



Targeting Myeloma Microenvironment as Antitumor Strategy



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Abstract

Despite the great advance in myeloma treatment, it still considered a fatal disease due to the permissive role played by the bone marrow (BM) microenvironment in disease establishment and progression. Understanding mechanisms of malignant plasma cells trafficking into and out of the BM may lead to improvement in prevention of disease progression and in overcoming drug resistance. The trafficking and homing of malignant plasma cells to the BM are regulated by soluble factors, and by direct interaction between plasma cells and bone marrow-resident cells. In the BM niche, malignant plasma cells reprogram the local BM microenvironment to induce malignant plasma cells retention, proliferation and drug resistance. Extramedullary disease develops in some patients, as a result of changes in plasma cells chemokine receptor expression or function and their independency of survival factors in BM niche. Furthermore, malignant plasma cells can prepare premetastatic niches for tumor dissemination in distant bone regions, by releasing cytokines, growth factors, and exosomes that remodel the extracellular matrix at these new sites.

Abbreviations: BM: Bone Marrow; BMSC: BM Mesenchymal Stromal Cells; MM: Multiple Myeloma; TME: Tumor Microenvironment; CXCR: Chemokine Receptor; PDE: Phosphodiesterase; VEGF: Vascular Endothelial Growth Factor; SDF: Stromal Cell-Derived Factor; BAFF: B-cell Activating Factor; HSP: Heat-Shock Proteins.

Introduction

Multiple myeloma (MM) is a hematological malignancy characterized by growth and expansion of clonal plasma cells almost exclusively in the bone marrow (BM) [1]. Multiple osteolytic lesions are present in most myeloma patients [2]. These lesions represent osteolytic bone metastasis rather than bone marrow infiltration, as in other hematological malignancies [3]. MM is still a fatal malignancy despite the great advance in its treatment. This is mainly attributed to the permissive role of the BM microenvironment in differentiation, proliferation, migration, survival, and drug resistance of the malignant plasma cells [1].

Malignant plasma cell trafficking and MM development

Malignant plasma cells reach the BM niche through sinusoids, where it proliferates favored by the tumor microenvironment (TME) [2]. The progression and 'metastasis' of MM occurs through trafficking of malignant plasma cells continuously in and out of the BM to reach new BM sites [2]. Occasionally, malignant

plasma cells egress from the BM to reach different organs causing extramedullary disease [4].

BM Microenvironment

The bone marrow microenvironment is also known as the bone marrow niche. It consists of a cellular and non-cellular component [3]. Each component exerts different effects on malignant plasma cells progression and both components work synergistically [1].

i. The cellular component is subdivided into hematopoietic cells (myeloid-derived suppressor cells, T lymphocytes, B lymphocytes, NK cells, regulatory T cells and osteoclasts) and non-hematopoietic cells (bone marrow stromal cells, fibroblasts, osteoblasts, endothelial cells, and blood vessels) [1].

ii. The non-cellular component includes the extracellular matrix, oxygen concentration, as well as cytokines, growth factors, and chemokines produced and/or affected by the cellular component of the BM microenvironment [1].

Homing

The migration of the malignant plasma cells to specific BM niches, their adhesion to the BM microenvironment, and the egress or mobilization of some of these cells into the peripheral circulation to home to other new BM sites is an active dynamic process. The process of cell migration through the blood to the BM niches is termed homing [2]. Homing and retention of normal and malignant plasma cells into the BM is mainly mediated by the interaction of chemokine receptor CXCR4 on malignant cell surface, with its ligand CXCL12. Other adhesion molecules of importance in mediating malignant plasma cells homing are the $\alpha 4\beta 7$ integrin (MAdCAM-1 and fibronectin receptor), and CD44. The interaction of CXCL12 with CXCR4 upregulates the $\alpha 4\beta 1$ integrin activity, allowing its binding to its ligand VCAM-1 expressed on the BM microvasculature. This event plays key role in malignant plasma cells recirculation. P and E-selectin and their ligands (P-selectin glycoprotein ligand-1, PSGL-1) expressed on the surface of malignant plasma cells also contribute to their attachment to the BM microvasculature [4].

Malignant plasma cells survival and proliferation

CXCL12, along with $\alpha 4\beta 1$, $\alpha 4\beta 7$, and $\alpha L\beta 2$ integrins, as well as CD44 are secreted by BM mesenchymal stromal cells (BMSC). Two main soluble mediators of the tumor necrosis factor superfamily contribute to survival and proliferation of malignant plasma cells: a proliferation-inducing ligand (APRIL) and B-cell activating factor (BAFF), which bind to B-cell maturation antigen (BCMA) on the cancer cell surface, and IL-6, whose receptor expressed on MM cells [4].

Educating the BM Niche

Upon MM niche stabilization, malignant plasma cells reprogram the local BM microenvironment, to provide further expansion signals for malignant plasma cells, which gradually become independent from initial normal niche support [4]. These responses occur through direct contact of malignant plasma cells with stromal, endothelial or osteolineage cells, as well as their stimulation by supportive cytokines [4]. This adhesive interaction between malignant plasma cells and marrow cells microenvironment results in secretion of growth and/or antiapoptotic factors including interleukin -6, insulin-like growth factor -1, vascular endothelial growth factor (VEGF), tumor necrosis factor - α , stromal cell-derived factor (SDF) 1 α , and B-cell activating factor (BAFF). These factors trigger multiple proliferative/antiapoptotic signaling cascades in malignant plasma cells: Ras/Raf/mitogen-activated protein kinase (MAPK) kinase (MEK)/extracellular signal-related kinase (ERK); Janus kinase (JAK) 2/signal transducers and activators of transcription (STAT)-3; phosphatidylinositol-3 kinase (PI3K)/Akt; nuclear factor (NF)- κ B; Wnt and Notch [2].

Extramedullary Disease

In the final phases of the disease, myeloma cells become egress from growth signals provided by the BM milieu and egress of from the BM to the bloodstream to colonize different organs. Malignant plasma cells egress from the BM is induced by decrease in CXCR4 expression and function [4] and by silencing of macrophage migration inhibitory factor (MIF) binding to CXCR4. The chemokine receptor CCR1 expressed on malignant plasma cells and its ligand CCL3 is also associated with increased circulating MM cells [4]. Furthermore, malignant plasma cells can prepare premetastatic niches which attract and maintain tumor dissemination in distant bone regions through release of growth factors, cytokines and exosomes that remodel the extracellular matrix at distant new bone site [4]. For example, bone marrow-derived hematopoietic cells expressing VEGFR1 home to tumor premetastatic sites forming cellular clusters. This process is coincidental with fibronectin upregulation at these sites to provide a permissive niche before tumor cells arrival [1]. Exosomes are a subfraction of extracellular vesicles that are associated with cell-to-cell communication [3]. Exosomes represent a source of long-distance transfer of mRNAs, proteins and growth factors to cell components of the BM microenvironment to alter their phenotype to foster a premetastatic niche suitable for expansion of arriving tumor cells [4].

Potential targets for blocking microenvironmental support of myeloma

Cytokines, cytokines receptors, their downstream protein kinases and transcription factors represent potential targets for blocking myeloma microenvironmental support.

CXCR4 inhibitor

Plerixafor (AMD3100) is a CXCR4 inhibitor that blocks CXCL12-CXCR4 interaction. This disrupts malignant plasma cells contact with the BM microenvironment and allows their mobilization into the circulation [4]. AMD3100 enhance the in vitro sensitivity to bortezomib by disrupting adhesion of malignant plasma cells to stromal cells. The combination of AMD3100 and bortezomib increased the ratio of apoptotic circulating cells compared to bortezomib-treated groups [2].

- **Disruption of the SDF-1/CXCR4 axis:** G-CSF or cyclophosphamide infusion in MM stem cell transplant patients in MM stem cell transplant patients disrupts the SDF-1/CXCR4 axis. This will decrease endogenous SDF-1 concentration in BM and will enhance mobilization or egress of cells outside the BM [2].

hsp90 Inhibitor

hsp90 inhibition will suppress cell surface expression of insulin-like growth factor-1R and interleukin-6R, as well as expression and/or function of Akt, Raf, IKK- α , and p70S6K. These

will decrease the amplitude of signaling via the PI3K/Akt/mTOR, Ras/Raf/MAPK, and IKK/NF- κ B pathways, leading to diverse downstream proapoptotic molecular changes [2].

Phosphodiesterase-5 (PDE5) Inhibitor

E.g. tadalafil:

It reduced MDSC function in relapsed/ refractory MM patients [5]. PDE5 inhibitors downregulate arginase 1 and nitric oxide synthase-2 expression and reduce the suppressive machinery of tumor recruited MDSCs in murine tumor models [1].

Conclusion

The clinical behavior of multiple myeloma depends not only on the genetic changes in tumor cells but also on their interaction with the microenvironment. Elucidation of the molecular mechanisms of MM niche are required to determine novel target approaches of beneficial effects on MM tumor progression and drug resistance.

References

1. Kawano Y, Moschetta M, Manier S, Glavey S, Gorgun GT, et al. (2015) Targeting the bone marrow microenvironment in multiple myeloma. *Immunological Reviews* 263(1): 160–172.
2. Hideshima T, Mitsiades CS, Stewart AK, Bergsagel P, Klein B (2009) Signaling pathways in myeloma. *Clinical Lymphoma & Myeloma* 9(2): S12-S17.
3. Hou J, Wei R, Qian J, Wang R, Fan Z, et al. (2019) The impact of the bone marrow microenvironment on multiple myeloma (Review). *Oncology Reports* 42(4): 1272-1282.
4. Garcia-Ortiz A, Rodriguez-Garcia Y, Encinas J, Maroto-Martin E, Castellano E, et al. (2021) The role of tumor microenvironment in multiple myeloma development and progression. *Cancers* 13(2): 217.
5. Noonan KA, Ghosh N, Rudraraju L, Bui M, Borrello I (2014) Targeting immune suppression with PDE5 inhibition in end-stage multiple myeloma. *Cancer Immunol Res* 2(8): 725–731.



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