Review Article

The role of bone marrow stromal cells in blood diseases and clinical significance as a crucial part of the hematopoietic microenvironment

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Abstract: Bone marrow stromal cells (BMSCs) usually refers to a group of multipotential, heterogenous members within the bone marrow that act as stem/progenitor cells of the bone tissue and are indirectly responsible for hematopoiesis. They could differentiate into diverse phenotypes, including endothelial cells, fibroblasts, adipocytes, osteoblasts, osteoclasts, etc. which together form the skeletal structure and compose most of the hematopoietic microenvironment (HME) sponsoring the regular production of blood elements. However, when blood diseases happening, these sponsors neglect their duty to become hypofunctional or even revolt to support tumor growth resulting in the suppression of normal hematopoiesis and progression of the disease. Consequently, in this review, we focus on BMSCs, a crucial part of the HME, discussing their changes under the pathological condition and expounding their profound roles involving in several hematopoietic diseases. By understanding the performance of BMSCs, more potential therapeutic applications and targets will be discovered and thus, the available regimen could be supplied to achieve a satisfactory curative effect.

Keywords: Bone marrow stromal cells (BMSCs); bone marrow mesenchymal stem cell; hematopoiesis; hematopoietic microenvironment (HME); aplastic anemia (AA); hematological tumor; multiple myeloma (MM); leukemia; tumor microenvironment; transplantation; graft versus host disease (GVHD)

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Introduction

At first, in the bone marrow, another non-hematopoietic population of multipotential members distinguished from hematopoietic stems cells was discovered to be the progenitor of myeloid stroma, which was usually termed "bone marrow stromal cells" (BMSCs) or "marrow mesenchymal stem cells" (MSCs) (1). Nowadays, further studies have demonstrated that BMSCs are a heterogenous, pluripotential group which expresses markers of multiple systems, differentiates into various lineages (e.g., endothelial cells, fibroblasts, adipocytes, macrophages, osteocytes, muscle cells, neurons, etc.), and is actually widely distributed in many parts of the body more than bone marrow (2-4). This infers that BMSCs can not only traditionally generate skeletal and mesenchymal counterparts such as bone, cartilage and fat, but also possess a great potency evolving into or repairing other tissues (1,5,6).

When concerned about the hematopoietic system only, BMSCs mainly act as the progenitor of bone and marrow structure and simultaneously are indispensable to long-term maintain hematopoiesis since they could establish the hematopoietic microenvironment (HME) that mostly

contains stromal elements and cytokines for hematopoietic stem cells (HSCs) residence and blood cells production (7-11). Therefore, in the blood system, BMSCs play roles as the founder of myeloid mesenchymal section and HME, as well as the sponsor of hematopoietic members.

Nevertheless, when blood diseases occur [e.g., hematopoietic failures like aplastic anemia (AA) or malignancies], BMSCs change to become indolent or corrupt, resulting in dysfunction in HME and finally cause aggravated situation and disruption of normal hematopoiesis (12,13). The disorder in BMSCs may also be regarded as an initiating agent of hematopoietic diseases (14). Thus, by exploring the function of BMSCs and transformations in illnesses, we could deeply understand mechanisms of disease development, and then search for novel potential targets, invent effective therapeutic protocols to control disease progression and obtain the best cure effect.

A brief discussion about features of BMSCs

BMSCs were firstly isolated as the progeny of the colony-forming-unit fibroblast (CFU-F) colonies that expanded when cultured single-cell suspensions of bone marrow *in vitro* and showed a spindle-shaped fibroblast-like morphology and an adherent habit (1,15-17). It is now clear that BMSCs form a complicated community with heterogeneous and pluripotential nature containing sorts of phenotypes, whereas no certain unique marker has been uncovered yet (18). Surface antigens of stromagenic differentiation like CD10, CD13, CD29, CD44, CD49e, CD73, CD90, CD92, CD105, CD146, CD166, SSEA4, Stro-1 and intracellular proteins could be detected synthetically for the identification (15,19-22). Furthermore, these myeloid progenitor stem cells express molecules mainly found in other organs like neural ganglioside GD2, nucleostemin, cardiac-specific symbols, and thus might be considered as special markers (23,24).

More importantly, not just express various markers, BMSCs could directly differentiate into multiple lineages with surprising potency and plasticity such as fibroblasts, adipocytes, endothelial cells, macrophages, osteoblasts and osteoclasts in general, which together generate the bone marrow mesenchymal tissue and what's more, could even differentiate into hepatocyte-like cells, nerve cells, cardiac phenotypes, muscle cells for injury repair (25-29) or support the regeneration of other tissues (23,30,31). Indeed, BMSCs are prone to home to sites more than bone marrow and are widespread in all parts of the body to function appropriately or pathologically, expressing lineage-related mRNA species, mediating liver fibrosis, targeting tumor stem cells, etc. (32-34).

For the hematopoietic system we focus on, BMSCs occupies an essential position in the formation of HME, or bone marrow microenvironment including each stromal cells, cytokines and extracellular matrix to maintain the normal hematopoiesis of HSCs, which owns a considerable transcriptomic profile (9,35). Data illustrates that microenvironmental niches usually refer to several parts consists of the endosteal niche (osteocytes), vascular niche (sinusoidal endothelium), and, more importantly, reticular niche consists of primitive BMSCs (CXCL12-abundant reticular cells and nestin-expressing cells) (36,37). In these niches, stromal cell types related to bone marrow tissues and extracellular matrix assembling in complicated networks, where HSCs can settle, proliferate, and mature, producing blood components through proximity to or intimate interaction with BMSCs and their derivatives (38-40). Evidence also suggests that factors synthesized by stromal cells like stem cell factor (SCF) from leptin receptor(+) cells, transforming growth factor-beta (TGF-β) from megakaryocytes, intercellular adhesion molecule-1 (ICAM-1), etc. are required to retain the propagation of HSCs (41-43).

However, in pathological conditions, HME experiences chaos in which BMSCs impede regulatory hematopoiesis and bring about the occurrence and progression of diseases, as elaborated below.

The role of BMSCs in benign hematopoietic disorders

AA is a kind of pancytopenia-bone marrow failure disease in which HSCs suffer injury by cross talking with the surrounding microenvironment and BMSCs (44). In AA, the clonogenic and proliferative competence of BMSCs is significantly attenuated and their effect to support hematopoiesis is slashed (45). Research has shown that high percentage of BMSCs from five children with severe aplastic anemia (SAA) stagnate in aberrant sub-G1 phase of cell cycle indicating a rising rate of apoptosis and they secrete anomalous increased cytokines of interleukin-6 (IL-6), interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β), which contribute to an abnormal microenvironment and immune dysfunction

of peripheral blood mononuclear cell (PBMC) (46). Similar evidences arise that BMSCs of AA patients markedly express lower concentrations of macrophage inflammatory protein (MIP)-1α (P<0.001) and higher TNF-α (P<0.001), granulocyte colony-stimulating factor (G-CSF) (P<0.001) and stromal cell-derived factor (SDF)-1α (P<0.01) transcripts compared to the control (47). Another deficiency of downregulated CD106(vascular cell adhesion molecule-1, VCAM-1) gene expression through the NF-κB signaling pathway *in vitro* is also exhibited in BMSCs from AA patients, and thus capillary tube-like formation and vasculogenesis *in vivo* are attenuated (48). BMSCs that produce altered hematopoiesis regulatory molecules reveal a vital role in the pathogenesis of AA.

Impaired function and defective proliferation of BMSCs exist in some more examples, such as immune thrombocytopenia (ITP) and thalassemia. BMSCs get regressive and senescent during ITP and exert less immunosuppression on T and B cells as well as induce regulatory DCs(regDCs) differentiated from $CD34^+$ hematopoietic progenitor cells through Notch-1/Jagged-1 signaling pathway, which leads to over-activated autoimmunity and platelet destruction (49,50). Additionally, Crippa *et al.* (51) elucidate that BMSCs from β-thalassemia (BT) patients prove a diminished hematopoietic supportive capacity. The most primitive BMSCs pool suffers pauperization by ascending ROS production *in vitro* while a reduced frequency of BMSCs *in vivo*, is verified. The study also views a weakened antioxidative response and lacking expression of associated genes in BT-BMSCs.

In brief, during the occurrence of benign hematopoietic diseases, BMSCs usually appear to be hypofunction and serious dereliction of duty, bringing about or aggravating anemia and damage of other hemocytes.

The role of BMSCs in malignant hematopoietic tumors

In hematological malignancies, however, the bone marrow milieu could be a cradle or a shelter for hematopoietic tumor development, and BMSCs may turn into the evil crime culprit aiding tumor reproduction and metastasis. They secrete some biological or angiogenic factors, enhance tumor-related genes expression, closely interact with malignant cells, or through numerous methods in this microenvironment to induce the growth and progression of cancer and finally impede normal hematopoiesis (52-54) *(Figure 1)*.

Multiple myelomas (MMs)

MM is an aberrant clonal-proliferation disease of plasma cells within the bone marrow, which causes extensive osteolytic destruction. BMSCs experience altered characterization when MM happens. The study of Arnulf *et al.* (55) noted that though regular phenotype, differentiation capacity, and long-term hematopoietic sponsor were retained, inferior potency suppressing T cell-reproduction and high concentration of IL-6 generation were found in BMSCs from MM patients. Moreover, Corre *et al.* (56) further discovered that expression property of 145 genes in BMSCs are distinct between MM and normal individuals, among which 46% might associate with the tumor-microenvironment crosstalk mainly increased IL-6 and growth and differentiation factor 15 (GDF15) levels. Other abnormal secretion profiles accounting for MM pathogenesis and progressions like IL-10, CD40/40L, VCAM1, ICAM-1, LFA-3, HO-1, HLA-DR, and HLA-ABC are also detected in MM-BMSCs (57).

MM is deemed to be a paradigm for exploring the interaction between tumor cells and the surrounding microenvironment (58,59). It has been emphasized repeatedly that the malignant MM cell generally communicates with its ecological niche(especially with BMSCs through close contact or biological factors like well-known IL-6, CXCR4 and RANKL which refers to receptor activator of nuclear factor-κB ligand) to get abnormal elevation, bone resorption, angiogenesis, drug resistance and could, in turn, inhibit the proper operation of BMSCs (60-62).

For the MM-BMSCs interaction, it's noteworthy in recent research that adherence of malignant plasma cells to mesenchymal stem cells enhances tumor necrosis factor receptor-associated factor 6 (TRAF6) expression reciprocally by NF-κB activation, fuels spliced form of X-box binding protein-1 (XBP1s) overexpression and induces altered transcriptomic profile *in vitro* in BMSCs, which together promote osteoclastogenesis and the growth/survival of tumor cells (63-65). Immunosuppressive molecule B7-H1 on myeloma cells induced by IL-6 from BMSCs links to T-cell downregulation and aggressive MM cell characteristics (66), while increased levels of GDF15, B-cell-activating factor(BAFF) and the transcriptional repressor Gfi1 synthesized by BMSCs may give rise to chemoprotective effect for MM cells, poor survival for patients and inhibition of osteoblast differentiation (67-69). Besides, McNee *et al.* (70) imply a novel mechanism that

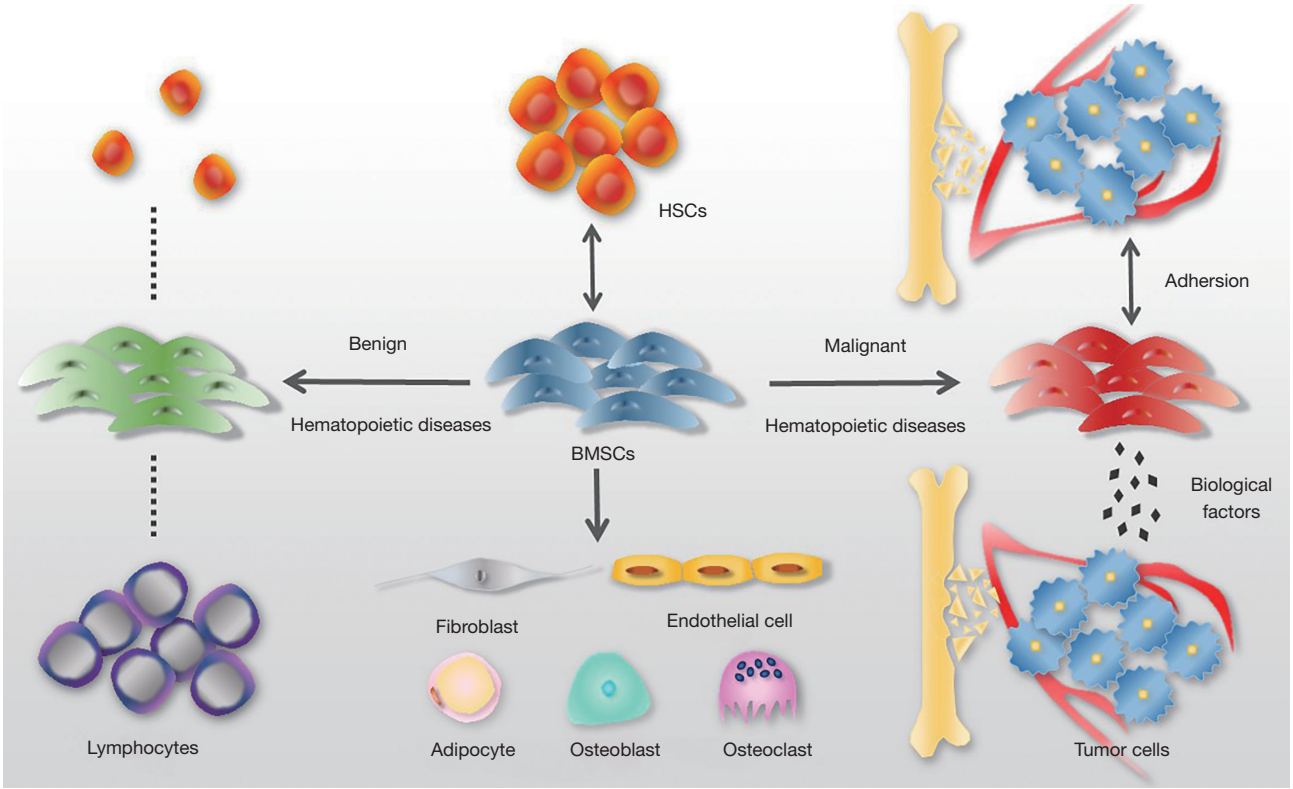

Figure 1 The role of BMSCs in different situations. Normal BMSCs could differentiate into various types of cells and support the growth of HSCs. In benign anemia, BMSCs become a failed sponsor resulting in a poor hematopoietic ability in HME. In other diseases such as ITP, BMSCs are unable to suppress the function of lymphocytes and thus brings about the immune overactivation effect. When the hematopoietic tumor occurs, BMSCs interact with malignant cells through biological factors or cell-cell contact, which leads to tumor proliferation, angiogenesis, osteolysis. BMSCs, bone marrow stromal cells; HSCs, hematopoietic stem cells; ITP, immune thrombocytopenia; HME, hematopoietic microenvironment.

citrullination of histone H3 arginine 26 in BMSCs from MM patients directly triggers the upregulation of IL-6 and thus incurs resistance to chemotherapy by MM cells. All of the exosomes derived from a normal donor, MM patient, and murine 5T33 BMSCs also favor tumor cell growth and drug resistance to bortezomib through several relevant survival pathways (e.g., c-Jun N-terminal kinase, p38, p53, and Akt) (71).

Meanwhile, study from patient bone marrow aspirates and C57BL/KaLwRij murine model of myeloma confirms that the plasma cell burden leads to a decrease in alkaline phosphatase osteoblasts and a rise in the incidence of STRO-1 (a stromal cell-related surface marker) positive BMSCs that express higher levels of plasma cell- and osteoclast-activating molecules (72). MM cell-produced CCL25 could, in turn, attract mesenchymal stromal cells and upregulated IL-6, IL-10, insulin growth factor-1, vascular endothelial growth factor (VEGF), and dickkopf homolog 1 expression in BMSCs promising tumor growth *in vitro* and *in vivo* (73).

Leukemia and lymphoma

Likewise, signatures of marrow stromal cells get changed when leukemia happens. The capacity of BMSCs from acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL) to maintain normal hematopoietic progenitor cells is markedly slashed compared to donors (74). Distinguished BMSCs protein expression characterizations are defined, and using RNA sequencing reveals transcriptional profiling with the deregulation of proteoglycans and adhesion factors in BMSCs with AML, whereas deregulated metabolic pathways and endocytosis in both DNA methylation and transcriptional features are uncovered by KEGG pathway

enrichment analysis (75-77).

Like MM, leukemia-BMSCs usually favor tumor cell growth, invasion, drug resistance, and disease progression. In acute leukemia, Wnt and Notch signaling activation in malignant cells stimulated by BMSCs contributes to the protection, survival and chemoresistance of tumor (78,79), while in either chronic myeloid or lymphocytic leukemia (CML or CLL), BMSCs could induce mature DC (mDC) into another regulatory DC subset resulting in an immune-tolerance situation with less T cells and more Tregs proliferation through TGF-β1, and could long-term maintain CLL-cell existence due to increased soluble prosurvival factors such as CXCL12 when cocultured in 5% oxygen concentration (80,81). Furthermore, there is evidence that extracellular vesicles or exosomes play a fundamental role in crosstalk between BMSCs and leukemia cells. CML cells-derived exosome promotes BMSCs to produce IL-8 modulating tumor cell survival both *in vitro* and *in vivo*. In turn, extracellular vesicles from BMSCs prevent apoptosis and boost migration of leukemia cells as well (82,83).

Last but not least, according to several studies, BMSCs primarily act to protect non-Hodgkin's lymphoma cells from apoptosis and can recruit follicular lymphoma cells supporting their survival (84). Conclusions depict that the protective effect may be attributed to the adhesion of malignant B cells to BMSCs through pro-survival adhesion molecule VLA-4, and ultimately the stimulation of either NF-κB pathway as well as related antiapoptotic proteins in lymphoma cells or BAFF expression in BMSCs (85-87).

Clinical significance of BMSCs in hematopoietic diseases

Transplantation and graft versus host disease (GVHD)

It has been reported that infusion with BMSCs in hematopoietic stem cell transplantation (HSCT) could repair the loss of stromal niche function and accelerate hematopoietic regeneration (88), and remarkable advantages of microenvironmental and hemopoietic compartments recovery within marrow are obtained via direct intra-bone marrow route rather than intravenous injection in mice (89-91). More importantly, the administration of BMSCs is thought to lower the incidence of GVHD following HSCT and even preserve graft-versus-leukemia activity (2,92,93). What is more, infusing BMSCs or BMSC-derived extracellular vesicles with unique microRNA property exerts great influence on the induction of T cell anergy, prevention of effector T cells differentiating from a naïve phenotype and maintenance of Treg population, which is superior to the conventional immunosuppressive regimen in curing severe acute GVHD refractory (94,95). The investigation also demonstrated that treating high grade acute GVHD with mesenchymal stromal cell end-products could achieve an overall survival of 71%±11% after a two-year follow up compared to 51.4%±9.0% in clinical statistics (96).

Potential targets of BMSCs in hematopoietic tumor treatment

Increasingly, mechanisms for tumor development correlated with BMSCs have been excavated, hence available targets could be applied to the therapeutic regimen. Experts have been working on to block the cross-talk between BMSCs and tumor cells; for example, bruton tyrosine kinase (Btk) inhibitor PCI-32765 suppresses MM cell growth induced by cocultured BMSCs and MM cell-mediated osteolysis both *in vitro* and *in vivo* (97). The pan-inhibitor of VEGF receptors, GW654652 as well as the VEGF receptor tyrosine kinase inhibitor PTK787/ZK222584, equally prevents the proliferation and migration of MM cells through inhibiting VEGF-triggered activation of downstream signaling factors, and IL-6 and VEGF secretion in tumor cells stimulated by the binding to BMSCs (98,99). Moreover, other agents like the inhibitor of oncogenic microRNA miR-21 in BMSCs, CXCR4 inhibitor AMD3100, arsenic trioxide, pentraxin 3 (PTX3) and sepantronium bromide (YM155) can not only disrupt stromal/plasma cell interaction and restrict tumor progression, but also improve the mesenchymal cell-mediated drug resistance and alleviate bone-resorbing activity in MM (100-104).

Additionally, in leukemia, targeting several pathways such as FGF2-FGFR1 and Wnt signaling which contributes to the leukemia-protective effect by BMSCs could get the disease relieved (78,105). Also, aiming at BMSCs-derived periostin that promotes CCL2 in B-ALL cells, together with platelet-derived growth factor receptors (PDGFRs) activated in CLL-BMSCs that is crucial for Akt stimulation, may reduce the tumor burden and an angiogenic switch to some extent (106,107).

Conclusions

We have summarized the features and actions of BMSCs in hematopoietic diseases. The conclusion is drawn that

this kind of heterogeneous, stem-like lineage is infertile during benign anemia and rebel to collude with malignant cells and establish a distant metastasis when tumor occurs. Thus, treatment associated with BMSCs is common in transplantation and molecule-targeted therapy. However, it is still controversial if BMSCs act as a friend or a foe in oncogenesis, since they are also able to cross-present quite a few tumor antigens to overcome the immunological tolerance and express the suicide gene for anti-tumor remedy (108-111). Considering the tumor-homing ability and heterogeneity of BMSCs, the interaction of stromal and cancer cells is supposed to be complicated leading to diverse outcomes. There is an urgent need to clarify the cluster of BMSCs further, and only by creating certain solutions according to particular situations can we obtain an optimal therapeutic effect.

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Footnote

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