EUROPEAN HEMATOLOGY ASSOCIATION

Multiple myeloma - Section 1

Immunopathology of multiple myeloma

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Take-home messages

- Multiple myeloma origin is related to antigen-driven processes.
- Multiple myeloma cells have bidirectional and major interactions with the bone marrow microenvironment enhancing growth, survival and drug resistance. These interactions lead to various alterations of the immune system.
- Targeting the immune system in multiple myeloma provides new very effective therapeutic strategies.

Abstract

Multiple myeloma (MM) is defined by the malignant proliferation of plasma cells, a major component of the immune system. MM is a heterogeneous disease featured by a multistep progression from monoclonal gammopathy of undetermined significance (MGUS) to symptomatic disease, with distinct molecular subgroups and clinical outcomes. The immune system related characteristics of the plasma cells determine specific features involved in myelomagenesis and progression. The mechanisms contributing to the plasma cell differentiation and the multiple interactions of the plasma cells with other immune cells are crucial in both myeloma cell growth and survival as well as development of drug resistance. In this review, we discuss the immunopathology of MM, from the early driving events to myeloma progression and its therapeutic implications.

Introduction

Multiple myeloma (MM) is a plasma cell malignancy with genomic and clinical heterogeneity.[1,2] The disease process is modulated by bidirectional interaction between MM cells and accessory cells in the bone marrow (BM) microenvironment which not only affect growth and survival of MM cells, but also development of drug resistance. As MM cells are of immune origin and in the vast majority of cases secrete clonal immunoglobulin and/or light chains,[3] its interaction with components of the BM immune microenvironment[4,5] leads to various alterations of the immune system. Some of the changes inhibit anti-MM immune responses as well as promote MM growth and survival. With the advent of new immunotherapy including monoclonal antibodies targeting the myeloma cells or the immune check-point inhibitors, or engineered T cells including chimeric antigen receptor (CAR) T cells, targeting the immune system is becoming a new treatment paradigm. Moreover, the effect of immunonomodulatory agents (Imids) on the immune system, especially increase in T and NK cells cytotoxicity including the antibody-dependent cell-mediated cytotoxicity, has greatly contributed to develop this therapeutic field.[6-8] Thus, the combination of Imids with monoclonal antibodies (anti-CD38 or anti-SLAMF7[9,10] or check-point inhibitors -anti PD-1) has already provided promising results. Monoclonal antibodies targeting MM cells are effective and will probably constitute next gold standard therapy.[11] Here, we review the main features of the immunopathology of MM and highlight its therapeutic implications. Therefore, understanding and improving immune function has application for both extending anti-MM responses as well as decrease susceptibility to infections observed in MM.

Origin of the MM cell – An antigen-driven process and myelomagenesis

MM is defined by presence of IgH translocations which are recurrent and considered to be generated during somatic hypermutations, VDJ recombination and class switch recombination.[12] Moreover, these distinct breakpoints suggest that the initial driver events occur at different stages of the B cell development and are related to AID/APOBEC activity as suggested by whole exome sequencing.[13,14] Several observations and studies have highlighted the role of an antigen-driven immune stimulation to trigger the development of MM. More recent reports of an anti-lysolipids activity in Gaucher disease, a lysosomal disease known to be associated with monoclonal gammopathies[15] and a similar anti-lysolipid activity in a subset of patients with monoclonal gammopathies without Gaucher

disease[15] suggest that the eradication of the causal and persistent antigen and/or the inhibition of the B cell receptor signaling could be an effective strategy in early stage MM. However, an antigen-driven mechanism hasn't been established for all types of myeloma and targeting B-cell signaling could be an effective strategy in only some myeloma subgroups.

Myeloma cells and the immune system

Dendritic cells (DC)

DCs play an important role in antigen presentation and interactions with other immune cells. In MM, 2 major subtypes of DCs, monocyte-derived (mDC) and plasmacytoid (pDCs),[16] have been shown to accumulate in the bone marrow (BM). Increased dysfunctional, mainly immature pDCs, expressing PD-L1, contribute to MM cells growth, survival, chemotaxis, and drug resistance as well as suppressed T cell responses. Targeting pDC using oligonucleotides or a TLR9 agonist is effective in impacting MM cells survival and restoring immune functions.[17,18]

T cells and T regulators

In MM, dysregulation of various T cell subsets have been observed. The circulating CD4/CD8 ratio, the Th1/Th2 ratio are decreased. More importantly, T regulator cell dysfunction and suppressed T cell responses have been reported in all stages of MM. This is driven by effect of cytokines, the interacting immune microenvironment in the BM and an abnormal antigen presentation by dendritic cells and other antigen presentation cells.[19-21] γδ T cells have been shown to have a cytotoxic activity against myeloma cells enhanced by MHC class I polypeptide-related sequence (MICA) expression on plasma cell surface and the use of bipohosphonates but its role remains uncertain.[22,23]

B cell

Several studies have shown that the total number of B cells is decreased in MM. In particular, the naïve and transitional B cells subsets are decreased in contrast with memory B cells that are increased in MM patients as compared with MGUS and healthy donors.[24,25] The modifications of the B cells subsets are important to understand the humoral immune deficiency that characterize MM patients and generate an impor-

Table 1. Main immunological abnormalities and therapeutic options in multiple myeloma.

Cellular Component	Observed Abnormalities in MM	Consequences	Therapeutic implication / potential therapeutic options
B Cells	Low level of naïve and transitional B cells	Humoral immunity deficiency and predisposition to infections	Early vaccination Antibiotic prophylaxis
T cells	Low levels of T cells Dysfunctional T cells	Reduced anti-myeloma cytotoxic activity	Imids Check-point inhibitors Activation of γδ T cells with bisphosphonates
T regulatory cells	Dysfunctional T reg	Contribute to immune evasion	Imids
T helper 17 cells	High level of TH17 and IL-17	Promotes MM cells survival and growth, T cell dysfunction and bone disease	Anti-IL17 antibody
Macrophages	High level of TAM featured by M2 phenotype	Enhance MM survival and chemoresistance	Reprogramming macrophages
Myeloid Derived uppressor cells	MDSC	Inhibit T and NK cells anti-myeloma responses	Check-point inhibitors
Natural Killer T cells	Dysfunctional NKT cells	Reduced anti-myeloma activity	Imids Check-point inhibitors
Natural Killer cells	Dysfunctional NK cells	Reduced anti-myeloma activity	Imids Check-point inhibitors
Dendritic cells	Increased number of dendritic cells (mDC and pDC)	Increase with the stage of the disease Enhance proliferation and growth of MM cells Contribute to immune evasion	Direct targeting using anti-IL3R immunoconjugate, TLR9 activator
Immune checkpoint	High PD1 expression on T and NK cells	Contribute to immune evasion	Check-point inhibitors
Immune checkpoint	High PDL1 expression on MM cells, pDCs, mDCs, MDSC	Contribute to immune evasion	Check-point inhibitors

TAM: tumor-associated macrophages, MDSC: Myeloid Derived suppressor cells, mDC: monocyte derived dendritic cells, pDC: plasmacytoid dendritic cells, PD1: Program-death 1, PDL1: Program-death ligand 1.

tant cause of death and morbidity.[26] No clear mechanisms have been demonstrated so far.

Myeloid Derived suppressor cells (MDSC)

MDSCs correspond to a heterogeneous group of myeloid cells able to suppress T cells, natural killer T (NKT), and natural killer (NK) cell antitumoral activity. MDSCs are significantly increased in the blood and in the bone marrow of MM patients, enhance MM cells proliferation and suppress T-cell–mediated immune responses. Reciprocally, MM cells induce MDSCs growth.[27,28] Imids and bortezomib, 2 of the most active MM drugs modify MDSCs phenotype suggesting that targeting MDSCs may represent a novel therapeutic strategy.[29]

T Helper 17

TH17 cells are a subset of T helper cells that contribute to inflammatory and auto-immune response regulation. In the context of high interleukin (IL)-6 and TGF beta, TH17 cells are increased in MM blood and bone marrow and secrete high levels of IL-17 in the blood which promotes myeloma cell growth and proliferation through IL-17 receptor that is expressed in MM cells.[30,31] IL-17 also induces suppression of Th1 responses and induces bone disease by activation of osteoclast function. Targeting IL17 with a specific antibody inhibit MM cells proliferation and osteoclast differentiation.[32]

NK and NKT cells

NK cells play an important role in immune surveillance and depletion of NK cells in mouse models highlighted their importance for myeloma progression.[33] NK cells play an important role in mediating antibody dependent cell cytotoxicity (ADCC). These activities are exploited by myeloma therapeutics including Imids as well as the recently approved antibodies daratumumab and elotuzumab. NKT cells are immune cells that recognize foreign and self (glyco)sphingolipid antigens when presented by the CD1d molecule. In addition to a direct cytotoxicity, NKT cells produce various type of cytokines that regulate and modulate other immune cell activities. The evaluation of NKT cells in MM has pointed out a marked deficiency of ligand-dependent interferon-production mainly in the context of disease progression, with variable CD1d level of expression and glycolipid presentation by the MM cells. The use of dendritic cells with α-galactosylceramide (a NKT ligand) is able to reverse this deficiency.[34] Several studies have shown that Imids increase NKT population and enhance its activity suggesting that therapy targeting NKT cells is effective in MM.[35,36]

Immune check-points

The anti-myeloma activity of immune cells is impacted by its ability to identify the MM cells as a target and by the co-stimulatory signaling. The programmed-death 1 (PD1)/programmed-death ligand 1 (PDL1) axis has been particularly evaluated in MM. High expression of PDL1 in MM cells and the BM microenvironment cells such as pDCs and MDSCs has been shown to decrease T and NK cytotoxicity. Although single agent therapy targeting PD-1 in relapsed/refractory MM has not shown significant activity,[37] the combination of checkpoint inhibitors with Imids has shown remarkable activity and is being evaluated in phase III studies. In addition to targeting PDL-1, other co-stimulatory axes are currently under investigation (CD137, LAG3, CTLA4 or TIM for example).[38-40]

Future perspectives

The improved understanding of immunopathology of myeloma has provided number of avenues for possible preventive as well as effective therapeutic strategies. The understanding of possible role of an antigen-driven immune stimulation via lysolipids activity may allow directed approaches in the early stages of the disease. While characterization of T and B cell function and the role of other immune microenvironmental cells has allowed for development of strategies using combination of Imids with antibodies targeting MM cells and/or immune checkpoint inhibitors. In addition, recent progress in adoptive transfer of cellular components, especially of activated lymphocytes[41] or as chimerical antigen receptor T (CAR-T) cells targeting either directly myeloma (BCMA)[42,43] or other B cells compartment,[44] have provided remarkable excitement for possible future curative strategies. Vaccine therapy using patients' dendritic cells are also undergoing clinical evaluation at early stage of the disease or as a consolidation therapy.[45]
In conclusion, multiple and complex immunological mechanisms contribute to myeloma genesis and myeloma progression. Their understanding provides a rationale to develop and evaluate new effective strategies in MM.

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