreover, AML-derived exosomes induced the expression of DKK1, a suppressor of normal hematopoiesis and osteogenesis, and induced a broad downregulation of HSC-supporting factors (SCF, CXCL12 and IGF1) in bone marrow MSCs, thus impairing their ability to support normal hematopoiesis.[48,50] Regarding mitochondrial transfer, two parallel studies reported that AML cells induced bone marrow stromal cells to transfer functional mitochondria to themselves, making them more resistant to chemotherapy[51,52] (Fig. 1C). These studies taken as a whole indicate that exosomes and mitochondrial transfer are means by which malignant cells communicate with normal cells and their environment.

5. Extramedullary hematopoiesis in disease

It should be noted that normal HSCs prefer to egress from bone marrow to spleen in the leukemic condition (Fig. 1B), so the number of HSCs in leukemia are increased and their cell cycle are not inhibited,[5,7,26,44] suggesting that the spleen may compensate for hematopoietic suppression in leukemic bone marrow. The spleen serves as a secondary site for hematopoiesis and may play a pivotal role in the development of malignancies, especially under hematopoietic stress.[53] We showed, using an ALL model, that ALL cells preferred to migrate to spleen than to the bone marrow after injection, and that this was controlled by MIP-3β.[54] A recent study using an orthotopic hepatocellular carcinoma model found that a non-canonical $Ter119^{+}CD45^{-}$ erythroblast-like cell population was induced in the spleens of tumor-bearing mice. These cells facilitated tumor progression by secreting the neurotrophic factor artemin into the blood.[55] Another study using the hepatocellular carcinoma model showed that extramedullary hematopoiesis (EMH) occurred in the spleen of tumor-bearing host, and both HSCs and myeloid progenitors were increased. Moreover, patients with different types of solid tumors exhibited increased splenic HSPC levels associated with poor survival. Selectively blocking the EMH was sufficient to enhance the therapy.[56] Therefore, understanding how malignant cells induce EMH, and why EMH is important for both hematological malignancies and solid tumors, would be attractive subjects to be investigated in the future.

6. Conclusions and perspectives

In conclusion, targeting the malignant microenvironment may prove a useful approach to complement existing therapies. Different types of hematological malignancies may reprogram the niche and suppress normal hematopoiesis in different ways, and thus it is important to keep in mind that therapies for one type of hematological malignancy may fail in others. Although numerous studies have helped us uncover some mechanisms on this topic, our knowledge is still limited. Future study should utilize new strategies, such as single cell RNA-Seq or advanced imaging technology, to further delineate the complex crosstalk among the multiple types of cells within the same malignant microenvironment.

Authors contributions

HC and GS wrote the initial draft. HC and TC approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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