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Bone Marrow Microenvironment in the Pathogenesis of AML

Olga Blau
Charité University School of Medicine
Germany

1. Introduction

Acute myeloid leukemia (AML) arises from a series of genetic abnormalities in a stem or progenitor cell that lead to uncontrolled growth. Data from the past few decades have implicated the hematopoietic microenvironment (HM) in the pathogenesis of hematologic malignancies (Ramakrishnan et al., 2009). Hematopoietic stem cells (HSCs) live in a highly specialized complex microenvironment, also known as a niche (Scadden et al., 2007; Konopleva et al., 2009). Two distinct microenvironmental niches defined: "osteoblastic (endosteal)" and "vascular" niches (Perry and Li, 2007). Recent studies suggest that these niches work together. Coordination between the osteoblastic and vascular niches regulates HSC selfrenewal, proliferation, differentiation and mobilization in and out of the bone marrow (BM). HSCs leave the osteoblastic niche, mobilize to the vascular niche, and enter the blood vessel. They subsequently may undergo transendothelial migration from the peripheral circulation and return first to the vascular niche and then to the osteoblastic niche (Lapidot et al., 2005; Cancelas and Williams, 2006). Within the niche, there are critical bidirectional signals that ensure the regulation of normal HSCs (Calvi et al., 2003) and maintenance of the quiescent long-term HSC pool (Fleming et al., 2008). The quiescent fraction of immunophenotypically defined HSCs has been previously demonstrated to correlate with long-term repopulating ability of BM (Passegue et al., 2005) and loss of this fraction is associated with inability to sustain serial transplantation, the most stringent *in vivo* assay of self-renewal (Fleming et al., 2008).

The HM consists of a complex structure of both non-hematopoietic and hematopoietic cells, extracellular matrix as well as soluble and membrane bound factors that cooperate to support normal hematopoiesis. It was known as early as the 1960s, based on experiments on mice, that normal hematopoiesis could not occur without a supportive environment (Russell et al., 1979). In vitro studies of the HM over the last several decades have mostly relied on the long-term marrow culture system, first reported by Dexter (1977).

The key component of the HM is mesenchymal stromal cells (MSC). These plastic-adherent cells currently described as mesenchymal stem cells are termed multipotent mesenchymal stromal cells, while the term mesenchymal stem cell should be reserved for a subset of these cells that demonstrate stem cell activity by clearly stated criteria (Horowitz et al., 2005). MSCs are primitive cells originating from the mesodermal germ layer and were classically described to give rise to connective tissues, skeletal muscle cells, and cells of the vascular system. Friedenstein and colleagues (1974) first described MSC as fibroblast-like cells that could be isolated from BM via inherent adherence to plastic in culture. He defined a population of cells as multipotential stromal precursor cells that were spindle-shaped and clonogenic in culture conditions, defining them as colony-forming unit fibroblasts. MSCs, in the traditional view, should refer to stem cells that are also capable of producing blood cells; however, blood cells are actually derived from a distinct cell population called the hematopoietic stem cells. This allows classified MSC as nonhematopoietic, multipotential stem cells that are capable of differentiating into mesenchymal and non-mesenchymal cell lineages (Chamberlain et al., 2007). These cells were able to differentiate into adipocytes, chondrocytes, osteocytes, and myoblasts, both in vitro and in vivo. In addition, it has also been demonstrated that MSCs are capable of differentiating into cardiomyocytes, neurons, and astrocytes in vitro and in vivo (Pittenger et al., 1999; Jori et al., 2005; Beyer Nardi et al., 2006; Tokcaer-Keskin et al., 2009). By generating functionally distinct cell types and structures, MSC play a crucial role in supporting hematopoiesis as key components of the HM (Sacchetti et al., 2007).

Phenotypically MSCs express a number of markers, none of which are specific only to MSCs. It is generally agreed that adult human MSCs do not express the hematopoietic markers CD45, CD34, CD14, or CD11. They also do not express the costimulatory molecules CD80, CD86, or CD40 or the adhesion molecules CD31, CD18, or CD56, but they can express CD105 (SH2), CD73 (SH3/4), CD44, CD90 (Thy-1), CD71, and Stro-1 as well as the adhesion molecules CD106, CD166, intercellular adhesion molecule, and CD29 (Sordi et al., 2005; Chamberlain et al., 2007). Although there are no unique cell surface markers for the identification of MSCs, minimal criteria to define human MSC have been published. According to such criteria, MSC must be plastic-adherent; and have to express CD105, CD90 and CD73; they must lack expression of CD45, CD34 and CD14; and they must show in vitro differentiation capabilities into osteoblasts, adipocytes and chondroblasts (Horowitz et al., 2005; Chamberlain et al., 2007). This *in vitro* system has allowed for the dissection of the components of the microenvironment and the study of the complex contact dependent and contact independent interactions that occur between the stromal compartment and hematopoietic stem cells that regulate stem cell fate decisions.

Normal hematopoiesis requires complex bidirectional interactions between the HM and HSCs. The HM can regulate hematopoiesis by interacting directly with HC and/or by secreting regulatory molecules that exert a positive or negative influence on the growth of HC. These interactions influence HSC self-renewal. HM controls the formation of blood cells through the production and secretion of cytokines, chemokines, and intracellular signals initiated by cellular adhesion (Konopleva et al., 2009). Chemokines are a large superfamily of small glycoproteins that are required in a various series of biological processes, including leukocyte trafficking, hematopoiesis, angiogenesis, and organogenesis. MSCs have the ability to migrate into tissues from the circulation, possibly in response to signals that are upregulated under injury conditions. Although the mechanisms by which MSCs are recruited to tissues and cross the endothelial cell layer are not yet fully understood, it is probable that chemokines and their receptors are involved, as they are important factors known to control cell migration (Chamberlain et al., 2007).

CXCL12/stromal cell-derived factor-1alpha (SDF-1α) and its receptor CXCR4 are involved in homing of HSC into BM (Abkowitz et al., 2003; Broxmeyer et al., 2005; Morrison and Spradling, 2008). Perivascular reticular cells secrete much higher levels of CXCL12 than other constitutive sources of CXCL12, such as osteoblasts, fibroblasts, and endothelial cells

(Sugiyama et al. 2006). These reticular cells, defined as CXCL12-abundant reticular cells, may serve as a transit pathway for shuttling HSC between the osteoblastic and vascular niches, where essential but different maintenance signals are provided (Perry and Li, 2007).

The molecular interactions between HC and MSC involve ligand-receptor relationship between adhesion molecules on the surface of HC and stromal cells or between such molecules on the cells surface with specific domains within certain extracellular matrix molecules. BM engraftment involves subsequent cell-to-cell interactions through the MSC-produced complex extracellular matrix (ECM) (Zuckerman and Wicha, 1983; Wight et al., 1986). Vascular cell-adhesion molecule-1 (VCAM-1) or fibronectin is critical for adhesion to the MSC (Miyake et al., 1991; Garcia-Gila et al., 2002). One very important type of interaction between the MSC and the HSC is the synthesis and presentation by MSC of hematopoietic growth factors. Interactions of HSC with stromal elements of BM play a role in the egress of mature blood cells from the BM (Chamberlain et al., 2007).

Whether MSC alterations influence hematological disorders and how such alterations contribute to the progression of the disease remains controversial. The molecular mechanisms for maintaining quiescence of normal stem cells may also facilitate leukemia stem cells (LSC) survival. Whereas LSC share certain features of self-renewal and differentiation with HSC, LSC differ in their deregulated proliferation and ability to invade and spread. LSC exhibit the capacity for long-term self-renewal (Holyoake et al., 2002; Warner et al., 2004; Liesveld et al., 2004) within the BM microenvironment, which is required for maintenance of the malignant clone (Braun and Shannon, 2008). LSCs are able to generate leukemic blasts, and the leukemic clone is organized as a hierarchy (Zhang et al., 2003). LSCs may steal the homeostatic mechanisms, take refuge within the HM during chemotherapy, and consequently contribute to eventual disease relapse (Warner et al., 2004; Lane et al., 2009). Consecutively, LSC are believed to arise through transforming events targeting HSC, which allow growth-independent survival and proliferation. MSC are capable of promoting the growth, survival and drug resistance of leukemic cells by providing the necessary cytokines and cell contact-mediated signals to LSC (Dazzi et al., 2006; Ramasamy et al., 2007). There is increasing evidence that microenvironment alterations may be important and pathogenic in leukemia leading to enhanced stem cell mobilization and the creation of alternate niches (Lataillade et al., 2008). Recent data indicate that, in parallel with leukemogenic events in the hematopoietic system, the niche is converted into an environment with dominant signals favoring cell proliferation and growth. In some cases, a combination of these events may be required (Li and Neaves, 2006). Therefore, LSC may receive the support of a BM niche for their survival and may in turn influence deregulation of the BM niche by their dominant proliferation-promoting signals.

AML may arise in an abnormal HM, resulting in the generation of multiple populations with varying initiation events. Ninomiya et al. (2007) modeled the homing, proliferation, and survival sites of human leukemia cells and of cord blood CD34+ cells. The transplanted leukemia cells initially localized on the surface of osteoblasts in the epiphysial region and then expanded to the inner vascular and diaphysial regions. 8 weeks after transplantation, the number of leukemia cells transiently increased by as much as 50%, predominantly in the epiphysial region. After administration of high-dose cytarabine, residual leukemia cells clustered and adhered to the blood vessels as well as to the endosteum, suggesting that leukemia cells receive anti-apoptotic signals not only from osteoblasts but also from vascular endothelium (Ninomiya et al., 2007).

Several studies have proposed that important quantitative and functional alterations occur in MSCs of patients with different hematological disorders (Borojevic et al., 2004; Flores-Figueroa et al., 2008). In some disorders, such as multiple myeloma, MSC show alterations in the expression of some cell adhesion molecules and cytokines, and reduced immunosuppressive efficiency (Wallace et al., 2001; Arnulf et al., 2007; Corre et al., 2007). Neoplastic plasma cells communicate with the environment through cell/cell contact as well cytokines to induce functional changes that support the malignant population (Mitsiades et al., 2006; Podar et al., 2007). In myeloproliferative disorders, has been shown, that megakaryocytes and macrophages play a principle role in the pathogenesis of the fibrotic reaction by secreting PDGF, FGF and TGFα cytokines (Chagraoui et al., 2006). In chronic myeloid leukemia (CML), Bhatia (1995) showed that MSC did not provide optimal support for normal hematopoietic cells. In contrast, growth of CML cells on CML-derived stroma was significantly better, suggesting that the microenvironment in CML was more supportive for the malignant clone. Using fluorescent activated cell sorting (FACS) and fluorescent in situ hybridization (FISH), it was determined that stromal macrophages were all bcr-abl positive and were directly responsible for the selective advantage of clonal bcr-abl cells to proliferate through a contact-dependent mechanism (Bhatia et al. 1995). Interestingly, other researches estimated that CML-derived MSC do not express the bcr-abl gene (Zhao et al., 2006; Jootar et al., 2006). In myelodysplastic syndrome (MDS) MSC show alterations in the levels of TNFα (Deeg et al., 2000). Furthermore, the MDS-derived monocytes respond abnormally to stromal signals, MDS monocytes fail to upregulate matrix metalloproteinase-9 (MMP-9) expression when exposed to stromal signals (Iwata et al., 2007). MMP-9 has been implicated in the cleavage of SDF1 from the microenvironment and may facilitate the egress of HCs from the BM to the peripheral blood (Heissig et al., 2002). In the solid tumors, tumor-derived MSC shown acquire aberrant methylation patterns due either to direct contact with or via factors secreted by the malignant cells (Hanson et al., 2006; Fiegl et al., 2006).

Dysfunction of a BM niche may contribute to leukemogenesis by supplying abundant growth factors that promote proliferation and/or inhibit apoptosis (Jones and Wagers, 2008). MSCs seem to have a relevant role in AML as they prevent spontaneous and induced apoptosis and may attenuate chemotherapy-induced cell death. This possibility has been confirmed by the finding that co-cultivation of a leukemic cell line with the murine stroma cell line MS-5 can block apoptosis (Konopleva et al., 2002).

The significance role of the HM in initiation of leukemia has been suggested by studies with mice deficient in phosphatase and tensin homolog (PTEN) (Yilmaz et al., 2006). PTEN deficiency in both HSC and the HM resulted in myeloproliferation that progressed to overt leukemia/lymphoma. However, inducible PTEN deletion in HSC in the presence of a wild type HM promoted HSC depletion without evidence of myeloproliferation or leukemic development. These results suggest that PTEN deficiency in HSC alone is not sufficient for malignant transformation. Rupec et al. (2005) reported that activation of NF-kB in myelopoietic cells and the absence of its inhibitor IκBα are not sufficient for induction of hypergranulopoiesis, but these changes in the non-hematopoietic compartment, such as fetal liver, resulted in increased numbers of dysplastic hematopoietic cells with progression into secondary AML. These results indicate that non-hematopoietic cells with inactive IκBα can initiate premalignant hematopoietic disorder, conceivably via activation of the Notch pathway. Additional studies indicate the role of Notch signaling in the interactions of HSC and the HM (Matsuoka et al., 2008) demonstrated that the tumor suppressor Fbxw7, which negatively regulates cyclin E, Notch, and c-Myc protein levels, plays a role in maintaining HSC quiescence and repressing potential oncogenic activity of HSC. Notably, Notch ligand Jagged is expressed by the HSC niche, and Jagged/Notch activation results in increased HSC number and niche expansion (Calvi et al., 2003).

Evidence from research conducted over the last few decades has clearly implicated abnormalities of the marrow microenvironment in the pathophysiology of hematologic malignancies. Marcondes et al. (2008) demonstrated that MSC derived from patients with MDS, in contrast to that from more advanced stages of MDS expressed 14- to 17-fold higher levels of IL-32 mRNA than healthy controls, and this constitutive IL-32 expression promoted apoptosis in MDS cells, reproducing the inefficient hematopoiesis and extensive apoptosis in MDS marrow. These findings indicate that stroma-produced IL-32 could contribute to the pathophysiology of MDS, and serve as a therapeutic target. Furthermore, this modified microenvironment phenotype was reproduced when the MSC were exposed to TNFα, known to be produced at high levels by MDS cells.

There are significant data to support mechanism, in which the malignant hematopoietic clone induces reversible functional changes in the HM that result in improved growth conditions for the malignant cells. Gene expression changes occurred in the stroma cell lines, HS5 and HS27a, derived from normal marrow in response to TNFα exposure (Stirewalt et al., 2008), known to be up-regulated in the bone marrow of patients with MDS. Previous experiments showed that interactions between MSC and HSC were required for TNFα to trigger apoptosis in hematopoietic cells (Goda et al., 2006).

Recent discoveries utilizing mouse models have provided the first experimental evidence for genetic changes in the HM contributing to or required for leukemogenesis. Raaijmakers et al. (2010) using transgenic mice showed that genetic alteration of HM can induce MDS with ineffective hematopoiesis and dysmorphic HCs, and with occasional transformation to AML. The authors used *Dicer1* deletion as a means of altering several gene products in subsets of mesenchymal osteolineage cells. *Dicer1* is an RNase III endonuclease essential for microRNA biogenesis (Bartel, 2004) and RNA processing (Krol et al., 2007), that regulates haematopoietic cell fate (Lu et al., 2008). Global repression of microRNA maturation by *Dicer1* deletion promotes cellular transformation and tumorigenesis (Kumar et al., 2007). Raaijmakers et al. (2010) show that deletion of *Dicer1* in HM cells of mouse may be sufficient to initiate a complex change of homeostasis with similarities to myelodysplasia. The authors demonstrated that the ability of HM abnormality to result in the emergence of a clonal neoplasm in a cell type of clearly distinct lineage with distinct secondary genetic changes (Raaijmakers et al., 2010).

Previously, Walkley et al (2007a, 2007b) demonstrated that conditional deletion of the Retinoblastoma gene (RB) in the BM microenvironment can contribute to the development of pre-leukemic myeloproliferative disease in mice. They showed that this was a result of interactions between myeloid cells and the microenvironment. The defect had to be present in both hematopoietic cells and the microenvironment to initiate disease. Widespread inactivation of RB, a central regulator of the cell cycle and a tumor suppressor, resulted in extramedullary hematopoiesis and myeloproliferative disease in the murine hematopoietic system. However, myeloid-specific loss of RB did not induce myeloproliferative disease or HSC abnormalities. Therefore, the myeloproliferative-like disorder in the RB mutants is the result of perturbed interactions between hematopoietic cells and the BM microenvironment

(Walkley et al., 2007a). The final model, reported by the same group, may be the most compelling. In this report, deletion of the Retinoic Acid Receptor γ (RARγ) in mice resulted in a chronic myeloproliferative disorder. Transplant studies revealed that RARγ-hematopoietic cells functioned normally when transplanted into normal mice. However, transplantation of normal hematopoietic cells into the RARγ-microenvironment resulted in a myeloproliferative disorder in the transplanted cells. TNFα was implicated in the pathogenesis of this MPD as the disorder was partially abrogated when TNFα null stem cells were transplanted into the RARγ-microenvironment (Walkley et al., 2007b). These studies showed that a defect in HM could be sufficient to generate a myeloproliferative disorder.

Until recently, there has been little evidence to support the role of primary stromal abnormalities in the pathogenesis of hematologic neoplasms. Some independent studies have documented the existence of genomic alterations in the stroma of leukemia patients (Flores-Figueroa et al., 2005; Blau et al., 2007; Lopez-Villar et al., 2009; Klaus et al., 2010). Different groups have shown the extensive variability of the aberrations, such as hypodiploidy, balanced and unbalanced translocations, whole chromosome gains, and deletions. All cytogenetic markers in MSCs never repeated aberrations identified in HCs. Since there were no associations between chromosomal aberrations in HCs and MSCs, we can state that MSCs were devoid of residue HCs. These findings suggest enhanced genetic instability of MSC in leukemia, and indicate the potential involvement of MSC in the pathophysiology of these conditions (Blau et al., 2007). Recently, Lopez-Villar et al. (2009) reported the presence of cytogenetic aberrations on MSC from MDS patients by array-based comparative genomic hybridization and fluorescence in situ hybridization, some of them specially linked to a particular MDS subtype, the 5q-syndrome.

These date indicate that there are significant functional abnormalities, genetic aberrations, and epigenetic changes in MSC in leukemia patients. Also of interest are the recent reports of abnormalities in the stroma that lead to malignancies of the hematopoietic compartment. Although historically, hematologic malignancies are thought to arise from a stem or progenitor cell abnormality, there may be groups of patients that have a primary stromal defect leading to the hematologic malignancy. Moreover, although a series of genetic and epigenetic events in a single cell may be necessary for oncogenesis, they may not be sufficient, and a permissive microenvironment has been suggested to be required for frank malignancy to emerge (Hanahan and Weinberg, 2007).

It is known that even years after allogeneic stem cell transplantation (alloSCT), and despite successful engraftment of donor-derived hematopoiesis, MSC are in general of host origin (Rieger et al., 2005). Some patients after alloSCT do not recover their stem cells despite receiving high levels of CD34+ progenitor cells. The presumed basis for this is that the preparation regimen has in some way affected the niche, so it no longer has the same nurturing capability. It was shown that transplanted HSCs migrate to the endosteal surfaces of bone within hours of intravenous injection (Nilsson et al., 1997). Endochondral ossification has been shown to be an essential prerequisite for the development of normal haematopoiesis in the BM (Zhou et al., 1995), indicating a possible fundamental interrelationship of ossification to the mature haematopoietic process in mammals. Recent reports have identified that a key cellular component of the HSC niche is cells of the osteoblast lineage, the cell type responsible for the formation of bone (Calvi et al., 2003; Zhang et al., 2003). Additionally, these studies raise the issue that under transplant conditions, there may be agents that rather than drive hematopoiesis, might affect the osteoblast component.

Understanding the niche has ramifications beyond simple biological interest. Niche biology and function has relevance not only in bone marrow transplantation, but in developing agents that may impact on the ability to generate a larger number of stem cells or increase the efficiency of stem cells to engraft in the transplant setting. By elucidating the role of the BM microenvironment in the pathogenesis of hematologic tumors, recent studies have provided the framework for identifying and validating novel therapies that target both leukemic cells and cells in their surrounding microenvironment (Konopleva et al., 2009). Thus in general, treatment strategies have been focused on the eradication of the stem or progenitor cell from which the malignancy arose. However, recent evidence suggests that focusing therapeutic strategies on the microenvironmental abnormalities can be extremely effective. The Imid family of agents has changed the treatment paradigm in diseases such as myeloma and MDS and highlighted the importance of targeting the microenvironment (Sokol et al., 2007; Melchert and List, 2007).

If primary stromal defects are identified in humans and implicated in the initiation of malignancy, this clearly will have great impact on the treatment strategies offered to patients. By explanation the role of the MSC in the pathogenesis of AML, recent studies have provided novel therapies that target both leukemic cells and cells of microenvironment. Studies of MSC can also aid in potentially modifying the relative abundance of normal versus malignant cells in the context of the post chemotherapy setting in AML. The underlying molecular mechanisms implicated in stem cell activation and homing to the niche will provide important insight into the precise mechanisms involved in interactions between leukemic and normal cells that contribute to drug resistance. This understanding will provide a framework for the rational combination of agents in clinical trials to overcome drug resistance and improve patient outcomes. Detection of alterations in MSCs suggests that unstable MSCs may facilitate the expansion of malignant cells. In view of these data, alterations in MSCs may be a particular mechanism of leukemogenesis. Especially, further understanding of the contribution of the BM niche to the process of leukemogenesis may provide new targets aimed at destroying LSC without adversely affecting normal stem cell self-renewal.

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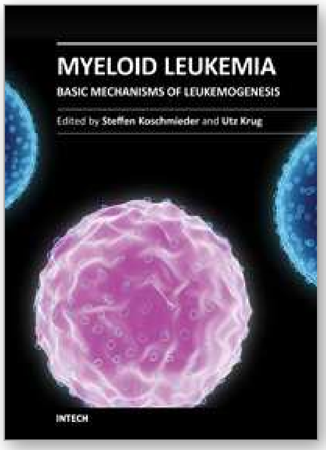

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The current book comprises a series of chapters from experts in the field of myeloid cell biology and myeloid leukemia pathogenesis. It is meant to provide reviews about current knowledge in the area of basic science of acute (AML) and chronic myeloid leukemia (CML) as well as original publications covering specific aspects of these important diseases. Covering the specifics of leukemia biology and pathogenesis by authors from different parts of the World, including America, Europe, Africa, and Asia, this book provides a colorful view on research activities in this field around the globe.

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Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821