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Citation	Manier, S., A. Sacco, X. Leleu, I. M. Ghobrial, and A. M. Roccaro. 2012. Bone marrow microenvironment in multiple myeloma progression. <i>Journal of Biomedicine and Biotechnology</i> 2012:157496.
Published Version	doi:10.1155/2012/157496
Accessed	February 19, 2015 11:50:37 AM EST
Citable Link	http://nrs.harvard.edu/urn-3:HUL.InstRepos:10512165
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Review Article

Bone Marrow Microenvironment in Multiple Myeloma Progression

S. Manier,^{1,2} A. Sacco,¹ X. Leleu,² I. M. Ghobrial,¹ and A. M. Roccaro¹

¹Dana-Farber Cancer Institute, Department of Medical Oncology, Harvard Medical School, 450 Brookline Avenue, HIM 246, Boston, MA 02215, USA

²Service des Maladies du Sang, CHRU de Lille, 59000 Lille, France

Correspondence should be addressed to A. M. Roccaro, aldo_roccaro@dfci.harvard.edu

Received 3 August 2012; Accepted 18 September 2012

Academic Editor: Sue-Hwa Lin

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Substantial advances have been made in understanding the biology of multiple myeloma (MM) through the study of the bone marrow (BM) microenvironment. Indeed, the BM niche appears to play an important role in differentiation, migration, proliferation, survival, and drug resistance of the malignant plasma cells. The BM niche is composed of a cellular compartment (stromal cells, osteoblasts, osteoclasts, endothelial cells, and immune cells) and a noncellular compartment including the extracellular matrix (ECM) and the liquid milieu (cytokines, growth factors, and chemokines). In this paper we discuss how the interaction between the malignant plasma cell and the BM microenvironment allowed myeloma progression through cell homing and the new concept of premetastatic niche.

1. Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the accumulation of monoclonal plasma cells in the bone marrow (BM), over 10% by definition [1]. In almost all cases, MM is preceded by a premalignant disease well known as monoclonal gammopathy of undetermined significance (MGUS) [2, 3]. MGUS affects 2% of the population above the age of 50 and it progresses to overt MM at a rate of 1% per year [4].

The biologic transition from normal plasma cells to MGUS and SMM to MM consists of many oncogenic events. An early event described in MGUS as well as MM is the dysregulation of a *cyclin D* gene [5]. Secondary translocations, sometimes involving an Ig locus, can occur at any stage of plasma cell dyscrasia. Activating mutations of *NRAS* and *KRAS* are each present in about 15% of multiple myeloma tumors. Constitutive activation of the nuclear factor κ B (NF κ B) pathway is mediated by mutations in some tumors during progression. In addition to these oncogenic events, the tumor cells are strongly dependent on the bone

marrow microenvironment [6]. Substantial advances have been made in understanding the biology of MM through the study of the BM microenvironment. Indeed, the BM niche appears to play an important role in differentiation, migration, proliferation, survival, and drug resistance of the malignant plasma cells providing the preclinical evidences for targeting MM cells and bone marrow stromal cells (BMSC) as an antitumor strategy in this disease [7]. The cellular compartment is composed of hematopoietic cells and nonhematopoietic cells including fibroblasts/BMSC, endothelial cells (ECs), osteoclasts, and osteoblasts. The non-cellular compartment is composed of the extracellular matrix (ECM) and the liquid milieu including cytokines, growth factors, and chemokines. MM cells home to the BM and adhere to ECM proteins and to BMSC. This trafficking (homing-egress) allows the progression or “metastasis” of the disease to new BM sites [7]. However the new host microenvironment is not well adapted to the cancer cells that metastasized into it, leading to the new concept of premetastatic niche [8]. Indeed significant changes occur in the microenvironment even before the first tumor cell homes

to the bone marrow, as already described in solid tumor models [8]. In this paper, we discuss how BM may support MM cell growth and disease progression.

2. The Bone Marrow Microenvironment

2.1. Cellular Compartment

2.1.1. Bone Marrow Stromal Cells (BMSCs) in MM Progression. MM cells adhere to BMSC and ECM into the BM. Tumor cells bind to ECM proteins, such as type I collagen and fibronectin *via* syndecan 1 and very late antigen 4 (VLA-4) on MM cells and to BMSC VCAM-1 *via* VLA-4 on MM cells. Adhesion of tumor cells to BMSC activates many pathways resulting in upregulation of cell cycle regulating proteins and antiapoptotic proteins [9]. Specifically, the interaction between MM cells and BMSCs triggers NF- κ B signaling pathway and interleukin-6 (IL-6) secretion in BMSCs. In turn, IL-6 enhances the production and secretion of VEGF by MM cells. The existence of this paracrine loop optimizes the BM milieu for MM tumor cell growth [10]. BMSC-MM cell interaction is also mediated through Notch. The interaction Notch-Notch ligand leads to activating Notch-signaling pathways both in MM cells as well as in BMSC, with induction of IL-6, vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF-1) secretion and is associated with MM cell proliferation and survival [11, 12]. Moreover, BMSC from MM patients expresses several proangiogenic molecules, such as VEGF, basic-fibroblast growth factor (bFGF), angiopoietin 1 (Ang-1), transforming growth factor (TGF)- β , platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), interleukin-1 (IL-1) [13]. Recently, BMSCs from MM patients have been shown to release exosomes, which are transferred to MM cells, thereby resulting in modulation of tumor growth *in vivo*, mediated by specific miRNA. This finding suggest that exosomes might constitute a novel mechanism for intercellular transfer of genetic information in the form of miRNA in clonal plasma cell disorders [14].

2.1.2. Endothelial Cells and Angiogenesis in MM Progression. BM angiogenesis represents a constant hallmark of MM progression, partly driven by release of pro-angiogenic cytokines from the tumor plasma cells, BMSC, and osteoclasts, such as VEGF, bFGF, and metalloproteinases (MMPs). Indeed, the adhesion between MM cells and BMSCs upregulates many cytokines with angiogenic activity, most notably VEGF and bFGF [15]. In MM cells, these pro-angiogenic factors may also be produced constitutively as a result of oncogene activation and/or genetic mutations [16]. Evidence for the importance of angiogenesis in the pathogenesis of MM was obtained from BM samples from MM patients [17]. The level of BM angiogenesis, as assessed by grading and/or microvessel density (MVD), is consistently increased in patients with active MM as compared to those with inactive disease or MGUS, a less advanced plasma cell disorder. Comparative gene expression profiling of multiple myeloma endothelial cells and MGUS endothelial cells has been performed in order to determine a genetic signature and to identify

vascular mechanisms governing the malignant progression [18]. Twenty-two genes were found differentially expressed at relatively high stringency in MM endothelial cells compared with MGUS endothelial cells. Functional annotation revealed a role of these genes in the regulation of ECM formation and bone remodelling, cell adhesion, chemotaxis, angiogenesis, resistance to apoptosis, and cell-cycle regulation. The distinct endothelial cell gene expression profiles and vascular phenotypes detected in this study may influence remodelling of the bone marrow microenvironment in patients with active multiple myeloma. Overall, these evidences suggest that EC presents with functional, genetic, and morphologic features indicating their ability to induce BM neovascularization, resulting in MM cells growth, and disease progression, providing preclinical evidences for using antiangiogenic compounds in the treatment of MM.

2.1.3. Osteoclasts in MM Progression. The usual balance between bone resorption and new bone formation is lost in many cases of MM, resulting in bone destruction and the development of osteolytic lesions [19]. Bone destruction develops adjacent to MM cells, yet not in areas of normal bone marrow. There are several factors implicated in osteoclast activation, including receptor activator of NF- κ B ligand (RANKL), macrophage inflammatory protein-1a (MIP-1a), interleukin-3 (IL-3), and IL-6 [20]. RANK ligand is a member of the tumor necrosis factor (TNF) family and plays a major role in the increased osteoclastogenesis implicated in MM bone disease. RANK is a transmembrane signaling receptor expressed by osteoclast cells. MM cell binding to neighboring BMSC within the bone marrow results in increased RANKL expression. This leads to an increase in osteoclast activity through the binding of RANKL to its receptor, on osteoclast precursor cells, which further promotes their differentiation through NF- κ B and JunN-terminal kinase pathway [21]. RANKL is also involved in inhibition of osteoclast apoptosis. Blocking RANKL with soluble form of RANK has been shown to modulate not only bone loss but also tumor burden in MM *in vivo* models [22]. Moreover osteoclasts constitutively secrete proangiogenic factors osteopontin that enhanced vascular tubule formation [23].

2.1.4. Osteoblasts in MM Progression. It has been reported that osteoblasts may contribute to MM pathogenesis by supporting MM cells growth and survival [24]. This could potentially result from the ability of osteoblasts to secrete IL-6 in coculture system with MM cells, thus increasing IL-6 levels within the BM milieu and therefore inducing MM plasma cells growth. Other mechanisms include the possible role of osteoblasts in stimulating MM cells survival by blocking TRAIL-mediated programmed MM cell death, by secreting osteoprotegerin (OPG), a receptor for both RANKL and TRAIL [25]. In addition, it is clear that suppression of osteoblast activity is responsible for both bone destructive process and progression of myeloma tumor burden. Several factors are responsible for suppression of osteoblast activity in MM such as DKK1 [26]. DKK1 is a Wnt-signaling antagonist secreted by MM cells and it

inhibits osteoblast differentiation. DKK1 is significantly overexpressed in patients with MM who present with lytic bone lesions. Myeloma-derived DKK1 also disrupts Wnt-regulated OPG and RANKL production by osteoblasts. Studies have shown that blocking DKK1 and activating Wnt signaling prevents bone disease in MM but is also associated with a reduction in tumor burden [27–29].

2.2. Noncellular Compartment

2.2.1. Interleukin-6 in MM Progression. IL-6 is a key growth and survival factor in MM [30]. IL-6 is primarily produced by BMSC and osteoblasts and mediates paracrine MM cell growth and is also secreted by MM tumor cells in an autocrine manner [31]. IL-6 secretion from BMSC is upregulated by many molecules/cytokines (i.e., CD40, TNF- α , VEGF, IL-1 β , TGF- β) and MM cell adherence. IL-1 β appears to be one of the major cytokines responsible for the paracrine production of IL-6 by the BMSC. The aberrant production of IL-1 β by the MM cells induces IL-6 production by BMSC, which in turn supports the growth and survival of the myeloma cells [32]. Importantly, NF- κ B plays a central role in cytokine- and adhesion-mediated IL-6 upregulation, and specific inhibition of NF- κ B blocks IL-6 secretion [33]. After binding with its receptor, IL-6 triggers activation of MEK/MAPK, JAK/STAT3, and PI3K/Akt signaling pathways [34]. IL-6 induces proliferation of the tumor plasma cells by activating the RAS/Raf/MEK-ERK signaling pathway. IL-6 is also able to inhibit the antiproliferation effects of cyclin-dependent kinase (CDK) inhibitors p21 and p27 through the PI3K/Akt pathway [31]. IL-6 activation of the JAK/STAT3 pathway induces tumor cells survival by up-regulation/activation of anti-apoptotic proteins Mcl-1 and Bcl-X_L and c-Myc. Clinically, elevated serum IL-6 levels are associated with a poor prognosis and reflect the proliferation fraction of MM cells within patients [35]. Otherwise IL-1 receptor targeted therapies have shown activity in increasing PFS of patients with smoldering disease [36].

2.2.2. Insulin-Like Growth Factor 1 in MM Progression. Insulin-like growth factor 1 (IGF-1) is involved in tumorigenesis of several solid cancers [37]. In MM, IGF-1 is secreted by the BMSC and osteoblasts and induces growth, survival, and migration of MM cells. The phosphorylation of IGF-1 receptor (IGF-1R), after IGF-1 binding, leads to activation of MAPK and PI3K/Akt signaling pathway [38]. Activation of Akt leads to activating the anti-apoptotic proteins Bcl-X_L, Bcl-2 and downregulating the proapoptotic protein Bim, thereby promoting cell survival. IGF-1 is also well known for its metabolic effects. Interestingly, IGF-1 could be involved in the pathophysiology that relates obesity and diabetes to neoplasia [37].

2.2.3. Vascular Endothelial Growth Factor (VEGF) in MM Progression. VEGF represents a well-known proangiogenic factor: its levels increase in several hematologic malignancies including MM [15]. In MM, VEGF is produced both by MM cells and BMSC, and its secretion is stimulated by different

cytokines and cell growth factors such as IL-6, bFGF, TGF- β or tumor necrosis factor (TNF)- α . It is an important factor in the formation of new vasculature; upon binding with VEGF receptor-1 and -2 (VEGFR-1 and VEGFR-2), it triggers proliferation, migration, differentiation, and survival of BMSC and EC, through several signaling pathway such as Ras GAP, FAK, PI3K/Akt, MEK/ERK, and STAT [15]. Blood vessels are required for tumor growth and progression for provision of vital oxygen and nutrients. It has been shown that increased microvessel density (MVD) in BM of MM patients is associated with poor prognosis.

3. Homing and Egress

The initiation of MM is likely from long-lived plasma cells that develop in germinal center of lymphoid tissues and home to the BM. Oncogenic events along with support of the microenvironment allow the growth, survival, and proliferation of these cells in the initial sites of the BM niche [7]. Furthermore, some studies showed the presence of a small number of circulating plasma cells in MM and its association with a poor prognosis [39]. Migration of cells through the blood to the bone marrow niches requires active navigation, a process termed homing. The first step in the homing process is the rolling of the MM cell along the EC through selectin. The adhesion and extravasation are induced by activation of integrin—expressed by MM cell—such as LFA-1 and VLA-4 [40]. The SDF-1/CXCR4 axis plays a critical role in homing of MM cells to the BM. Studies to identify expression of chemokine receptors in MM have shown large variations in CXCR4 expression ranging from 10 to 100%. SDF-1 induces migration of MM cells *in vitro* and homing into the bone marrow *in vivo*. Moreover, CXCR4 knockdown led to significant inhibition of migration to SDF-1 in MM cell lines and primary CD138+ cells [41]. MM is characterized by the disseminated involvement of the BM, and its progression involves a continuous circulation of the MM cells in the peripheral blood and homing back to the BM. Mobilization or egress of cells out of the bone marrow could be enhanced by disrupting the SDF-1/CXCR4 axis. This may occur by decreasing SDF-1 by protease in the BM milieu [42], or by upregulation of CXCR4 expression by hypoxia. Indeed, the bone marrow niche is quite hypoxic (1%-2% O₂) [43]. It has also been shown that hypoxia leads to inactivation of E-cadherin and activation of transcription factors regulating epithelial-mesenchymal transition, including Snail and Twist, indicating that this mechanism can participate to the egress process.

4. Premetastatic Niche

Although preparation of the premetastatic niche has not been studied in MM, several works have shown the importance of the premetastatic niche in solid cancer metastasis to the bone marrow. Indeed, the new host microenvironment is not well adapted to the cancer cells that metastasized into it [8]. Therefore, significant changes in the stroma, endothelial cells, ECM constituents, cytokines, and chemokines need

to occur to allow for the growth and survival of these metastatic cells. Preparation of the metastatic niche occurs even before the first metastatic cell arrives. Evidence has emerged that growth factors and cytokines secreted by the tumor prepare tissues for tumor cell engraftment [44]. For example, bone marrow-derived hematopoietic cells that express VEGFR1 as the fibronectin receptor VLA-4 are localized to the premetastatic sites before the arrival of tumor cells [44]. Moreover, microvesicles such as exosomes have been shown to alter the premetastatic niche in different studies [45]. Exosomes are small vesicles (30–100 nm) of endocytic origin, which are released in the extracellular milieu by several cell types. Previous studies have shown the intriguing role of exosomes in tumor progression. Recently, melanoma-derived exosomes have been shown to induce neoangiogenesis at pre-metastatic niche sites. RAB1A, RAB5B, RAB7, and RAB27A, regulators of membrane trafficking and exosome formation, are highly expressed in melanoma cells. Rab27A RNA interference decreased exosome production, preventing bone marrow education and reducing tumor growth and metastasis. These data show that exosome production, transfer and education of bone marrow cells support tumor growth and progression to the bone marrow [46].

5. Conclusion

Several reports have clearly indicated that MM pathophysiology is supported by a strong interaction between the clonal plasma cells and the surrounding bone marrow microenvironment; indeed, there are several autocrine or paracrine circuits of growth that support the transformation from an MGUS stage to an active MM stage. By understanding the interaction occurring between BMSC and MM cells, and vice versa, we have now available the preclinical rationale for testing novel therapeutical approaches in order to better target not only the MM cell clone, but also the BM milieu, thus preventing MM disease progression.

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