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The Role of the Bone Marrow Microenvironment in the Evolution and the Treatment of Multiple Myeloma

Martine Kristen*

Department of Medical Oncology, University of British Columbia, Canada

Introduction

Multiple Myeloma (MM) is a hematologic malignancy characterised by the presence of abnormal plasma cells (PC) in the bone marrow (BM). Despite the introduction of innovative medicines, MM remains mostly incurable, with a recurrent pattern that eventually leads to refractory disease and patient death. Extrinsic factors are more important than tumour-intrinsic factors in explaining the differences in progression rates. The surrounding BM microenvironment (BM-ME) has been demonstrated to influence the differentiation, proliferation, and survival of aberrant PCs, which supports this hypothesis. More importantly, some of these changes have been associated to relapse and treatment resistance in multiple myeloma, which has an impact on patient survival [1].

The composition of the BM-ME influences the course of MM from its precursor stages of monoclonal gammopathy of unknown significance (MGUS) and Smoldering MM (SMM) to clinical MM disease progression and therapy responsiveness. Targeting cellular and extracellular components of the BM niche has become a critical therapy strategy since MM tumour growth is strongly dependent on its surrounding BM microenvironment. Despite the large number of studies on the BM-ME in MM, we still have a limited understanding of molecular changes and extensive networking within the microenvironment.

Plasma cells (PCs) are B cell compartment irreversibly differentiated cells that remain in the bone marrow and produce serum immunoglobulins. In vivo, bone marrow myeloma cells have a restricted capacity for self-renewal and proliferation.

The source of the cancerous plasma cells is unknown. Although the plasma cell is the most common cell in myeloma, there is evidence that a precursor compartment exists since a number of peripheral blood lymphocytes have the same Para protein isotype and clonal immunoglobulin gene rearrangements as myeloma plasma cells. It's likely that myeloma cells develop from a memory B cell or plasma blast in the lymph nodes' germinal centres. The discovery of the myeloma stem cell is still a work in progress [2].

The malignant cells within the BMM undergo a multistep transformation process that leads to the development of MM. A premalignant phase of MGUS can be detected in almost all patients who develop multiple myeloma. Through a series of sequential genetic and epigenetic events accumulated in the malignant plasma cell, several changes in the BMM that support the myeloma clone, and most likely a failure of the immune system to eliminate the malignant clone, the normal plasma cell is transformed to the premalignant MGUS/SMM state and eventually to symptomatic multiple myeloma [3].

The karyotype study of MM patients frequently reveals a number of recurrent numerical anomalies, such as hyperdiploidy, chromosome 13 deletion, and particular translocations affecting the 14q32 locus. The application of modern molecular technologies allows for the identification of new subgroups and pathogenic pathways in MM, allowing for a better knowledge of the disease's pathogenesis as well as the development of new targeted therapeutics.

***Address for Correspondence:** Martine Kristen, Department of Medical Oncology, University of British Columbia, Canada, E-mail: martinekristen@gmail.com*

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The University of Arkansas for Medical Sciences (UAMS) identified seven subclasses of myeloma using a new grouping system based on microarray gene expression profiling data. The first is characterised by overexpression of the multiple myeloma SET domain (MMSET) and/or fibroblast growth factor receptor 3 (FGFR3) genes. The MAF gene is upregulated in the second class, which is determined by. Upregulation of CCND1 or CCND3 due to distinguishes the CD1 and CD2 groups. The fifth group's defining feature is hyperdiploidy. Due to low dickkopf 1 (DKK1) expression and high e, the last two groups were characterised by a low occurrence of bone disease [4].

Important Cellular Components of the BMM in Myelomatogensis

Because they have numerous activities including as self-renewal, differentiation, cell signalling, tumour homing, and immunomodulation, mesenchymal stem cells (MSCs) support, maintain, and regulate normal HSCs .Adhesion molecules (VCAM-1, ICAM-1, and ALCAM), growth factors (stem cell factor (SCF), transforming growth factor (TGF), epidermal growth factor (EGF), Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF), and hepatocyte growth factor (HGF)), cytokines (interleukins IL-1, IL-1, IL-6, IL-7, and IL-8), angi (PGE2, HLA-G and indole amine 2,3-dioxygenase).

MSCs, on the other hand, are unregulated in various haematological malignancies and contribute to disease start and/or progression. MSCs from myeloma patients (MM-MSCs) interact with MM cells, changing the expression of antigenic and growth factors (such as CD40/40L, VCAM-1, ICAM-1, LFA-3, and HO-1) as well as many cytokines (IL-6, IL-10, TGFb1, macrophage inflammatory protein-1b (MIP-1b), and IL-7). Some MM-MSC abnormalities reduce osteoblastic activity or promote drug resistance in myeloma cells, such as bortezomib resistance caused by elevated NF-kB activation due to IL-8 production and other reasons [5].

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