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Review Article

The perspectives of interleukin-10 in the pathogenesis and therapeutics of multiple myeloma

*Cheng-Der Liu[a,†], Chun-Chun Chang[b,†], Wei-Han Huang[a,c,d]**

[a]Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan, [b]Department of Laboratory Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan, [c]Department of Clinical Pathology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan, [d]Department of Hematology and Oncology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan

†Both authors contributed equally to this work.

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Abstract

Multiple myeloma (MM) is typically featured by the increased levels of inflammatory cytokines in the neoplastic plasma cells (PCs) producing monoclonal immunoglobulin. PCs proliferate in the bone marrow, which will lead to extensive skeletal destruction with osteolytic lesions, osteopenia, or pathologic fractures. The diagnostic biology of MM has progressed from morphology and low-sensitivity protein analysis into multiomics-based high-throughput readout, whereas therapeutics has evolved from single active agent to potential active drug combinations underlying precision medicine. Many studies have focused on the cytokine networks that control growth, progression, and dissemination of the disease. The complexity of cytokines in MM development remains to be elucidated comprehensively. Apart from knowing that interleukin (IL)-6 is important in the pathogenesis of MM, it has been shown that IL-6 is a paracrine factor supplied by the microenvironment comprising of those cells from the myeloid compartment. Due to IL-10 was considered an immunosuppressive cytokine to promote cancer escape from immune surveillance, the role of IL-10 in this regard has been underestimated although recent advances have reported that IL-10 induces both PC proliferation and angiogenesis in MM. In addition, cumulative studies have suggested that IL-10 plays an important role in the induction of chemoresistance in many cancers; a virtual requirement of autocrine IL-10 for MM cells to escape from an IL-6-dependent proliferation loop was implicated. In this review, we summarize the available information to elucidate a new understanding of the molecular and functional roles of IL-10 in MM.

Keywords: *Interleukin-10, Interleukin-10 targeting, Multiple myeloma, Proliferation, Tumorigenesis*

Introduction

The involvements of cytokines in the pathogenesis and progression of neoplastic diseases have been widely reported. The use of cytokines as therapeutic targets becomes a rationale because the developed strategies can be well validated in both cell-based and animal models. The major challenge in adopting cytokine targeting methods for anti-cancer research arises from their profound influences on numerous processes in parallel. Moreover, alterations of the cytokine system are expected to modulate immune response. The current knowledge concerning the precise role of cytokine networks in cancer development and metastasis remains insufficient. Nevertheless, the comprehensive understanding of cytokine networks in cancer biology appears as a prerequisite to the development of cytokine-dependent therapeutic protocols for cancer diseases.

Multiple myeloma (MM) is a PC disorder that currently remains incurable; therefore, the search for new and effective therapeutic agents for MM treatments is urgently required. The aberrant immune dysfunction of MM ultimately leads to tumor growth and reduction of the patient survival rate. Modulation of immune responses by MM cells is expected to provide a means to debilitate early antitumor responses at the cytokine-mediated immunosuppressive tumor niche. Although both inflammatory and anti-inflammatory systems exhibit diverse influences on MM cell biology, both autocrine and paracrine effects of determinant cytokines play a role in MM cell proliferation [1]. In MM cells, a pronounced chemoattractant activity was noted with the enhanced levels of CXCL12, CCL5, MIP-1β, and CXCL10, while their associations with

**Address for correspondence:*
Dr. Wei-Han Huang,
Department of Clinical Pathology, Hualien Tzu Chi Hospital,
Buddhist Tzu Chi Medical Foundation, 707, Section 3,
Chung-Yang Road, Hualien, Taiwan.
E-mail: weihanhuan@gmail.com

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the expression of immunoregulatory interleukins (ILs) such as IL-4 and IL-10 were also documented [2].

Given the support from the spectrum of inflammation to MM is inadequate; those cytokine-mediated immune or cellular modulatory functions, such as pro-proliferative or antiproliferative effects, can elicit the distinct cytokine effects in the genesis and progression of MM. IL-10 and IL-6 were considered two of the most dominant cytokines and both can regulate the proliferation and cellular characteristics of myeloma cells. Apart from IL-10 has been implicated as a proliferation factor for MM cells, its augmented serum concentrations are correlated with the advanced MM stages, angiogenic cytokines, and proliferation markers [3-5]. Although the mechanistic insights of IL-10 in MM pathogenesis remain unclear, cumulative evidences suggest that IL-10 could be considered a therapeutic target when seeking to develop an anticancer protocol for MM therapy [6]. This review mainly focuses on exploring the potential roles of IL-10 in MM cancer biology and IL-10 targeting methods as an anti-cancer therapeutic approach against MM.

Molecular pathology of multiple myeloma disease

Since its first discovery in 1848, MM appears as an incurable malignancy underlying a spectrum of diseases with identified phenotypes ranging from monoclonal gammopathy of unknown significance (MGUS) to PC leukemia [7,8]. MM was defined as a clonal B cell neoplasia which is amplified from the growth of malignant PCs in the context of the bone marrow environment [9]. MM diseases account for 1% of cancers and approximately 10% of all hematologic malignancies, representing the second most common hematological malignancy that causes over 100,000 deaths annually per year worldwide [10].

MM initiation and progression rigorously depends on genetic and epigenetic aberrations occurring at the time of onset and are acquired during the developmental course of the disease [7,8]. In addition, the tumor growth and survival are dependent on the support from the BM microenvironment [11]. The following two key players are central to the pathogenesis of MM: (1) the native genetic lesions in the neoplastic clone, and (2) the mutual interactions between myelomatous PCs and the BM microenvironment. Hyperdiploid and nonhyperdiploid MM represent two major groups of the disease. The former is characterized by the trisomies which are typically seen in the odd-numbered chromosomes, whereas the latter possesses genomic translocations within the immunoglobulin heavy chain loci. The occurrence of secondary translocations and mutations during disease progression was noted for MYC gene [12]. Gain-of-function mutations in oncogenes such as BRAF and CCND1, KRAS, and NRAS versus loss of function of tumor suppressors, including CDKN2A and CDKN2C, DIS3, P53, RB1, and mutations in the nuclear factor-κB pathway genes were also characterized in MM diseases [13,14]. In addition to the well-defined genetic aberrations, epigenetic changes caused by aberrant DNA methylation, histone modification patterns, and deregulated miRNA profiles have been considered the hallmarks of MM pathogenesis [15-17].

The prognostic factors in multiple myeloma

Understanding the prognostic markers of MM has been progressed significantly over the last 10 years. The prognosis of patients with MM as well as other cancers mainly depends on the following four key factors: tumor burden, patient factors, disease biology, and availability and response to therapy [18]. The data from prognostic studies in myeloma patients mostly come from evaluations at the time of diagnosis. However, it is unclear how the prognostic value of these factors might change with the new emerged therapies. It was reported that high levels in serum calcium, lactate dehydrogenase, and percentage of abnormal PCs in bone marrow were tightly correlated with poor prognosis in MM disease [19]. Risk stratification of MM is central to the understanding of the prognosis and to the concerns on the modifications of therapeutic modalities. The prognostic markers of MM in risk stratification are varied according to the selected experimental models in myeloma studies; hence, the development of risk-adaptive therapeutic strategies becomes to be the central dogma under the above regard. The current standard prognostic markers in MM are highlighted because of their implications in current clinical practice [20].

A recent study demonstrated that cytokines and angiogenic factors (CAFs), such as fibroblast growth factor-2, hepatocyte growth factor (HGF), vascular endothelial growth factor, and platelet-derived growth factor-β, at the plasma levels, can be used to predict patients' significant response to treatments [21]. Of importance, the levels of CAFs at diagnosis and their alterations after therapy can be used to classify different risk groups underlying the outcome and response to MM therapy. The associations between MM and IL-6 concentrations have implications for poor prognosis of this disease [22]. Similarly, the serum levels of IL-10 were also concerned as biomarkers to evaluate its impact on the treatment responses and outcome in MM [5]. Therefore, the identification of specific risk factors of MM remains a critical issue. Application of the stratification of patients based on the distinct biomarkers to predict the treatment response and prognosis is of great help in choosing the best course treatment for MM in future.

Current understanding of interleukin-10 in multiple myeloma pathology

Tumor growth is typically associated with a spectrum of inflammation alone with an increase in pro-inflammatory cytokine levels, known to support the progression of neoplasia [2,23]. Several mediators are elicited by the bone marrow environment and myeloma cells through paracrine or autocrine loops [9]. The BM microenvironment derived from MM patients exhibits high degrees of EGF, HGF, IL-2R, IL-16, and those interferon-γ (IFN-γ)-induced cytokines [24,25]. Many of these cytokines have been suggested to be the promoting factors in MM development, thereafter triggering cell growth or cellular adhesion for MM cells [2]. The lineage subsets of

PCs or T lymphocyte can secrete cytokines to create a niche in the BM environment and subsequently foster malignant cell development [26]. Because IL-6 has been shown as one of the growth factors for myeloma cells, several studies have demonstrated a crosslink between serum IL-6 and disease stage [27]. IL-6 induces the proliferation of myeloma cells via a paracrine pathway, which is secreted from those surrounding stromal cells and/or from the myeloma cells themselves [28]. The characterizations of IL-10 and its receptor, as well as receptors for gp130-related cytokines in promoting myeloma cell growth, were shown in experimental investigations [29]. Our recent studies characterized a critical importance of IL-10/STAT3 pathway in cell proliferation of B neoplastic lineages [30].

Several proliferation factors for myeloma cells such as insulin-like growth factors, IL-15, and IL-10 have been reported [31]. IL-10 is known as the most powerful anti-inflammatory cytokine, which is secreted by monocytes/macrophages, NK cells, T and B lymphocytes, and mast cells [32]. By acting as an immunosuppressive cytokine, IL-10 suppresses immune responses by modulating both innate and adaptive immune systems. Although the mechanistic insight remains to be investigated, cancer cells should be able to exploit the immune suppressive activity of IL-10 to escape from immune surveillance. The role of IL-10 may be especially critical for myeloma cells to escape from an IL-6-dependent proliferation loop through malignant progression [Figure 1]. IL-10 was shown to increase the proliferation of MM cell lines and neoplastic cells isolated from MM patients. Autocrine IL-10 is expected to promote the cell growth of MM cells through unknown mechanisms. Gu *et al*. demonstrated that IL-10 promoted the activation of MM cells by inducing an oncostatin M autocrine loop [33]. Altered concentrations of IL-10 produced by Treg or MM cells could modulate the host immune response, thus resulting in a reduction of dendritic cells (DC) function by promoting constitutive activation of STAT3 [32]. In addition, IL-10 could suppress the all-trans retinoic acid-mediated proliferation inhibition of MM cells [34,35]. Both IL-10 and IL-10R single-nucleotide polymorphisms have been implicated in the pathogenesis of many tumors, including hematologic disorder MM [36,37]. Taken together, advances in IL-10 research appear to be a critical determinant that can lead to understanding the insightful molecular picture of MM cancer biology. Characterizations on the expression and production of IL-10 in MM patients will be important for subcategorization and the establishment of a case-oriented therapy for these patients. Moreover, deciphering the associations between IL-10 expressing patterns and MM pathology would prove significant information in characterizing genesis and the progression of myeloma.

The potential link between interleukin-10 and the PD1/PD-L1 axis

The protein expression of PD-L1 on the surface of cancer cells, including MM patients, provides a rationale to adopt new strategies for MM therapy using PD-L1/PD1 targeting methods. Drugs with the potency to modulate the transcriptional and post-transcriptional regulation of PD-L1 could be considered alternative therapeutic strategies for the treatment of MM [Figure 2] [38]. Action of the above drugs to be combined with PD-1/PD-L1 inhibitors would be able to avoid the potentially problematic combinations of immunomodulators. Therapeutic approaches based on targeting the PD-1/PD-L1 axis in MM cells have been applied in preclinical models and several clinical trials [39]. Nivolumab and pembrolizumab are two primary PD-1 inhibitors being employed in MM therapeutics [40]. Several studies have reported that PD-L1 is prevalently expressed in PCs from patients with MM but not from healthy donors, and the expression levels are higher in patients with MM than MGUS [41]. There is, therefore, a need for alternative combinations of drugs or different approaches to target this pathway.

Those cytokines found in an immune-reactive tumor microenvironment (TME) may induce PD-L1 expression on tumor and/or immune cells through distinct signaling mechanisms although they are currently unclear. The existence of PD-L1 in the TME may offer another rationale to develop strategies

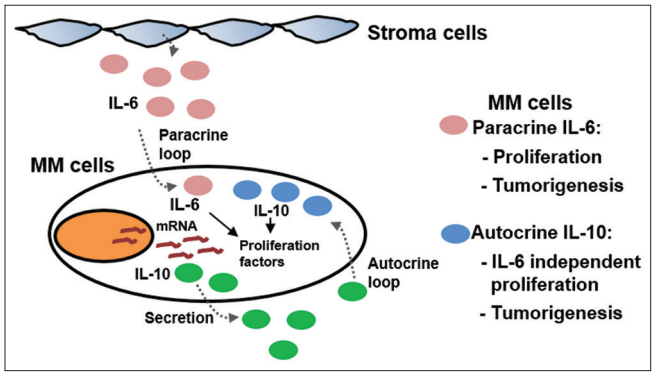

Figure 1: Autocrine interleukin-10-dependent cell proliferation in myeloma cells. Interleukin-10 is produced in multiple myeloma cells and secreted to the extracellular environment. Interleukin-10 enters into multiple myeloma cells via the autocrine loop in order to trigger cell proliferation-associated pathway. The downstream signaling activates proliferation factor to support multiple myeloma cell growth. The interleukin-10 effects allow multiple myeloma cells to escape interleukin-6-dependent cell proliferation although interleukin-6 by itself can promote multiple myeloma cell growth

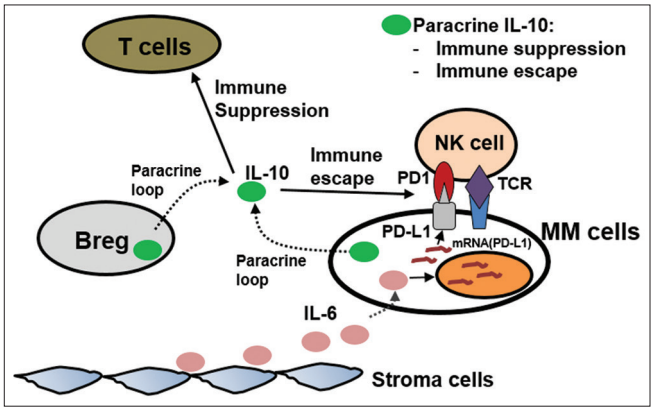

Figure 2: Interleukin-10 has a role in promoting immune evasion of multiple myeloma cells from T cell-mediated immune surveillance. Stroma cells release interleukin-6 to induce PD-L1 expression, thus creating a niche to resist the action of killer cells. Interleukin-10 derived from multiple myeloma cells or regulatory B cells can enhance the maintenance of PD-L1/PD1 axis to sustain the immune evasion effect

aiming to mitigate the expression of this immunosuppressive ligand, thus enhancing the efficacy of PD-1 blockade. A positive correlation between IL-6 and PD-L1 expression has been reported in many tumor tissues. Production of IL-6 by stromal cells can lead to induction of PD-L1 in MM cells, while it can be reversely downregulated by blocking JAK/STAT3 pathway [31]. The combination of anti-IL-6 and anti-Tim-3 was recently suggested to be an effective marker-guided therapeutic strategy [42]. Preclinical results also indicated that targeted inhibition through IL-6 blockade may enhance the anti-PD-L1 effect in pancreatic ductal adenocarcinoma [43]. Recent findings demonstrated the compensatory release of IL-10 as a potential resistant mechanism to undermine the efficacy of anti-PD1/anti-PD-L1-mediated monotherapies, suggesting that IL-10 is linked to PD1/PD-L1 signaling pathway [44]. In a human lung adenocarcinoma subject, IL-10 was shown to counteract IFN-γ effects on PD1/PD-L1 pathway, leading to the resistance of the tumor to anti-PD1/PDL1 immunotherapy [45]. Recent advances in diffuse large B-cell lymphoma (DLBCL) reveal an IL-10/JAK2/STAT3-dependent PD-L1 expression route [46]. In particular, IL-10 receptor antibody-mediated neutralization methods were shown to be effective in blocking DLBCL cell survival [47]. Altogether from the above knowledge, we propose a model to delineate how IL-10 mediates resistance to PD1/PD-L1 targeting immunotherapy in MM patients [Figure 2]. Release of IL-6 from the surrounded cell can augment PD-L1 expression on MM cells, thus establishing the PD-L1/PD1 axis. Although the mechanism remains unclear that whether IL-10 can enhance the maintenance of PD-L1/PD1 axis, in particular, IL-10 expression will be further activated soon as the immune evasion is undermined by antibody-mediated neutralization. To the above regard, IL-10 blockade emerges as an optimal choice in combinations with the PD-L1/PD1 targeting immune therapies.

Conclusion

The diagnosis and treatments of MM have changed dramatically in the past decade. An increasing number of studies have focused on growth factor-related issues in MM diseases, and the deeper understanding of the cytokine networks appears to be a major determinant for this purpose. It remains unclear from the point of clinics by which how those IL-10 levels in MM subjects are related to clinical manifestations of this disease. The discovery of PD-1/PD-L1-mediated immune escape in MM has led to the use of PD-1/PD-L1 blockade to be a great potential anti-MM strategy. The above rationale is further credited by the studies highlighting that PD-L1 is highly expressed on PCs isolated from patients with MM but with relative low on normal PCs [48].

A growing number of studies reveal that targeting multiple components of disease-associated pathways at once, termed combination therapies, might produce a stronger effect for a disease than individual treatments. The arisen questions to what degree they may be used in combination therapy could be solved by employing systems biology or hypothesis-driven studies to identify the most promising candidates for clinical trials. Furthermore, the new mechanistic insights into drug synergies can be extensively investigated. Several therapeutic strategies have been considered the candidates to be included in combination therapy regimens for MM, such as monoclonal antibodies, immunomodulatory agents, immunotoxins, bi-specific T-cell engagers, and chimeric antigen receptor T-cell therapies, although the treatment paradigm should be systematically refined [49]. An enhanced understanding of MM disease mechanisms is an urgent need for developing more effective targeted treatments. The implementation of novel and rationally designed therapies is the prerequisite in developing MM treatments that ensures better response rates and improved survival.

The biological properties of IL-10 have been characterized not only in promoting both PC proliferation and angiogenesis but also in relevance to PD-L1/PD1 axis, which certainly imply a significant role in the pathogenesis and development of MM. Apparently, the current understanding of the pathogenic role of lL-10 in MM is underestimated. The characteristic of IL-10 to induce chemoresistance in cancers is likely linked to its immune suppression function [50]. Those IL-10 blocking methods mainly come from the developed antagonist targeting IL-10, IL-10 receptors, and pathway factors, such as JAK and STAT3. We propose that the role of IL-10 may be especially critical in myeloma cells that display an IL-6-independent proliferation loop. The controversial effects of IL-10 in the cancer microenvironment could be due to the context complicity. Monotherapy with PD-1 inhibitors did not produce promising results, while combinations with other drugs used in the treatment of MM appeared to be effective [40]. According to the recent concerns about the safety issues regarding the use of PD-1/PD-L1 inhibitors combined with immunomodulators in the treatment of MM, several trials have been terminated [51]. The advances in our understanding of the cross-talk between IL-10 and PD1/PD-L1 in the TME provide clues for targeted interventional therapy that may prove more effective against cancer treatment in MM patients. Although the precise role of IL-10 in cancer development remains to be comprehensively investigated, it cannot deny the promising potential of choosing IL-10 targeting methods in combinations with immune therapy in MM treatment paradigm.

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Conflicts of interest

There are no conflicts of interest.

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