Myeloid -derived suppressor cells and Multiple myeloma

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The myeloma microenvironment refers to the specialized environment surrounding multiple myeloma cells within the bone marrow. Multiple myeloma is a cancer of the plasma cells, a type of white blood cell that produces antibodies. The tumor cells in multiple myeloma can disrupt the normal functioning of the bone marrow and interact with various components of the surrounding microenvironment.

The myeloma microenvironment is complex and consists of various cell types, including immune cells, stromal cells, and endothelial cells, as well as extracellular matrix components and soluble factors such as cytokines and growth factors. These components interact with the myeloma cells in a dynamic manner, influencing their growth, survival, and response to therapy.

Understanding the myeloma microenvironment is critical for developing effective therapies for multiple myeloma, as targeting interactions between myeloma cells and their microenvironment has emerged as a promising approach for treatment. Additionally, the microenvironment plays a role in disease progression and the development of drug resistance in multiple myeloma.

MDSC and multiple myeloma development:
Researchers have reported a significant finding regarding the immune microenvironment in patients with precursor conditions such as monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM). Their studies revealed that both MGUS and MM patients exhibit markedly higher levels and frequencies of myeloid-derived suppressor cells (MDSCs) within the bone marrow. MGUS and MM patients BM have signiflcantly higher level frequencies of granulocytic/polymorphonuclear MDSC (PMN-MDSC), and not monocytic MDSC (M-MDSC). MDSCs are a heterogeneous population of immune cells known for their immunosuppressive properties. This discovery suggests that the presence of MDSCs may contribute to immune dysfunction and facilitate disease progression in MGUS and MM patients. Understanding the role of MDSCs in these precursor stages could potentially offer new insights into disease pathogenesis and may lead to the development of targeted immunotherapeutic approaches aimed at modulating MDSC activity to impede or delay the progression of MGUS to symptomatic MM.

Myeloid derived suppressors cells (MDSC) play major roles in regulating immune homeostasis and immune responses in many conditions, including cancer.
MDSC interact with cancer cells within the tumor microenvironment (TME) with direct and indirect mechanisms: (1)Production of soluble factors and cytokines, (2)Expression surface inhibitory molecules, (3)Metabolic rewiring ,(4)Exosome release

MDSC activity in the tumor microenvironment (TME) is driven by several mechanisms: depletion of essential nutrients for CD8+ T-cells, production of immune suppressive cytokines and soluble

factors, expression of inhibitory molecules like PD-L1, and metabolic rewiring that favors tumor growth over immune effector cell function.

A substantial portion, ranging from 20% to 40%, of MDSC express Programmed Cell Death-Ligand 1 (PD-L1+), rendering them adept at engaging and suppressing immune effector cells such as Vg9Vd2 cells and natural killer (NK) cells equipped with the Programmed Cell Death-1 (PD-1) receptor. Remarkably, MDSC maintain PD-L1 expression in conditions like MGUS) and MM, irrespective of disease stage, including MM in remission, where the majority of myeloma cells have been eradicated from the bone marrow (BM). This persistence of PD-L1+ MDSC poses a challenge to the immunomodulatory effects of drugs like bortezomib or lenalidomide following autologous stem cell transplantation.

MDSC, pivotal in immune regulation, wield significant influence over immune equilibrium in healthy individuals, as well as the orchestration of immune responses across diverse scenarios like infectious diseases, autoimmunity, aging, pregnancy, transplantation, and obesity. Within the realm of cancer, MDSC's suppressive prowess is cunningly harnessed by tumor cells, enabling evasion of immune surveillance and fostering their own survival and proliferation.

Derived from bone marrow hematopoietic stem cells, MDSC manifest in two primary subsets within the human system: PMN-MDSC and M-MDSC. The former bears resemblance, both phenotypically and morphologically, to neutrophils, identified by markers like CD15 and/or CD66b, while the latter mirrors monocytes, characterized by CD14 expression. Notably, a third subset, early-MDSC (e-MDSC), exhibiting distinct phenotypic traits, has recently emerged among cancer patients.

How MDSC development:
There are two overlapping step involving the MDSC development
MDSC development unfolds in two partly overlapping phases. Initially, cytokines and soluble factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), granulocyte colony-stimulating factor (G-CSF), interleukin 6 (IL-6), and vascular endothelial growth factor (VEGF), which are secreted by tumor cells and/or BMSC in the tumor microenvironment (TME), drive the differentiation of MDSC from hematopoietic progenitor cells by activating STAT3 and STAT5 pathways.

Moreover, MDSC expansion through the hepatocyte growth factor (HGF), c-Met, and STAT3 phosphorylation which contributed by mesenchymal stromal cells (MSC). Subsequently, a second phase is initiated by a distinct set of cytokines and inflammatory soluble factors, such as interleukin 13 (IL-13), toll-like receptor (TLR) ligands, and prostaglandin E2 (PGE2), leading to functional activation of MDSC via the STAT1 and NF-kB pathways.

The TME exhibits a strong inclination towards promoting the expansion and activation of MDSC, often at the expense of other myeloid-derived cells such as monocytes, macrophages, and dendritic cells (DC).

Srivastava et al 2010 reported that Myeloid-derived suppressor cells (MDSC) inhibit T-cell activation by depleting cystine and cysteine as well as deplete the TME of tryptophan which restrains T cell proliferative responses through an integrated stress response and mTor signaling inactivation.

Therapeutic interventions

The correlation between the frequency of MDSC and the clinical outcome identifies these cells as potential targets of immune-based therapeutic interventions . Therapeutic targeting MDSC is not easy given their multifaceted biological functions and multiple interactions in the TME Possible strategies are: 1) to restrain their accumulation in the PB and TME; 2) to prevent their functional activation in the TME; 3) to block their protumoral interactions with myeloma cells and bystander cells.

In summary, MDSC exert a significant influence in shaping the immune suppressive Tumor Microenvironment (TME) in Multiple Myeloma (MM).Further research is needed to elucidate the precise mechanisms underlying MDSC-mediated immunosuppression in the context of precursor stages of multiple myeloma and to explore the therapeutic implications of targeting MDSCs in this setting.

Reference:

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