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Recent advances in molecular pathogenesis of multiple myeloma – Role of cytokine: Review of literature

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Abstract
There is a growing body of evidence that a network of cytokines is involved in the growth, progression, and dissemination of multiple myeloma. Some are actually produced by the malignant plasma cells including interleulkin-1 beta (IL-1β) tumor necrosis factor-alpha (TNF-α), vascular endothelial growth factor (VEGF), and a functionally active truncated version of macrophage colony-stimulating factor (M-CSF). These and other cytokines act as mediators of tumor cell growth, survival, migration, and development of drug resistance.

Keywords: Myeloma, Cytokine, Growth factor.

1. Introduction

Multiple myeloma is a clonal plasma cell neoplasm characterized by the proliferation of plasma cells in the bone marrow, monoclonal protein, osteolytic bone lesions, renal disease, and immunodeficiency [1]. The sequential evolution of active myeloma from monoclonal gammopathy of undetermined significance (MGUS) is widely recognized. The sequence of events that lead to this progression has been extensively researched [2]. Delineation of the mechanisms mediating plasma cell proliferation, survival and migration in the bone marrow microenvironment may enhance the understanding of pathogenesis, and a better understanding of the molecular pathogenesis is fundamental to developing more effective prognostic, therapeutic and preventive approaches [3].

Role of Cyokine

Interleukin-6

Interleukin-6 (IL-6), formerly known as B-cell growth factor or hybridoma growth factor is among the most important proliferation and survival factors in multiple myeloma. It is a pleiotropic cytokine with a wide range of biological activities in T cells, B cells, hepatocytes, fibroblasts, hematopoietic cells, and neural cells functioning as a growth factor and anti-apoptotic factor. It is produced by several cell types, including monocytes, fibroblasts, T cells, B cells, endothelial cells, and various tumor cells. It has also been observed that myeloma cells and cell lines are capable of producing IL-6 and IL-6 receptors, resulting in autocrine stimulation [4].

IL-6 acts on the signal-transducing protein gp130, activating Ras/Raf/mitogen activated protein kinase (MAPK) kinase (MEK)/ extracellular signal-related kinase (ERK), Ianus kinase (IAK)/signal transducer and activator of transcription (STAT), and phosphatidylinositol-3 kinase (PI3-K)/Akt (PKB) downstream signaling path- ways in myeloma cells. The JAK-STAT pathway results in the up-regulation of antiapoptotic proteins, Mcl-1 and Bcl-X, whereas the Ras-MAP kinase pathway up-regulates the transcription factors such as ELK-1, AP-1 and NF-IL-6. Cell growth, survival and drug resistance of myeloma cells are mediated via the activation of both IAK2/STAT3 and PI3-K/Akt signaling cascades. In addition, the constitutive activation of STAT3 may also be important in the pathogenesis of multiple myeloma, independent of IL [3, 5, 6].

The *in vitro* responsiveness of myeloma cells to IL-6 has been shown to be directly related to their in vivo proliferative status and hence to the severity of the disease [7]. Further, a high soluble IL-6 receptor (sIL-6R) serum level has been shown to be associated with a poor response to chemotherapy, therefore suggesting the possibility of identifying in advance a subset of patients with a high risk of treatment failure. These observations warrant the evaluation of the effectiveness of anti-IL-6 antibodies in the management of multiple myeloma [8].

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) is a multifunctional cytokine that plays an important role in triggering tumor cell migration and angiogenesis. It also possesses a modest proliferative effect on myeloma cells. The production of EGF in the bone marrow environment is up-regulated by myeloma cell adhesion to bone marrow stem cells (BMSCs) and by IL-6. Moreover, VEGF reciprocally enhances the production of IL-6 from stromal cells suggesting the existence of a paracrine interaction between myeloma and marrow stromal cells triggered by visor and 1L-6 [9, 10].

Insulin-Like Growth Factor—1

Insulin—like growth factor-1 (IGF-1) activates two distinct signaling pathways in multiple myeloma cells, the MAP kinase and PI3-K pathways, leading to both proliferative and antiapoptotic effects. In comparison to IL-6, IGF-1 induces a more potent protection against dexamethasone. Insulin-like growth factor-1 also mediates the adhesion and migration of myeloma cells via β1 integrin. As a result, IGF-1 has been

identified as a novel therapeutic target and antibodies as well as small molecule inhibitors against IGF-1 have been identified as potential therapeutic approaches [11].

Interleukin-3

Interleukin-3 (IL-3) stimulates the growth of myeloma cells independent of IL-6 [12, 13]. Increased levels of IL-3 mRNA in myeloma cells and IL-3 protein levels in bone marrow from multiple myeloma patients also may be important in the pathogenesis of multiple myeloma bone disease, as IL-3 has been shown to stimulate osteoclast formation and inhibit osteoblast formation.

Interleukin-1 beta

Interleukin-1 beta (IL-1B) possesses a potent osteoclast genic activity; it enhances the expression of adhesion molecules and induces paracrine IL-6 production, causing osteolytic bone disease. Aberrant expression of IL-1B may be involved in the transformation of MGUS to multiple myeloma. Elevated lL-1B mRNA levels have been detected in multiple myeloma patients but anti-IL-1βantibodies failed to completely abolish the osteoclastogenic activity of myeloma [14].

Tumor Necrosis Factor-Alpha

Tumor necrosis factor-alpha (TNF-α) is important for function, differentiation, and transformation of B-lymphocytes. It induces secretion of IL-6 by bone marrow stem cells, and is also a strong inducer of NF-kB activation, up-regulating adhesion molecules, with resultant binding of myeloma cells to bone marrow and cell adhesion—mediated drug resistance. Although specific antibody inhibitors of TNF-α have not shown clinical response, thalidomide and its analogues have potent anti-TNF-α activity, and can overcome cell adhesion-mediated drug resistance [15].

Hepatocyte Growth Factor

The cytokine hepatocyte growth factor (HGF) and its receptor (c-met) are expressed on myeloma cells. Elevated serum levels of HGF have been found to be predictors of poor survival and lack of response to chemotherapy. It is involved in angiogenesis, epithelial cell proliferation, and osteoclast activation. HGF is an indirect factor involved in the pathogenesis of myeloma bone disease as it up-regulates the expression of IL-11 from human osteoclast-like cells, while TGF- β1 and IL-1 potentiate the effect of HGF on IL-11 secretion. HGF has also been found to reduce bone formation rates in myeloma patients by inhibiting bone morphogenetic protein (BMP) signalling [13, l6].

Other Cytokines

Stromal cell-derived factor-1alpha (SDF-1α), the ligand for chemokine receptor CXCR4, is present in supernatants from multiple myeloma patient BMSCs, whereas CXCR4 is expressed on myeloma cells. In addition to the activation of the signal transduction cascade, SDF-1ot also induces secretion of IL-6 and VEGF in BMSCs, thereby further promoting myeloma cell growth, survival, drug resistance and migration [17]. Transforming growth factor beta (TGF-β) secreted by myeloma cells triggers paracrine IL-6 secretion in BMSCs; conversely, TGF-β receptor inhibitors down-regulate IL-6 secretion in BMSCs and associated paracrine myeloma cell growth. The exact role of basic fibroblast growth factor (bFGF), a growth factor with proangiogenic properties is being investigated. Elevated bone marrow and peripheral serum bFGF levels have been reported in patients with multiple myeloma; however, the source of bFGF in patients with myeloma is not completely elucidated. The translocation involving FGF receptor 3 (FGFR3) is observed in approximately 15% of myeloma patients. This has formed the basis of the hypothesis that FGF signaling is involved in the pathogenesis of myeloma [3, 18, 19].

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