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Perspective

Interleukine-6 in the Bone Marrow Microenvironment: A Good Target to Stop the Progression of Multiple Myeloma. A Promising Perspective

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Multiple myeloma (MM) is a malignant lymphoproliferative disorder of unknown etiology. Risk factors - including ionizing radiation and chemicals - and genetic factors play a major role in the onset and development [1]. The clinical presentation at onset differs from completely asymptomatic with no evidence of organ damage to an acute life threatening condition. Despite the advancement of many therapeutic agents that have considerably improved the overall survival of patients, MM continues being an incurable disease. Regardless of stem cell transplantation and novel therapies, the vast majority of patients with MM will eventually relapse and become refractory to standard therapy. Besides the genetic heterogeneity, the interaction between myeloma cells and cancer microenvironment is partly responsible for the failure of treatments.

The progression of normal plasma cells into neoplastic cells is a complex genetic and molecular process [2,3] involving alterations in the bone marrow microenvironment [4,5] where myeloma cells - which express C-X-C chemokine receptor (CXCR)-4 - interact through adhesion molecules with stromal cells (BMSC), lymphocytes, osteoclasts, osteoblasts, and endothelial cells [5].

Activation of osteoclasts and osteoblasts dysfunction, angiogenesis, immunoresponse - or lack of it-, matrix metalloproteases (MMPs) activation, and inhibition or modulation of anti-tumour immune responses are some of the processes involved in the development and progression of MM. Amongst the factors involved in the MM pathogenesis, it is worth to mention cytokines such as interleukins - IL-6, IL-8 and IL-10;

pro-angiogenic factors such as vascular endothelial growth factor (VEGF), angiopoietin (Ang), fibroblast growth factor beta (FGF-β) and transforming growth factor beta (TGF-β); and grow factors such as granulocyte colony stimulating factor (GCSF). All of these mediators, and many more, are involved in the onset of MM. However, if there is a crucial intermediary that plays a significant role in both, the initiation and progression of MM, that responsibility should be assigned to one of the well-known factors produced in the bone marrow: IL-6, which promotes the growth and survival of the malignant plasma cells and mediates drug resistance [6].

Interleukine-6

The well-known pro-inflammatory cytokine with pleiotropic activity IL-6 has an important role in the pathophysiology of MM supporting the growth and survival of the malignant plasma cells in the bone marrow. The signalling pathway involving a kinase and a transcription factor IL-6/JAK2/STAT3 is essential to the progression and development of MM [7].

IL-6 - expressed by many cell types including macrophages, fibroblasts, and endothelial cells - is produced as a response to IL-1 and tumour necrosis factor alpha (TNF-α), and regulated by TGF-β [8]. It stimulates the secretion of acute phase immune response proteins, and has multiple effects on hematopoietic and other cells [9], acting as a growth factor for activated B-cells.

It has been shown that enhancing sensitivity of the myeloma cell to IL-6 contributes to the growth and expansion of the neoplastic cells [10]; however, the role of the soluble receptors for IL-6 (sIL-6R) is controversial, although elevated serum levels of IL-6 and its soluble receptor predict a poor prognosis [10-12].

IL-6 promotes myeloma cell proliferation and protects cells from apoptosis [13] through the regulation of signaling pathways involved in proliferation and apoptosis of MM cells including cyclin D2, cyclin-dependent kinase-4 (CDK4), Bcl-XL, and Caspase-3 [14].

Additionally, IL-6 - which enhances bone destruction-, is also produced by osteoclasts resulting in further increase of cell proliferation and inhibition of apoptosis [15]. T cells from the bone marrow produce IL-17, which further increases osteoclast formation [16].

Treatment of myeloma patients with antibodies against IL-6 has shown anti-tumour positive result [8,17]. However, the therapeutic effect usually stop after a prolong treatment, as it has been seen using the IL-6 inhibitor dexamethasone [18], specific IL-6 [19] or IL-6R blockade [20]. So far, the treatment of mice with IL-6 and IL-6R antibodies has resulted in a modest delay in tumour growth; targeting IL-6 in plasma cell diseases is currently evaluated in clinical trials with monoclonal antibodies.

In absence of IL-6, myeloma cells can adapt the expression profile of their receptor and switch to other gp130 cytokines rendering the IL-6R treatment inefficient. However, some researchers have suggested that gp130 could be a promising target for cancer therapy [21], supporting the idea that targeting the gp130 receptor would overcome the eventual lack of efficacy with IL-6R treatment [22].

A deeper understanding of the immunological basis of these agents, and the challenges faced by immunotherapy in clinical trials will be useful in selecting the most promising anti-IL-6/IL-6R therapies. Currently, research efforts are focused on personalize treatments for patients that can potentially benefit from IL-6 blocking therapies [23]. The use of anti-IL-6 antibody therapy at earlier stages of the disease might also be beneficial, and some clinical studies are undergoing in this direction. Obviously, more studies are needed and there is still a lot that we need to discover, but targeting adequately IL-6 and/or its receptors might be a promising treatment for MM.

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