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Concise Review: The Malignant Hematopoietic Stem Cell Niche

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ABSTRACT

Hematopoietic stem cell (HSC) proliferation, self-renewal, and trafficking are dependent, in part, upon signals generated by stromal cells in the bone marrow. Stromal cells are organized into niches that support specific subsets of hematopoietic progenitors. There is emerging evidence that malignant hematopoietic cells may generate signals that alter the number and/or function of specific stromal cell populations in the bone marrow. At least in some cases, the resulting alterations in the bone marrow microenvironment confer a competitive advantage to the malignant HSC and progenitor cells and/or render them less sensitive to chemotherapy. Targeting these signals represents a promising therapeutic strategy for selected hematopoietic malignancies. In this review, we focus on two questions. How do alterations in bone marrow stromal cells arise in hematopoietic malignancies, and how do they contribute to disease pathogenesis? STEM CELLS *2016; 00:000–000*

SIGNIFICANCE STATEMENT

There is emerging evidence that malignant hematopoietic cells may alter the bone marrow microenvironment. In at least some cases, these alterations allow for the selective expansion of malignant cells or render them less sensitive to chemotherapy. In this review, we discuss current research characterizing the interactions between malignant hematopoietic cells and stromal cells in the bone marrow. In particular, we highlight recent studies that have begun to identify the signals generated by malignant hematopoietic cells that alter the bone marrow microenvironment. Targeting these signals represents a promising new therapeutic strategy for selected hematopoietic malignancies.

HEMATOPOIETIC NICHE(S) IN THE BONE MARROW

There has been considerable interest in defining bone marrow stromal cell populations and the signals they generate that contribute to hematopoietic stem cell (HSC) maintenance. Here, we provide a brief summary of this research. For a more in depth discussion, interested readers are referred to several excellent reviews on this topic [1, 2]. The stem cell niche has been defined, in part, by localizing HSCs in the bone marrow and then identifying and characterizing the neighboring stromal cells. Initial studies using transplantation of labeled HSC-enriched populations into irradiated recipient mice showed that HSCs tended to localize to endosteal regions in bone marrow, implicating osteolineage cells in the stem cell niche (reviewed in [1, 2]). However, irradiation induces significant alterations in the bone marrow microenvironment, including a loss of endothelial cells [3] and an expansion of osteoblasts [4]. Thus, subsequent studies have focused on localizing HSCs under steady-state conditions. Two recent studies using transgenic reporters that mark functional HSCs showed that the majority of HSCs under steady-state conditions are perivascular and distributed throughout the bone marrow [5, 6]. The perivascular space in the bone marrow is populated by a diverse population of stromal cells, including perivascular mesenchymal stromal cells (MSCs) that have been defined as CXCL12-abundant reticular (CAR) cells [7], leptin-receptor$^+$ stromal cells [8], or nestin-GFP$^+$ stromal cells [9]. Each of these (overlapping) cell populations express high levels of key niche factors such as CXCL12 and stem cell factor and have been implicated in HSC maintenance [7, 8, 10–12]. The perivascular space also contains several other cell types that have been implicated in HSC regulation, including endothelial cells [3], arteriolar pericytes [9],

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sympathetic nerves [13, 14], nonmyelinating Schwann cells [15], and megakaryocytes [16, 17]. The role of osteolineage cells in HSC maintenance is controversial, but current evidence suggests that immature osteolineage cells rather than mature osteoblasts may contribute to the regulation of HSCs (reviewed in Calvi et al. [2]). Thus, the HSC niche is comprised of a heterogeneous population of stromal cells, each of which may generate signals that collectively contribute to HSC maintenance.

Alterations in the Bone Marrow Microenvironment in Hematopoietic Malignancies in Humans

Alterations in the bone marrow microenvironment have been reported in most human hematopoietic malignancies. Perhaps the best characterized alteration is the development of reticulin fibrosis in the bone marrow of patients with primary myelofibrosis, a type of myeloproliferative neoplasm (MPN). Primary myelofibrosis is characterized by reticulin fibrosis in the bone marrow and splenomegaly (secondary to extramedullary hematopoiesis). Early in the disease process, there often is an increase in immature/dysplastic megakaryocytes. Current evidence suggests that it is the malignant megakaryocytes, possibly through secretion of transforming growth factor-β (TGF-β), that induce the marrow fibrosis [18, 19]. In chronic myelogenous leukemia (CML), another type of MPN, there is a marked increase in bone marrow vasculature, which may be secondary to increased stromal cell expression of placental growth factor (PlGF) [20].

In acute lymphoblastic leukemia (ALL), stromal cell expression of key lymphoid trophic factors, including CXCL12, interleukin-7, and B-cell activating factor are reduced [21, 22]. Interestingly, the magnitude of the decrease in CXCL12 does not correlate well with the percentage of leukemic blasts in the bone marrow, suggesting that simple replacement of stromal cells by leukemic cells does not account for the decrease in CXCL12 [21]. Studies of MSCs derived from the bone marrow of children with ALL show that their MSCs have increased adipogenic capacity but a reduced ability to support hematopoietic progenitor proliferation [23].

Alterations in the bone marrow microenvironment are also seen in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). In MDS, in contrast to ALL, CXCL12 expression is increased [24, 25]. This is due, at least in part, to the expansion of CXCL12-positive CD271^{+} perivascular stromal cells [24]. A recent study reported that in 38% of cases of MDS or AML, increased β-catenin signaling and β-catenin nuclear accumulation in osteoblasts are present [26]. Studies of bone marrow MSCs from patients with MDS or AML have shown reduced osteogenic differentiation and premature senescence [27, 28]. Finally, bone marrow derived MSCs from patients with MDS or AML have increased expression of key niche factors that may selectively support the growth of the malignant clone over normal hematopoietic cells [29].

How Do Alterations in Bone Marrow Stromal Cells Arise in Hematopoietic Malignancies

There are at least two general mechanisms by which alterations in bone marrow stromal cells arise in hematopoietic malignancies; (a) germline or somatic mutations in stromal cells may alter their function; or (b) malignant hematopoietic cells may signal to stromal cells to alter their function. In this section, we examine the evidence for each of these mechanisms.

Germline Mutations in Stromal Cells

There have been a number of studies showing that certain germline mutations that alter stromal cell function lead to a myeloproliferative/MDS-like phenotype in mice. Deletion of *Dicer1* (which is essential for microRNA biogenesis) from mesenchymal bone marrow stromal cells results in impaired osteoblast differentiation and the development of MDS with the capability of transforming to AML [30]. Likewise, deletion of *Rarg* (retinoic acid receptor γ) [31], *Rb1* (retinoblastoma 1) [32], *Mib1* (an essential component for Notch ligand endocytosis) [33], or the DNA-binding domain of Rbpj (RBP-J_k, which also is required for Notch signaling) [34] in bone marrow stromal cells results in a myeloproliferative-like disorder in mice. These are important proof-of-principle experiments that suggest that disruption of Notch signaling and certain other signaling pathways can contribute to the development of myeloid malignancies. However, their direct relevance to human hematopoietic malignancies is uncertain, since germline mutations of these genes, except for *RB1*, have not been linked to human myeloid malignancy. On the other hand, there is evidence that in a few selected syndromes, germline mutations may induce changes in stromal cells that contribute to hematopoietic malignancy. For example, Shwachman Diamond syndrome is a bone marrow failure syndrome that is due to loss-of-function mutation of *SBDS* [35]. It is associated with a very high rate of transformation to MDS/AML [36]. Deletion of *Sbds* in bone marrow stromal cells induces an MDS-like disease in mice [30]. Consistent with this finding, stromal cells from patients with Shwachman Diamond syndrome have an impaired capacity to support hematopoietic progenitor proliferation in vitro [36]. Since *SBDS* deficiency is associated with mitotic spindle destabilization and genomic instability [37], it is possible that both cell intrinsic and stromal alterations contribute to the high rate of myeloid malignancy in Shwachman Diamond syndrome.

Somatic Mutations in Stromal Cells

Several studies have detected genetic and epigenetic changes in bone marrow stromal cells from patients with myeloid malignancies. One study found chromosomal abnormalities in 16% of cases in which MSCs were cultured from the bone marrow of patients with AML; these abnormalities were distinct from those found in the matched leukemic cells and were not found in healthy controls [38]. A second study reported chromosomal abnormalities in 5% of cultured MSCs from patients with AML or MDS [39]. A modest reduction in global hypomethylation also was observed. Parabiosis studies in mice suggest that there is little trafficking of mesenchymal progenitors from one site in the bone marrow to another [40]. Consequently, it is unlikely that MSCs carrying somatic mutations disseminate throughout the skeleton. Thus, while the local bone marrow microenvironment may be altered, the contribution of somatic mutations in MSCs to the pathogenesis of hematopoietic malignancies is uncertain.

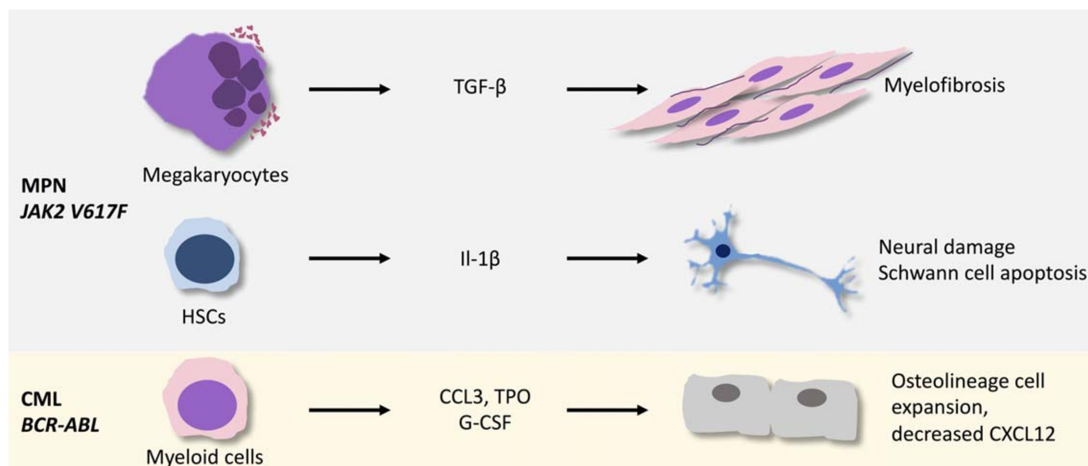

Figure 1. Malignant hematopoietic cells in MPNs generate signals that alter the bone marrow microenvironment. Megakaryocytes in MPNs produce TGF-β, which targets mesenchymal stromal cells (MSCs) to induce myelofibrosis. There also is evidence that increased expression of IL-1β by HSCs in MPN induce alterations in the microenvironment by damaging sympathetic nerves and Schwann cells. In CML, (lower panel), malignant myeloid cells, through production of CCL3, TPO, and G-CSF, induce the expansion of osteolineage cells with reduced expression of CXCL12 and other niche factors. Abbreviations: CML, chronic myelogenous leukemia; G-CSF, granulocyte colony-stimulating factor; HSCs, hematopoietic stem cells; IL-1β, interleukin-1β; MPN, myeloproliferative neoplasm; TGF-β, transforming growth factor-β; TPO, thrombopoietin.

Non-Cell Intrinsic Alterations in Stromal Cells

There is considerable data suggesting that excessive production of TGF-β by megakaryocytes plays an essential role in the development of marrow fibrosis in MPNs, presumably by acting on MSCs. First, cultured megakaryocytes from patients with primary myelofibrosis have markedly increased TGF-β production [41]. Second, transgenic mice with increased megakaryocytes due to enforced thrombopoietin expression [42] or loss of *Gata1* in megakaryocytic lineage cells [43] develop severe marrow fibrosis. Finally, genetic loss of TGF-β in hematopoietic cells prevents the development of marrow fibrosis that is seen with thrombopoietin overexpression [18]. Of note, Wen et al. recently reported that treatment with an inhibitor targeting the AURKA kinase, which induces megakaryocyte differentiation and polyploidization, also reduced marrow fibrosis in a mouse model of MPN. [19] These data suggest that agents that target the megakaryocyte/TGF-β pathway, such as AURKA kinase or TGF-β inhibitors, represent a promising new therapeutic strategy for MPNs.

There is evidence that other malignant hematopoietic cell populations in MPNs may generate signals that alter stromal cell function (Fig. 1). Arrant et al. reported that interleukin-1β production by HSCs carrying the *JAK2 V617F* mutation cause neural damage and Schwann cell apoptosis. [44] This is important, since previous studies showed that sympathetic nerves and Schwann cells generate signals that regulate mesenchymal stromal cells in the bone marrow [13, 15]. Indeed, a loss of nestin-GFP$^+$ stromal cells and a decrease in bone marrow CXCL12 was observed in *JAK2 V617F* mice. Zhang et al. used a murine model of *BCR-ABL* CML to show that leukemic cells produce increased amounts of granulocyte colony-stimulating factor (G-CSF). [45] G-CSF is known to induce HSC mobilization, in part, by suppressing stromal cell CXCL12 [46–48]. Accordingly, bone marrow CXCL12 expression was reduced and leukemic HSCs mobilized to the periphery in the *BCR-ABL* mice [45]. Using an inducible *BCR-ABL* mouse model of CML, Schepers et al. showed that myeloid cells, through (in part) production of CCL3 (MIP-1α) and thrombopoietin, induce the expansion of functionally altered osteolineage cells. [49] In turn, they showed that the abnormal osteolineage cells have decreased expression of important niche factors, including CXCL12, which may contribute to the development of MPN in this model. Finally, Schmidt et al. showed the murine CML cells, through a VLA4/VCAM1 dependent mechanism, stimulate production of PlGF from stromal cells, which, in turn, stimulates angiogenesis [20].

There is some evidence that malignant cells in MDS or AML can induce changes in bone marrow stromal cells. Similar to *JAK2 V617F* MPN, infiltration of *MLL-AF9* AML cells in the bone marrow induces alterations in the sympathetic nervous system that lead to a decrease in nestin-GFP$^+$ stromal cells and NG2$^+$ cells, while promoting osteoblast expansion [50]. MSCs cultured from patients with MDS have increased expression of key genes implicated in HSC regulation [29]. Interestingly, co-culture of normal MSCs with hematopoietic cells from patients with MDS reproduces this phenotype, suggesting an instructive mechanism. Consistent with this finding, Balderman et al. showed that the bone marrow microenvironment is altered in the *NUP98-HOXD13* mouse model of MDS, including an increase in endothelial cells and dysfunctional osteolineage cells. [51] Transplantation of *NUP98-HOXD13* hematopoietic cells into wildtype recipients reproduced these alterations in the bone marrow microenvironment. Importantly, transplantation of *NUP98-HOXD13* hematopoietic cells into *NUP98-HOXD13* recipient mice led to a higher rate of leukemia compared with wildtype recipients, implicating the altered bone marrow microenvironment in leukemic progression.

Finally, there also is evidence that malignant lymphoid cells may alter the bone marrow microenvironment by generating signals that target stromal cells. Using a human pre-B ALL xenotransplantation model, Coleman et al. showed that stem cell factor production by leukemic cells suppresses stromal CXCL12 expression and inhibits their capacity to support

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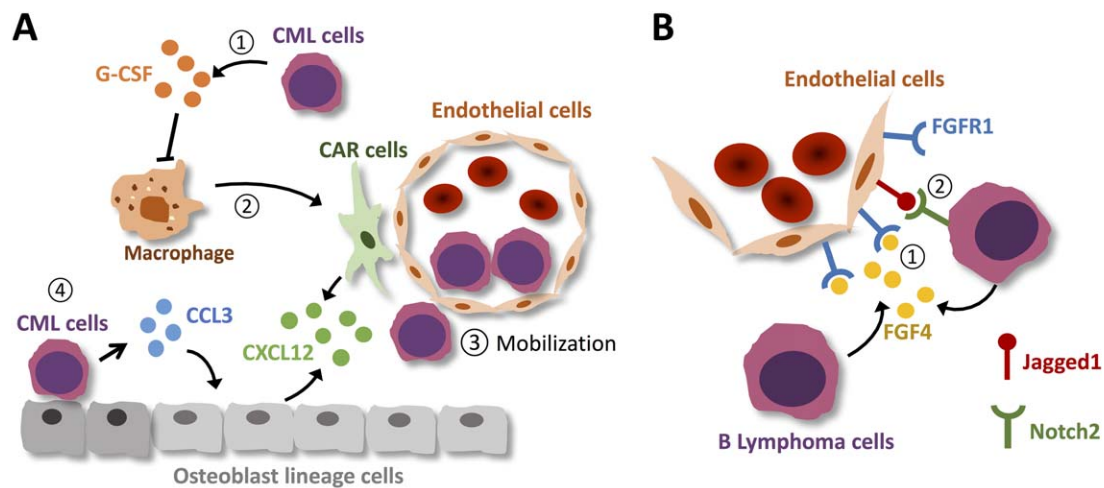

Figure 2. Paracrine loops involving malignant hematopoietic cells and stromal cells. **(A)**: In CML, myeloid cells produce G-CSF (1) that acts on macrophages to suppress CXCL12 expression in stromal cells (e.g., CAR cells) (2), which in turn, leads to the mobilization of leukemic cells into the circulation (3). CML myeloid cells also may alter the bone marrow microenvironment through production of CCL3, thrombopoietin (not shown), and through direct stromal cell contact to induce the expansion of dysfunctional osteolineage cells (4). These altered osteolineage cells have decreased production of CXCL12 and other niche factors, which compromises their ability to support normal hematopoietic stem cells. **(B)**: B lymphoma cells produce FGF4 that signals through the FGFR1 on endothelial cells to increase their expression of the Notch ligand, Jagged1 (1). This increase in endothelial Jagged1 then activates Notch2 on B lymphoma cells to induce their proliferation (2), completing the paracrine loop. Abbreviations: CAR, CXCL12-abundant reticular; CML, chronic myelogenous leukemia; FGFR1, fibroblast growth factor receptor-1; FGF4, fibroblast growth factor-4.

normal HSCs. [52] Cao et al. described a novel paracrine loop in which fibroblast growth factor-4 (FGF4) expression by B lymphoma cells induces expression of the Notch ligand Jagged1 on endothelial cells through activation of the FGF receptor-1 (FGFR1). [53] This study focused on the vasculature in lymph nodes; whether Jagged1 is induced on bone marrow endothelium in B cell malignancies is currently unknown.

Collectively, these data suggest that germline or somatic mutations in bone marrow stromal cells are a rare cause of stromal cell dysfunction. Rather, malignant hematopoietic cells target stromal cells through the expression of specific factors, such as TGF-β, interleukin-1β, or FGF4.

Contributions of Altered Niche Function to Hematopoietic Malignancy Development and Progression

A key question in the field is to define the importance of bone marrow stromal signals to the pathogenesis, progression, or sensitivity to chemotherapy of hematopoietic malignancies. This question has direct relevance to the likelihood that targeting interactions between stromal cells and malignant hematopoietic cells will have therapeutic benefit.

There is strong evidence, at least in mouse models of hematopoietic malignancy, that signals from specific stromal cell populations play a key role in the pathogenesis and progression of certain hematopoietic malignancies. Two groups independently showed that T-ALL cells are dependent on CXCR4 signaling and exquisitely sensitive to genetic or pharmacologic CXCR4 inhibition [54, 55]. Remarkably, deletion of *Cxcl12* from endothelial cells, but not leptin receptor$^+$ perivascular stromal cells, markedly attenuated T-ALL propagation [55]. These data suggest that CXCL12 expression from endothelial cells is uniquely required for efficient T-ALL proliferation and/or survival. In CML, Bowers et al. showed that expression of Jagged1 is increased on osteoblasts isolated from mice with BCR-ABL induced CML [56]. Jagged1 negatively regulates the proliferation of both normal and BCR-ABL HSCs [56]. Accordingly, ablation of osteoblasts in this model accelerates leukemic progression. Likewise, osteoblasts have been implicated in the maintenance of leukemic stem cell quiescence in ALL [57]. Here, osteoblast expression of osteopontin may be important. Osteopontin is known to regulate normal HSC quiescence [58]. Boyerinas and colleagues showed using a human ALL xenograft model that neutralization of osteopontin is associated with increased B-cell ALL cell cycling and sensitivity to chemotherapy [57]. Interestingly, the contribution of osteolineage cells to leukemic progression may be disease specific [56]. Whereas parathyroid hormone stimulation of osteolineage cells inhibits *BCR-ABL* induced CML, it augments AML induced by the *MLL-AF9* oncogene [59].

As discussed in the prior section, malignant hematopoietic cells may generate signals that alter the bone marrow microenvironment. There is emerging data suggesting these changes may provide malignant HSCs with a competitive advantage over normal HSCs (Fig. 2). Zhang et al. showed that *BCR-ABL*$^+$ CML cells induce altered expression of key cytokines and chemokines in the bone marrow, including decreased CXCL12 and increased G-CSF expression [45]. These alterations led to the selective expansion of *BCR-ABL*$^+$ HSCs (compared to wildtype HSCs) and the migration of leukemic cells to the spleen. Likewise, Schepers et al. showed that *BCR-ABL*$^+$ CML cells induce an expansion of osteoblasts with altered expression of key adhesive molecules [49]. These altered osteoblasts have a reduced capacity to support wildtype but not *BCR-ABL*$^+$ HSCs. Cao et al. described a novel paracrine loop that promotes the expansion of B lymphoma cells [53]. Specifically, they showed FGF4 expression from malignant B cells induces expression of Jagged1 on endothelial cells. Jagged1 in turn, stimulates

Notch2 signaling on leukemic cells enhancing their aggressiveness and resistance to chemotherapy (Figure 2).

A recent study suggested that leukemic cells may also influence the stromal response to chemotherapy. Specifically, in mice engrafted with human ALL cells, chemotherapy results in the formation of a novel but transient niche comprised of nestin$^+$ leptin receptor$^+$ MSCs that surround the residual ALL cells [60]. Similar niche structures also were observed in the bone marrow of patients with ALL following chemotherapy [60]. Expression of CCL3 from ALL cells is required for the efficient recruitment and/or expansion of these MSCs to form this transient niche. Finally, the authors provide evidence that these niche cells generate signals that confer resistance to chemotherapy to its resident ALL cells. Specifically, increased local production of pro-growth factor differentiation factor-15 appears to play a key role in ALL cell chemoresistance.

Although not focused on the bone marrow, two studies showed that endothelial cells produce factors that influence sensitivity of lymphoma cells to chemotherapy [61, 62]. Specifically, Gilbert et al. showed that interleukin-6 is released from endothelial cells following genotoxic stress and promotes the survival of lymphoma cells [61]. Moreover, Tavora et al. showed that exposure of endothelial cells to doxorubicin, a DNA-damaging chemotherapeutic, induces expression, in a focal adhesion kinase-dependent manner, of a number of inflammatory cytokines (including interleukin-6) that renders lymphoma cells less sensitive to chemotherapy [62].

Implications and Open Questions

In summary, there is evidence that malignant hematopoietic cells generate signals that alter the number and/or function of specific stromal cell populations in the bone marrow. The resulting alterations in the bone marrow microenvironment may allow for the selective expansion of malignant hematopoietic progenitors or confer resistance to chemotherapy. Targeting these signals represents a promising therapeutic strategy for hematopoietic malignancies. For example, there is an ongoing clinical trial of a β3-adrenergic agonist to restore the damaged niche in patients with MPNs (NCT02311569). There are several outstanding issues in this field that merit further investigation. First, additional research is needed to define the signals generated by malignant hematopoietic cells that regulate stromal cells. Do specific molecular types of leukemia or MDS generate distinct signals? If so, therapies could be tailored for the particular hematopoietic malignancy. Second, most of the current data are derived from mouse models. It will be important to confirm and extend these studies to human hematopoietic malignancies. Third, further research is needed to characterize the signals generated by stromal cells that regulate normal and malignant HSCs and to define how these signals are altered in hematopoietic malignancies. In particular, it will be important to understand how alterations in the bone marrow contribute to malignant cell expansion and/or resistance to chemotherapy. For example, there are data suggesting that reduced bone marrow CXCL12 expression may contribute to the expansion of BCR-ABL$^+$ cells [25]. Why would the resulting decrease in CXCR4 signaling confer a competitive advantage to BCR-ABL$^+$ HSCs? A better characterization of the interaction between malignant hematopoietic cells and the bone marrow stromal cells may eventually allow us to develop a "Precision Medicine" approach to select specific therapeutics targeting specific alterations in the bone marrow microenvironment in hematopoietic malignancies.

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Disclosure of Potential Conflict of Interest

The authors indicate no potential conflicts of interest.

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