

Role of Interleukin 16 in Multiple Myeloma Pathogenesis: A Potential Novel Therapeutic Target?

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Interleukin-16 (IL-16) is a cytokine produced by activated CD8-positive (CD8⁺) T cells, and its receptor is the CD4 molecule (1,2). It was originally named lymphocyte chemoattractant factor because it was one of the first characterized cytokines with chemoattractant activity for human T cells. In this issue of the Journal, Atanackovic et al. (3) have investigated IL-16 expression in multiple myeloma cell lines and in bone marrow from patients with multiple myeloma and have assessed its functional significance using *IL-16* gene silencing.

IL-16 induces phosphorylation of protein tyrosine kinase p56lck in CD4-positive (CD4⁺) T cells through the binding or cross-linking of CD4 molecules (4,5). IL-16 can thus induce CD4⁺ T-cell activation, which is indicated by the expression of human leukocyte antigen (HLA) class II molecules and/or the IL-2 receptor (CD25) (4–6). Although there is still no evidence that IL-16 can directly induce apoptotic cell death, CD4-mediated stimulation of T cells can promote apoptosis in the presence of certain other stimuli that act via the T-cell receptor, including viral and bacterial infections (7,8). Thus, IL-16 derived from activated CD8⁺ T cells may play an important role in the activation and subsequent death of CD4⁺ T cells in patients with multiple myeloma, who are known to have defective cellular and humoral immunity that worsens as their disease progresses.

The role of IL 16 in regulating T-cell function has been explored in other diseases. T-cell functional abnormalities similar to those in multiple myeloma have been observed in systemic lupus erythematosus, including a decreased CD4:CD8 ratio and increased HLA-DR expression by CD8⁺ T cells. In systemic lupus erythematosus, an increase in serum IL-16 levels has been correlated with disease activity (8), and IL-16 is thought to play an important role in the decrease in CD4⁺ T-cell numbers and function (9,10). Similarly, the quantitative and qualitative abnormalities of CD4⁺ T cells and immune dysfunction in patients with multiple myeloma, who are predisposed to more frequent infections, may, at least in part, be attributed to IL-16. IL-16 has been reported to be a diagnostic marker in Sézary syndrome (11), as well as a biomarker in patients with ovarian cancer (12), prostate cancer (13), nasopharyngeal cancer (14), colorectal cancer, and gastric cancer (15). Indeed, it has also been reported that serum levels of IL-16 correlate with disease activity in multiple myeloma (16), suggesting the potential prognostic utility of IL-16.

The effects of IL-16 can be direct on immune or other cells or indirect via modulation of cytokines. For example, in addition to its role in regulating recruitment and activation of CD4⁺ T cells to sites of inflammation (2,17), IL-16 stimulates production of proinflammatory cytokines by monocytes, including interleukin

6 (IL-6), tumor necrosis factor- α , interleukin 1 β , and interleukin 15, with related biological sequelae (17). In fact, IL-6 mRNA is detected as early as 4 hours after IL-16 stimulation of peripheral blood mononuclear cells, with IL-6 protein secretion detected by 24 hours (17). Moreover, IL-16 can synergize with other cytokines to expand CD34-positive cells (18). Importantly, IL-6 is a major growth, survival, and drug resistance factor in multiple myeloma. In multiple myeloma, IL-6 is produced either in an autocrine fashion by tumor cells or in a paracrine fashion by accessory cells in the bone marrow milieu, including bone marrow stromal cells and osteoclasts (19,20). It is therefore possible that IL-16 from osteoclasts or other bone marrow accessory cells can stimulate paracrine multiple myeloma cell growth.

Importantly, multiple myeloma models that include the bone marrow microenvironment have allowed the identification of targets and the validation of targeted therapies in the multiple myeloma cell and the identification of mediating interactions between multiple myeloma and accessory cells and within the bone marrow milieu. Indeed, agents that have been validated in these models to overcome multiple myeloma cell growth, survival, and conventional drug resistance conferred by the bone marrow milieu include the proteasome inhibitor bortezomib and the immunomodulatory drug lenalidomide; they have rapidly proceeded to clinical trials and US Food and Drug Administration approval and have transformed multiple myeloma therapy and markedly improved patient outcome (21,22). Efforts to target cytokines in the bone marrow milieu are ongoing in multiple myeloma therapy, including the use of anti-IL-6 and anti-B-cell activating factor antibodies. A validated role for IL-16 in mediating growth, survival, and drug resistance in the bone marrow could motivate analogous clinical trials.

In this issue of the Journal, Atanackovic et al. (3) have shown that all multiple myeloma cell lines evaluated strongly expressed pro-IL-16 and that IL-16 was secreted by multiple myeloma cell lines. Moreover, IL-16 mRNA levels were higher in bone marrow of patients with myeloma than in the bone marrow of healthy donors; among patients with multiple myeloma, IL-16 mRNA levels correlated with the extent of bone marrow plasmacytosis. Immunohistochemistry studies suggested that IL-16 was overexpressed in the tumor cell compartment; however, *IL-16* gene or protein expression in CD138-positive cells from patients with multiple myeloma was not examined. Small interfering RNA (siRNA) knockdown of IL-16 expression as well as a monoclonal antibody against IL-16 inhibited the growth of two multiple myeloma cell lines (EJM and KMS-12-BM); however, exogenous (recombinant) IL-16 had no effect on the proliferation of these

cells. In another multiple myeloma cell line (RPMI-8226), siRNA knockdown of IL-16 was associated with increased expression of Jun and Fos; however, the functional significance of the increased expression is unclear. In preliminary studies, Atanackovic et al. (3) showed that the proliferative response to IL-16 on the one hand, and the inhibition of multiple myeloma cell growth by an anti-IL16 antibody on the other hand, may be related to expression of IL-16 receptors CD4 or CD9 on the surface of the multiple myeloma cell line. However, there were no data examining this relationship at the gene, protein, or functional level in cells from patients with multiple myeloma. Finally, given the importance of the bone marrow microenvironment in target identification and validation of novel potential therapies described above, it would have been informative to see in vitro models or in vivo xenograft models examining the impact of the bone marrow on expression and secretion of IL-16 and its functional significance for multiple myeloma cells versus the response to anti-IL16 antibody. Such studies would allow an examination of the potential effects of targeting IL-16 on host accessory cells, including immune cells, as well as the ability of such therapies to overcome the growth, survival, and drug resistance phenotype conferred by the bone marrow milieu. The study by Atanackovic et al. has therefore established the framework for further exploration of the role of IL-16 in multiple myeloma pathogenesis and its potential for therapeutic application.

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Notes

The authors declare no conflict of interest.

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