The Bone Marrow Microenvironment in Waldenström Macroglobulinemia

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KEYWORDS

• Waldenström macroglobulinemia • Bone marrow niche • Homing
• Microenvironment • Cytokines • Immune cells • Angiogenesis

KEY POINTS

- An endosteal niche and vascular niche in the bone marrow provide support for lymphoplasmacytic cells.
- CXCR4 expressing malignant B cells home to the bone marrow in response to SDF-1.
- Bone marrow cells, including mast cells, monocytes, T cells, and endothelial cells, promote a favorable environment for malignant cells in Waldenström macroglobulinemia.
- Cytokines, including CCL5, IL-6, IL-21, and CXCL13, promote malignant B-cell growth, and CXCL13 levels are associated with responses to BTK inhibitors.

INTRODUCTION

Waldenström macroglobulinemia (WM) is a rare low-grade B-cell lymphoproliferative disorder defined by infiltration of lymphoplasmacytic lymphoma in the bone marrow (BM) and an increase synthesis by malignant cells with subsequent accumulation in the serum of monoclonal immunoglobulin M (IgM) that can cause hyperviscosity and other symptoms in the affected patients.[1] Recently, substantial research has been focused on understanding the pathogenesis of WM and to define the underlying molecular mechanisms involved in the disease. This work has confirmed not only the importance of mutations within the malignant cells but also highlighted the role for the BM microenvironment in promoting malignant B-cell growth, tumor cell survival, and IgM production. Using whole-genome sequencing analysis, initial work identified a somatic variant in the Myeloid Differentiation factor 88 (*MYD88*) gene that results in an amino acid leucine substitution by proline (L256P), and this mutation is seen in the vast majority of patients with WM.[2]

MYD88 is integral in processing signals external to cell and acts as an adaptor protein for interleukin-1R (IL-1R) and Toll-Like receptor (TLR) signaling pathways. Recent

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data have also shown a role for MYD88 in B-cell receptor signaling. Overall, its role is to recruit signaling molecules and kinases that ultimately converge in nuclear factor (NF)κB activation.[3] TLRs are involved in regulating the innate immune response, and stimulation of TLR, induced by environmental signals, recruits MYD88 to the cytoplasmic domain of TLR. It then forms a complex with IL-1R associated kinase 4 (IRAK4) and IRAK1 and initiates a signaling cascade that subsequently activates NFκB.[4] Bruton tyrosine kinase (BTK) is also a component of TLR signaling that specifically binds to MYD88 and activates signaling cascades in response to environmental signals.[5] In WM, the mutant form of *MYD*88 is shown to form a complex with BTK and induces constitutive activation of TLR, which amplifies the signaling process, and results in increased survival and proliferation of the tumor cells.[6] In addition to promoting NFκB signaling, the *MYD88* mutation has been shown to trigger Janus kinase/Signal transducer and activator of transcription 3 (JAK/STAT3) signaling and promote the secretion of cytokines, including IL-6, IL-10, and interferon-β (IFN-β) in the BM microenvironment. The accumulation of these cytokines in the tumor microenvironment enhances the survival of malignant cells via an autocrine mechanism,[7,8] implying that the *MYD88* mutation not only dysregulates malignant cell growth, but also amplifies signals from the BM environment, thereby further promoting uncontrolled lymphoma cell growth and increased IgM production.

A number of recent studies have focused on understanding the role of the BM microenvironment in WM, and these studies are exploring the role of other nonmalignant cells, cytokines, and other growth factors in WM pathology. Studies have suggested a reciprocal interaction between WM cells and the elements of the BM and shown that this interaction provides a growth support for WM cells. In this review, the authors summarize data regarding the key elements in the BM microenvironment that support the growth of lymphoplasmacytic lymphoma cells and stimulate monoclonal IgM production.

COMPONENTS OF THE BONE MARROW NICHE

The physical environment surrounding the malignant cell is important, and the architecture of the BM milieu incorporates both cellular and noncellular components. A wide variety of cell types, including blood cells and their lineages, including fibroblasts, mesenchymal cells, osteoblasts, osteoclasts, adipocytes, and endothelial cells are present, as well as noncellular components, such as extracellular matrix, cytokines, chemokines, growth factors, and metabolites.[9,10] Various studies have shown that a complex, yet coordinated array of the interactions exists between the cellular and acellular entities of the BM microenvironment. These interactions are a key determinant of survival and self-renewal of the hematopoietic stem cells (HSCs) in the BM and also in the differentiation of various cell types under physiologic conditions.[9,10]

Previous research has shown that 2 distinct specialized microenvironments, described as an endosteal niche and a vascular niche, are present in the BM, and these niches are shown to provide support for HSCs. The endosteal niche is localized at the interface of the trabecular bone with the BM elements, where the HSCs are in close proximity to cells such as osteoblasts. These cells maintain the self-renewal capacity of the HSCs and regulate their function. Interaction of HSCs with osteoblasts is mediated either directly through cell-cell contact or indirectly via secretory factors that are produced by osteoblasts and bind to their cognate receptor on HSCs. The endosteal niche therefore plays an essential role in sustaining HSCs, thereby allowing them to maintain the self-renewal capacity of the BM. In contrast, the vascular niche supports HSCs that are located near sinusoidal blood vessel structures, and the vascular