

# Myeloid-derived suppressor cells in cancer

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## Abstract

Active suppression of tumor-specific T lymphocytes can limit both immune surveillance and immunotherapy. Several mouse tumors, either transplantable or spontaneously arising, alter the normal myelopoiesis and cause the expansion of a population of CD11b+/Gr-1+ cells in the blood, lymphoid organs and at the tumor site. These cells were recently defined as myeloid-derived suppressor cells (MDSCs). MDSCs are likely part of a conserved response to inflammatory signals and are harnessed by growing tumors to exert different functions, including support for stroma and neovasculature formation. However, in addition to their direct activity on tumor growth, MDSCs are now recognized as potent negative regulators of tumor-specific CD8+ T cells.

While tumor-recruited CD11b+ myeloid cells were known mediators of tumor-associated immune dysfunctions, the true nature of these suppressive cells and the fine biochemical pathways governing their immunosuppressive activity have been clarified only in last years. By means of combined genome-wide expression profiling, biochemical analyses, and functional studies in knock out mice, we identified a population of CD11b+, inflammatory-type monocytes expressing the alpha chain of the IL-4 receptor (IL-4R $\alpha$  - CD124), that is elicited by growing tumors and activated by IFN- $\gamma$  released from T lymphocytes. CD11b+/CD124+ cells produce IL-13 and IFN- $\gamma$  and integrate the downstream signals of these cytokines to trigger the molecular pathways suppressing antigen-activated CD8+ T lymphocytes. In particular, IL-13 and IFN- $\gamma$  cooperate in CD11b+/CD124+ cells to activate the enzymes arginase and nitric oxide synthase that metabolize the amino acid L-arginine and are among the final mediators of the suppressive machinery acting on CD8+ T lymphocytes. These suppressor cells challenge the current dogma of classic and alternative macrophage activation and show how the inflammatory response elicited by tumors has detrimental effects on the adaptive immune system. Moreover, definition of the metabolic pathways used by MDSCs to alter T lymphocyte reactivity to the antigens has unveiled potential targets for novel therapeutic interventions. At least two families of unrelated drugs, nitroaspirin and phosphodiesterase 5 inhibitors, were shown to affect the immunosuppressive pathways of MDSCs in preclinical tumor models.

In addition to their prevalent activity on CD8+ T cells, recent data support a role for MDSCs in the activation of T regulatory lymphocytes (Tregs). In particular, MDSCs can uptake tumor-associated antigens, present them to naturally-occurring, tumor-specific Tregs inducing them to proliferate. Moreover, therapeutic interventions, which effectively abrogate the immunosuppressive machinery of MDSCs, also results in the reduction of Treg numbers in tumor-bearing hosts. In cancer patients, the nature of MDSCs is still poorly defined since evidence exists for both monocytic and granulocytic features. We recently found that myeloid cells with immunosuppressive properties accumulate both in mononuclear and

polymorphonuclear fractions of circulating blood leukocytes of patients with colon cancer and melanoma, thus confirming the generalized alteration in the homeostasis of the myeloid compartment observed in mouse models. Similarly to mouse MDSCs, CD124 is up-regulated in both myeloid populations but its presence correlates with an immunosuppressive phenotype only when mononuclear cells, but not granulocytes, of tumor-bearing patients are considered.

In order to dissect the molecular pathways involved in MDSC differentiation, we recently defined *in vitro* culture conditions to elicit MDSCs from human and mouse bone marrow cells. These cells share phenotype and functions of tumor-induced MDSCs and can be adoptively transferred to recipient mice inducing antigen tolerance. Interestingly, adoptive transfer of syngeneic bone marrow-derived MDSCs to diabetic mice transplanted with allogeneic pancreatic islets resulted in the allograft acceptance of the and long term correction of the diabetic status.

Preclinical evidence strongly supports a beneficial effect of approaches targeting either MDSCs or their inhibitory pathways on the anti-tumor immune response, either endogenous or elicited by immunization/adoptive transfer of tumor-specific T cells. Development of new treatments will thus have a double role: defining new immune modulators to improve the effectiveness of the immunotherapy of cancer but also clarify better the role of MDSCs in tumors of different derivation as well as in various stages of cancer progression. On the other side of the same coin, techniques allowing generation and adoptive transfer of MDSCs might represent a novel tool to control diseases characterized by excessive activation of the immune systems such as either autoimmune diseases or allograft rejection.