Myeloid-derived suppressor cells

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To protect the host from the harmful effects of excessive immune stimulation during acute and chronic infections, and to limit the generation of autoimmune responses towards tissues antigens released by trauma, the bone marrow is stimulated to release immature myeloid cells (IMCs) into the blood. These IMCs and some of their progeny, which might include certain tumor-associated macrophages (TAMs), can restrain the activation of T cells. They are therefore known as myeloid-derived suppressor cells (MDSCs) to highlight their common myeloid origin and immunoregulatory properties. It is now clear that MDSCs also have poorly defined roles in wound healing and tissue repair. Tumours have evolved to "harness" these properties of MDSCs to restrain antitumour immunity and to promote tumour expansion in the surrounding environment and at distant sites, through effects on angiogenesis and metastasis. New therapies to repress MDSC activity are crucial for the efficient control of tumour cells by immune responses. Protocells to generate MDSCs might be useful in pathologies involving excessive immune stimulation, such as autoimmune diseases and transplant rejection.

Generation and accumulation

MDSCs are an extrinsic part of the myeloid lineage and are a heterogeneous population comprised of myeloid progenitors and precursors of granulocytes, monocytes/macrophages and dendritic cells. BM is generated in the bone marrow, differentiating into mature granulocytes, macrophages or dendritic cells. Various cytokines and soluble factors released during pathological conditions, such as infection, injuries, tumors and inflammation (and also from transplanted organs), cause the proliferation of IMCs and a partial block of their differentiation. This results in the accumulation of MDSCs, which then migrate to secondary lymphoid organs and tissues (lung and liver) where they either reside or function in local tissue microenvironments. MDSC-mediated immune suppression can be associated with the expansion of T cell populations. In secondary lymphoid organs, MDSC-mediated suppression requires the direct presentation of antigens by MDSCs to T cells. The activity of MDSCs can also be enhanced by activated T cells in this way. At cancer sites, microenvironmental signals support constitutive activation of the orphan tumour necrosis factor receptor (TNFR) family member 1 in MDSCs, which affects nearby T cells in an antigen-nonspecific manner.

T-cell suppression

MDSCs can suppress T cell effectors function in various ways. Several factors can modulate the suppressive levels of ARG, NADPH oxidase and NOS2, which is the primary intracellular final effect on the microenvironment including the release of Reactive oxygen species (ROS) and NO. Further, ICOS and IL-2, being the most prevalent molecules in the inflammatory milieu, suppressed production of high NO levels. Moreover, ICOS-CD28 interaction can be sequestered by MDSCs. All of these factors influence the intracellular signaling pathways that control T cell proliferation and antigen-stimulation. MDSC-mediated immune suppression can also be associated with the expansion of T cell populations. In secondary lymphoid organs, MDSC-mediated suppression requires the direct presentation of antigens by MDSCs to T cells. The activity of MDSCs can also be enhanced by activated T cells in this way. At cancer sites, microenvironmental signals support constitutive activation of the orphan TNFR family member 1 in MDSCs, which affects nearby T cells in an antigen-nonspecific manner.

Tumorigenesis and tissue repair

MDSCs are induced by TLR activation to support tumour cell invasion. By similar mechanisms, MDSCs can migrate to a pre-metastatic niche by promoting local angiogenesis and recruiting immune-suppressive cells, including MDSCs, to the site of tumour cell invasion. TLR activation and angiogenesis can occur in response to various stimuli: by pathogen recognition by TLRs and ligation of TLR4 by lipopolysaccharide; and by the chemokine CCL2, which can be induced by TLR activation, to recruit monocytes/macrophage precursors to the site of tissue injury. These cells can then differentiate into MDSCs that promote tumour growth by secreting ARG1 and NOS2, which affect tumour cell proliferation and angiogenesis. Inhibition of these enzymes by specific drugs can therefore reduce tumour growth.

Therapeutic induction of MDSCs

MDSCs can be induced in vitro by various methods, including cytokine stimulation, TLR activation, and exposure to oxidative stress. This can be used in vitro to induce the generation of MDSCs, which can then be used in vivo to inhibit tumour growth. The generation of MDSCs in vitro can be induced by exposure to IFN-γ, LPS, or IL-1β, which stimulate the release of ARG1 and NOS2, and the generation of reactive oxygen species. These effects can be further enhanced by the addition of TLR agonists, such as Pam3CSK4 or CpG DNA, which activate the production of ARG1 and NOS2. The generation of MDSCs in vivo can be induced by the injection of IFN-γ, LPS, or IL-1β, which stimulate the release of ARG1 and NOS2, and the generation of reactive oxygen species. These effects can be further enhanced by the addition of TLR agonists, such as Pam3CSK4 or CpG DNA, which activate the production of ARG1 and NOS2.
References


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