Understanding Multiple Myeloma and Immuno-Oncology Approaches

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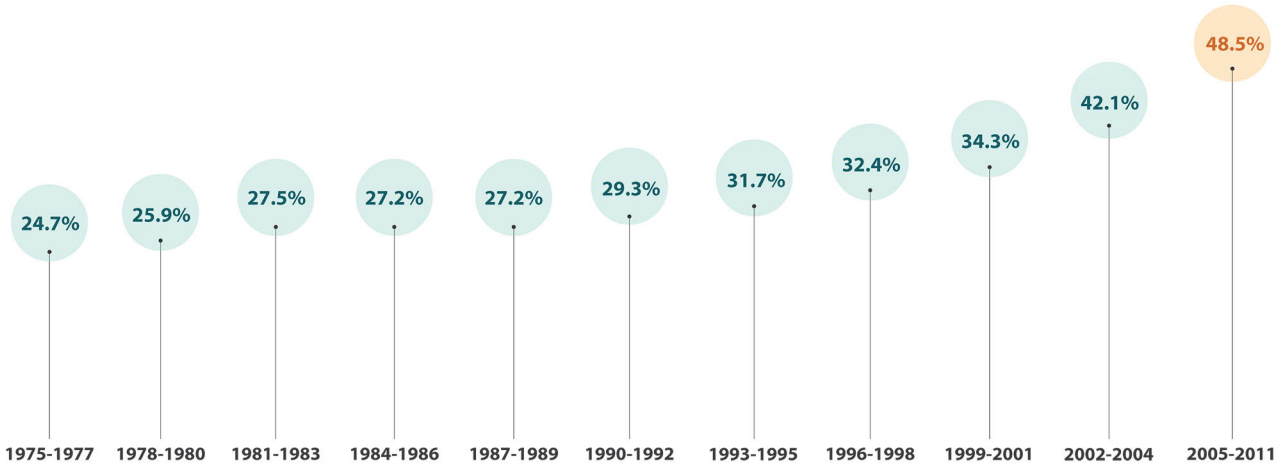
Introduction to Immuno-Oncology (I-O) in multiple myeloma

Multiple myeloma epidemiology

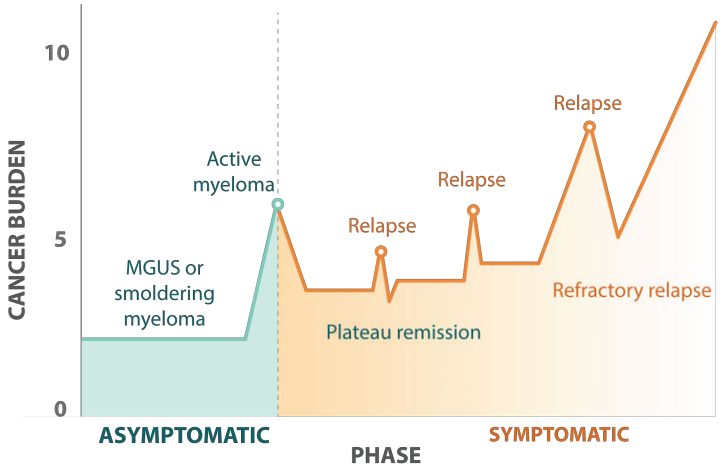
It is estimated that in the United States, over 26,000 patients will be diagnosed with multiple myeloma and over 11,000 patients will have died of the disease in 2015.[1] Although the 5-year survival of patients with multiple myeloma has improved from 25% to 47% since 1975[1,2] due in large part to new and improved treatment modalities, for over half of patients, multiple myeloma remains a largely incurable disease.[2] Therefore, a large unmet need exists for additional medical advances in multiple myeloma.



Five-year survival rate in multiple myeloma has increased from twenty-five to forty-five percent from 1975 to 2009[2]

Disease course of multiple myeloma

The disease course of multiple myeloma for some patients, is characterized by a pattern of remission and relapse, with a decreasing duration of response and an increasing use of salvage regimens. This is a reflection of the emergence of drug resistance, which makes multiple myeloma a complex disease to treat.[3]



Disease course of multiple myeloma for some patients is characterized by a pattern of remission and relapse

Treatment modalities in multiple myeloma

The options traditionally available for the treatment of multiple myeloma are radiation, chemotherapy, and targeted therapy, which are all intended to target the tumor, as well as stem cell transplantation.

Immunotherapies are agents that work with the immune system and can be divided into **passive and active immunotherapies**.[4] Passive immunotherapies act on the tumor and indirectly engage immune cells to elicit an antitumor immune response.[4,5] Active immunotherapies act directly on immune effector cells to elicit an antitumor immune response.[4-6]

Passive immunotherapies in some cases use immune-based mechanisms to fight cancer, but they do not require the patient's own immune system to initiate a response.[4-6] Some of these types of therapies include tumor-directed monoclonal antibodies and cell therapies.[5-9] Active immunotherapies act directly on the body's own immune system to elicit an immune response to fight cancer,[4,6] and can include therapeutic cancer vaccines[5,6,10] and cytokines.[11]

Immuno-oncology (I-O) is an evolving treatment modality designed to harness the capability of the patient's own immune system to fight cancer.[12]

I-O is based on the premise that the immune system is the body's natural tool for recognizing and fighting disease. Unlike traditional approaches that target the tumor, I-O focuses on empowering the intrinsic capabilities of the immune system.

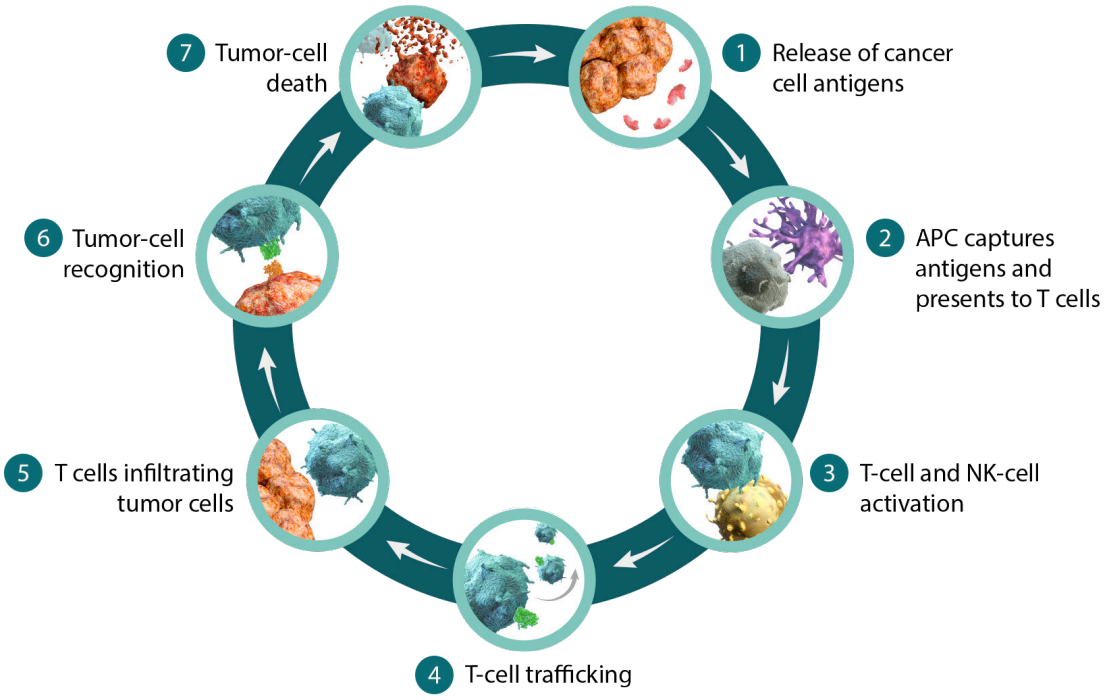
Role of the immune system in multiple myeloma

The immune system has natural anti-tumor activity

The immune system is comprised of both the innate and adaptive immune systems. The innate immune system is an antigen-independent process that acts as the first line of defense against infection and is characterized by a rapid response with limited specificity and memory. Cells of the innate immune system include macrophages, natural killer (NK) cells, mast cells, dendritic cells, eosinophils, neutrophils, and basophils. The adaptive immune system is a slower antigen-dependent and antigen-specific process. Cells of the adaptive immune system include T cells and B cells which have capacity for memory, enabling a more rapid and efficient response upon subsequent exposure to an antigen.[13,14]

The immune system has the ability to identify and eliminate cancer cells, including myeloma cells. Tumor cells are eliminated by the immune system via a self-propagating cyclical process known as the cancer-immunity cycle.[15,16] This cycle can be divided into 7 major steps that starts with antigen release by cancer cells and ends with cancer cell death.

The cycle is characterized by the accumulation of immune-stimulatory factors that promote immune cell responses. However, it is also characterized by the expression of inhibitory factors that prevent or limit the immune response through feedback mechanisms. Negative feedback mechanisms are in place to keep the cycle in check and prevent overstimulation of the immune response. Without this mechanism, autoimmunity can become a problem if the immune system starts to attack normal cells.[17]



The cancer-immunity cycle

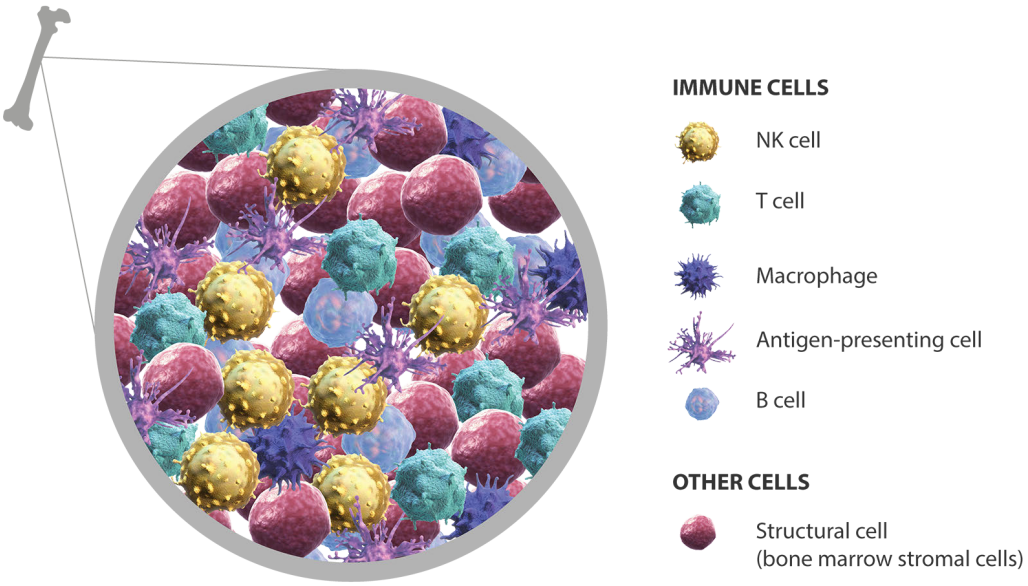
Natural killer cells are important in multiple myeloma

As part of the innate immunity, natural killer cells are among the body's first line of defense against myeloma cells.[18,19] They use various activating, inhibitory, adhesion, and cytokine receptors in order to detect myeloma cells while sparing normal cells.[20-22] Once the myeloma cell is recognized, NK cells may then become activated to exert cytotoxicity through the targeted release of cytotoxic granules, among other mechanisms.[23-25]

Multiple myeloma and the bone marrow microenvironment

Myeloma cells must be considered in their microenvironment. The local milieu for myeloma cells comprises bone marrow stromal cells, extracellular matrix proteins, and extracellular fluid containing cytokines and growth factors.[3]

Natural killer cells integrate activation and inhibition signals to recognize and eliminate myeloma cells.[21,24,26] But, as multiple myeloma progresses, NK-cell, T-cell, and antigen-presenting cell function becomes altered, leading to an immunosuppressive bone marrow microenvironment.[21,27-31] Proliferation and function of immune cells are impaired, which may lead to impaired cancer cell recognition, and lower survival.



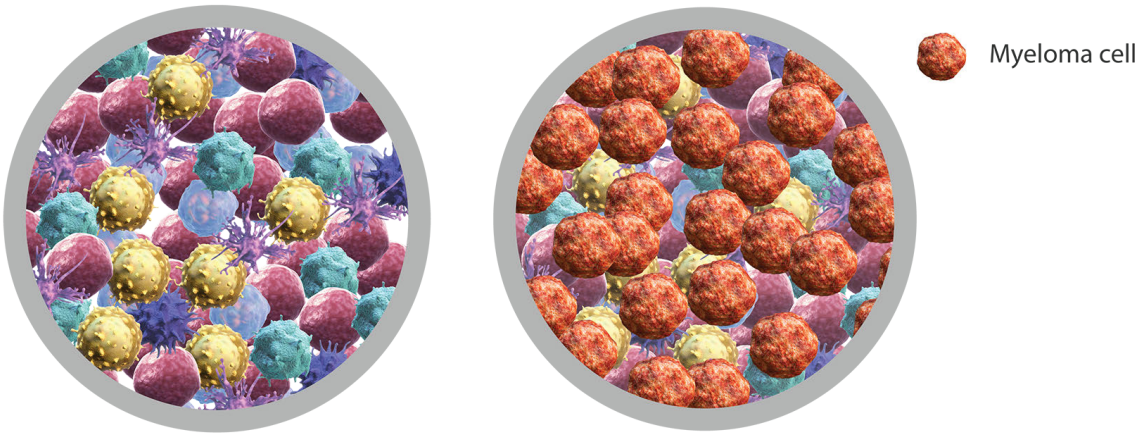
Multiple myeloma and the bone marrow microenvironment

Tumor evasion of the immune system

Mechanisms of tumor evasion

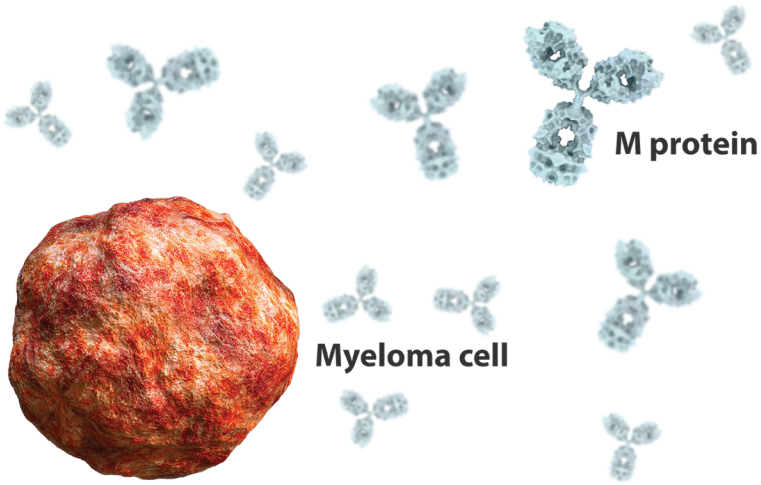
The interactions between myeloma cells and their environment can facilitate immune suppression and also enhance myeloma cell growth. In cancer patients, dysregulation at various points in the cancer immunity cycle can facilitate immune evasion and allow cancer cells to grow.[16] A hallmark of patients with multiple myeloma is suppression of the endogenous immune response, both adaptive (antibody-mediated) and innate (cell-mediated).[32]

- **Crowding out immune cells** – In healthy bone marrow, hematopoietic stem cells are able to differentiate into blood cells including T cells and natural killer cells as well as plasma cells, which produce immunoglobulins that are able to elicit an immune response.[33] However, in multiple myeloma, malignant cells proliferate uncontrollably and impair normal blood-forming cells and plasma cells in the bone marrow, resulting in the inability to mount an immune response.[34]



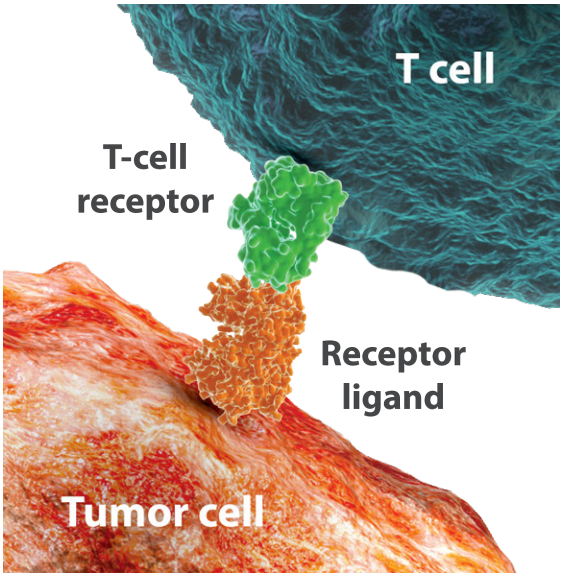
Healthy bone marrow and cancerous bone marrow with multiple myeloma

Release of M protein – Myeloma cells also overproduce a defective, monoclonal immunoglobulin, M protein, which has limited antigen reactivity.[34] As a result, in multiple myeloma there may be deficits in antigen presentation leading to a less robust immune response.



Myeloma cells and the overproduction of M protein

Cell-cell activation and inhibition – Ligands on myeloma cells may bind to receptors on T cells, resulting in reduced cytotoxicity or apoptosis of the T cell.[29] Immune-checkpoint proteins are an example of this mechanism. For example, myeloma cells may express ligands to these immune-checkpoint receptors on T cells. When these receptors and ligands interact, the end result is T-cell deactivation, leading to a less robust immune response.[35]



Ligands on myeloma cells binding to receptors on T cells

Examples of cell-cell activation and inhibition in multiple myeloma

- **NK cell suppression:** Myeloma cells secrete immunosuppressive cytokines that alter the expression of activating and inhibitory receptors on NK cells.[21,31,36-40] Myeloma cells can also induce tolerance in APCs and interfere with NK-cell function.[29] As a consequence, NK cell proliferation, cytotoxicity, and survival are impaired.[21,40]

- **T regulatory cell expression:** Myeloma cells can facilitate the expansion of regulatory T cells, or Tregs. Tregs are important in preventing autoimmune disease, but in the case of multiple myeloma, their expansion may facilitate immune suppression.[41]

- **T cell cytotoxicity:** Myeloma cells can also reduce cytotoxicity of T cells directly, making the T cells less able to recognize and kill myeloma cells. As a consequence, myeloma cells are able to evade the immune system and proliferate.[29]

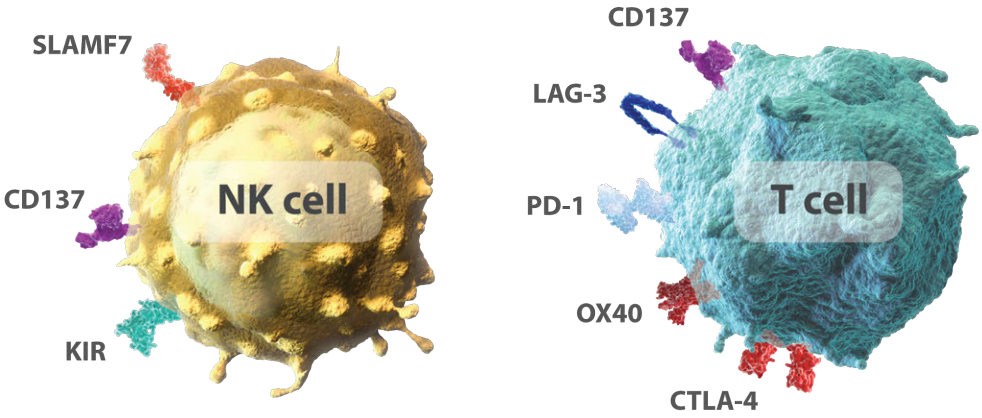
- **Co-stimulatory and checkpoint pathways:** Myeloma cell growth may also be associated with an imbalance in the natural feedback mechanisms that modulate the immune response.[39,40,42] Myeloma cells may cause down-regulation of co-stimulatory receptors, which dampen the immune response. Or they may exploit or up-regulate expression of immune checkpoints, or inhibitory signaling pathways, which facilitate immune suppression. Investigating these pathways may lead to a better understanding of how immune evasion may be overcome.

- **Down-regulation of immune accessory cells:** Immune accessory cells play a role as well. For example, plasmacytoid dendritic cells normally trigger effector T cells and host responses. However, in multiple myeloma, these plasmacytoid dendritic cells have a decreased ability to induce host T-cell proliferation. At the same time, they actually promote growth in the myeloma cells.[43]

Immune system co-stimulatory and checkpoint pathways

Myeloma cells can cause increased expression of inhibitory receptors on immune cells in order to evade recognition and cytotoxic effects.[44] Researchers are exploring the potential of how modulating ligand-receptor interactions may influence cytotoxicity against myeloma cells.[44,45] Additionally, there are receptors on immune cells that increase proliferation and cytokine production when they are activated.[46]

Ongoing research is being done to understand how modulating these pathways may theoretically enhance the ability of immune cells to induce myeloma cell death.[46] Several of these pathways are being investigated, including CD137, KIR, PD-1, and SLAMF7.[35,46-48,49-52]



Pathways under current investigation include CD137, KIR, PD-1, and SLAMF7

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