nature REVIEWS IMMUNOLOGY

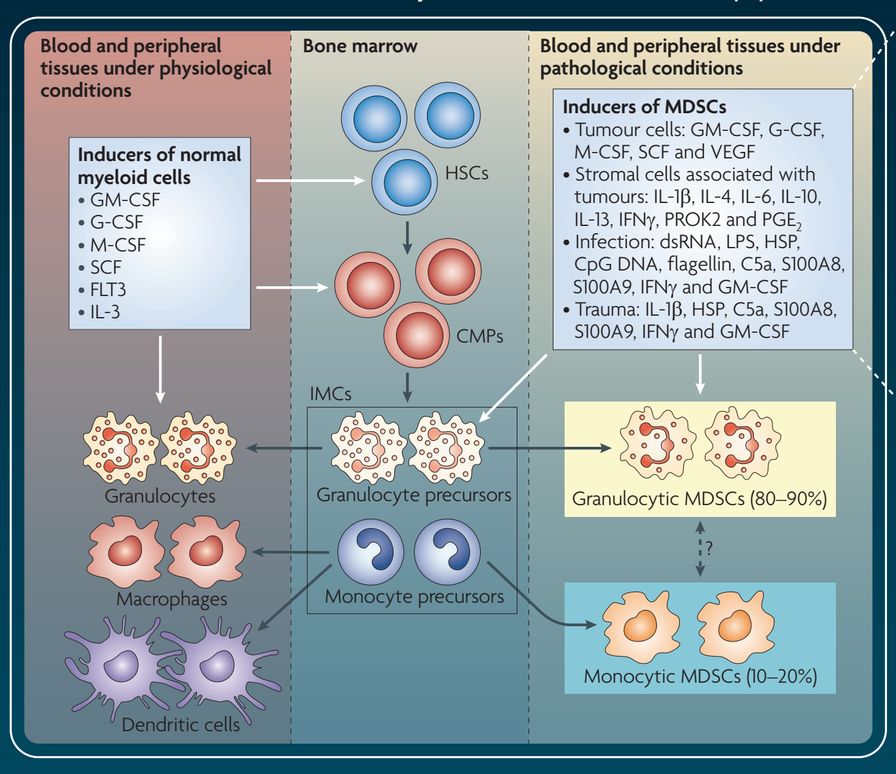
Myeloid-derived suppressor cells

Vincenzo Bronte and Dmitry Gabrilovich

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 tissue 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 tumour-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 restrain MDSC activity are crucial for the efficient control of tumour cells by immune responses. Protocols to generate MDSCs might be useful in pathologies involving excessive immune stimulation, such as autoimmune diseases and transplant rejection.

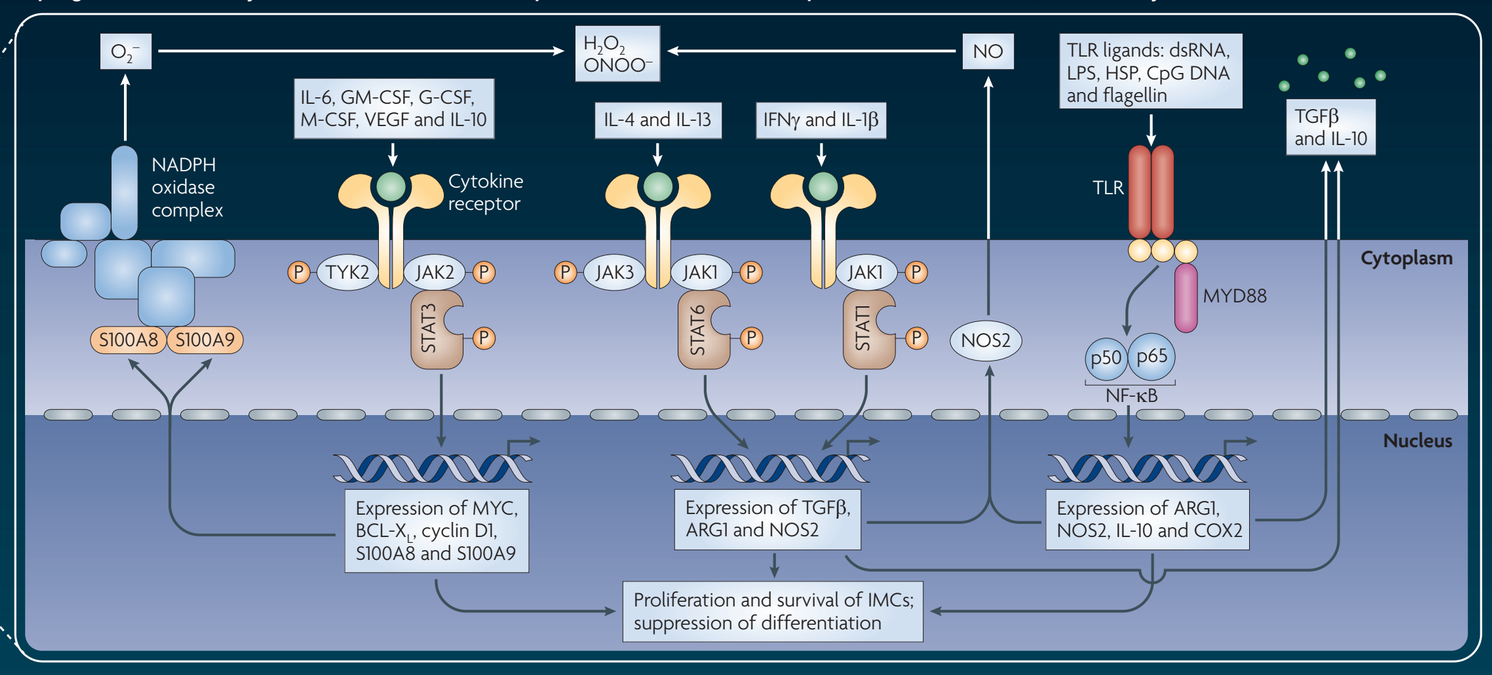
Generation and accumulation

MDSCs are an intrinsic part of the myeloid cell lineage and are a heterogeneous population comprised of myeloid cell progenitors and precursors of granulocytes, macrophages and dendritic cells. In healthy individuals, IMCs generated in the bone marrow differentiate into mature granulocytes, macrophages or dendritic cells. Various cytokines and soluble factors released during pathological conditions, such as cancer, infection, trauma and autoimmunity (and after bone marrow transplantation), 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 (such as the tumour site), where they exert their effects on other cell populations.



Activation and proliferation

The proliferation of MDSCs is associated with activation of these cells in a pathological context. Activation is mediated through several transcription factors and results in the upregulation of expression of immunosuppressive factors, such as ARG1 and NOS2, upregulation of activity of the NADPH oxidase complex and an increase in the production of NO, ROS, RNS and cytokines.

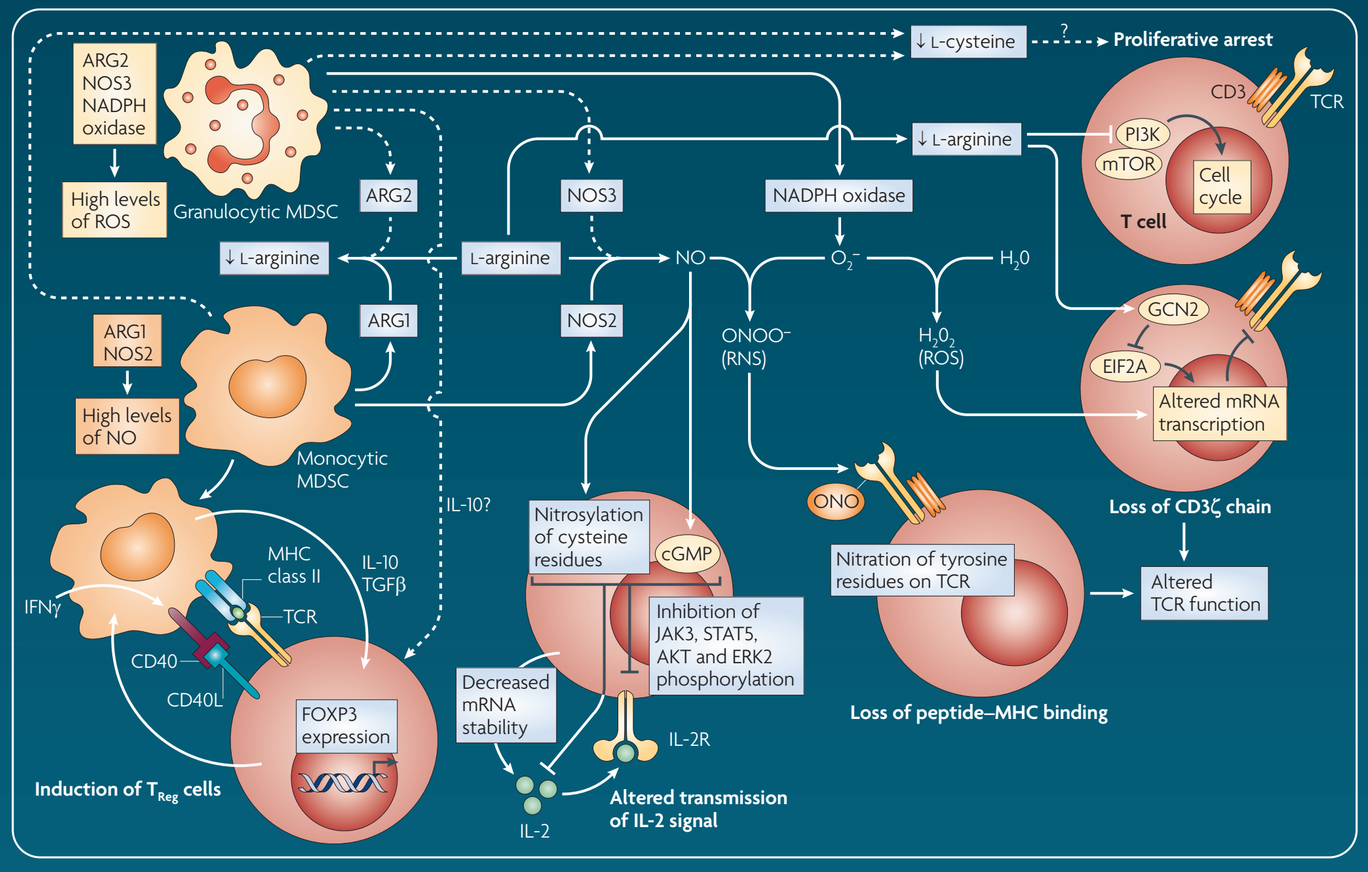


MDSC markers

Marker		Mouse splenic MDSCs																Human peripheral blood MDSCs								
		CD11b	Gr1	Ly6C	Ly6G	CD31 (PECAM1)	F4/80	CD1d	CD16	CD32	CD54	CD68	CD80	CD115	CD124	CCR2	CX_3CR1	CD11b	CD14	CD15	CD16	CD33	CD66b	CD124	VEGFR1	HLA-DR
Expression level	Granulocytic MDSCs	High	High	Low	High	–	–	+	+	+	Low	–	±	±	+	–	High	+	–	+	Low	+	+	+	+	–
	Monocytic MDSCs	High	Mid	High	–	±	+	+	+	+	High	+	±	+	+	+	Low	+	+	±	–	+	±	+	–	Low

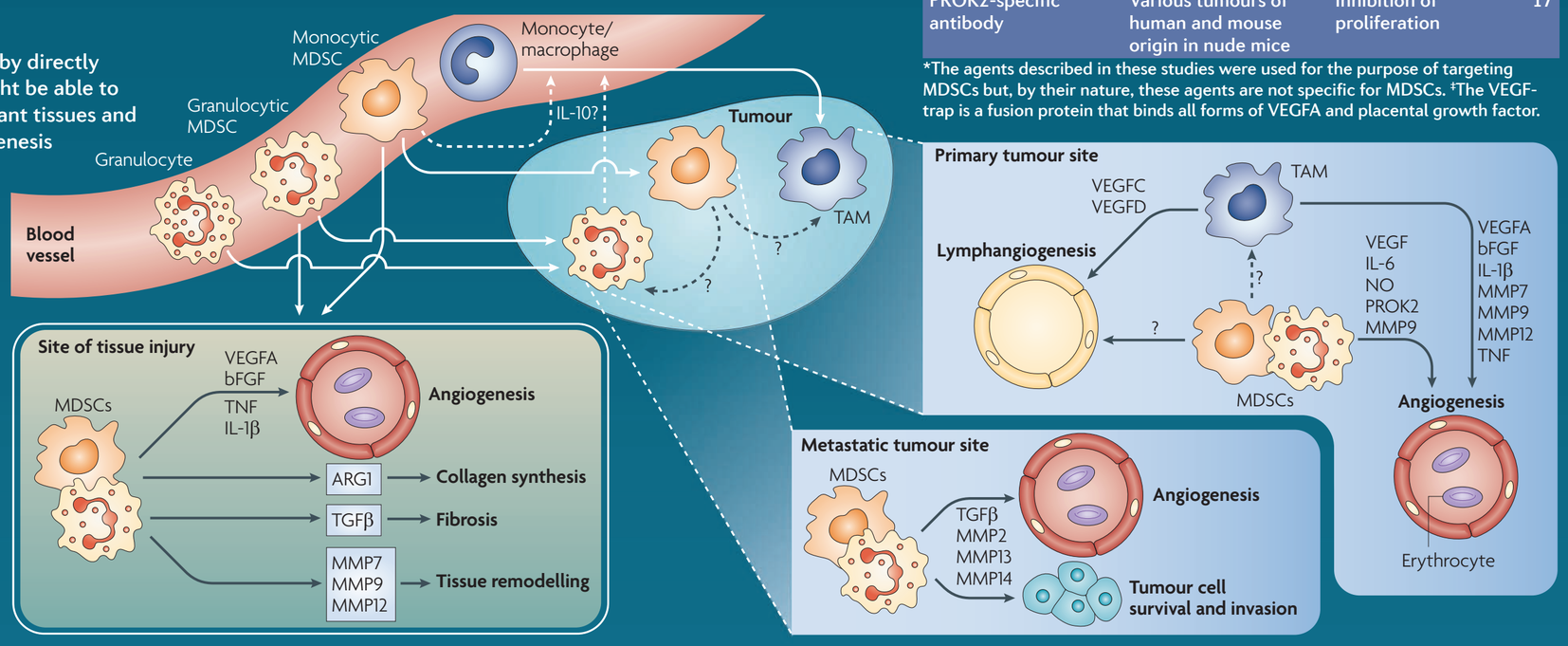
T cell suppression

MDSCs can suppress T cell effector functions in various ways. Several factors can modulate the expression levels of ARG, NADPH oxidase and NOS in MDSC subsets, with the final effect on the microenvironment including depletion of L-arginine, release of RNS and ROS (with $ONOO^-$ and H_2O_2 being the most prevalent molecules, respectively) or unopposed production of high NO levels. Moreover, L-cysteine can be sequestered by MDSCs. All of these molecules influence the intracellular signalling pathways that control T cell proliferation after antigen stimulation. MDSC-mediated immune suppression can also be associated with the expansion of T_{Reg} 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 tumour sites, microenvironmental signals support constitutive activation of the immunosuppressive programme in MDSCs, which affects nearby T cells in an antigen-nonspecific manner.



Tumorigenesis and tissue repair

MDSCs in the tumour environment produce factors that support tumour growth by directly promoting tumour angiogenesis and lymphangiogenesis. In addition, MDSCs might be able to differentiate into TAMs that have similar activity. MDSCs can also migrate to distant tissues and participate in the formation of a pre-metastatic niche by promoting local angiogenesis and the survival of arriving tumour cells. MMPs produced by MDSCs can support tumour cell invasion. By similar mechanisms, MDSCs can migrate to a site of tissue injury and participate in tissue remodelling and angiogenesis.



Therapies to restrain the activity of MDSCs

Therapeutic agent*	Type of cancer tested	Effect on MDSCs	Refs
COX2 inhibitor (SC58236)	Mammary carcinoma (mice)	Inhibition of proliferation	1
Amino-biphosphonate	Mammary tumours (mice)	Inhibition of proliferation	2
Phosphodiesterase-5 inhibitor (sildenafil and tadalafil)	Mammary carcinoma, colon carcinoma and fibrosarcoma (all mice)	Inhibition of proliferation and of suppressive effects	3
KIT-specific antibody	Colon carcinoma (mice)	Inhibition of proliferation	4
Nitroaspirin	Colon carcinoma (mice)	Inhibition of suppressive effects	5
Triterpenoid	Colon carcinoma, thymoma and lung cancer (all mice)	Inhibition of suppressive effects	6
All-*trans* retinoic acid	Sarcoma and colon carcinoma (mice) Metastatic renal cell carcinoma (human)	Inhibition of proliferation	7 8
25-hydroxyvitamin D3	Head and neck cancer (human)	Moderate inhibition of proliferation	9
Gemcitabine	Lung and breast cancer (mice)	Inhibition of proliferation	10, 11
VEGF-trap‡	Solid tumours (human)	None	12
VEGF-specific antibody (avastin)	Metastatic renal cell cancer (human)	Weak inhibition of proliferation	13
Doxorubicin-cyclophosphamide	Breast cancer (human)	Weak inhibition of proliferation	14
Antagonists for CXCR2 (S-265610) and CXCR4 (AMD3100)	Breast cancer (mice)	Inhibition of proliferation	15
Tyrosine kinase inhibitor (sunitinib)	Renal cell cancer (human)	Weak inhibition of proliferation	16
PROK2-specific antibody	Various tumours of human and mouse origin in nude mice	Inhibition of proliferation	17

*The agents described in these studies were used for the purpose of targeting MDSCs but, by their nature, these agents are not specific for MDSCs. ‡The VEGF-trap is a fusion protein that binds all forms of VEGFA and placental growth factor.

Therapeutic induction of MDSCs

Source of MDSCs	Type of immune pathology tested	Effect of MDSCs	Refs
Activated following $CD8^+$ T cell-induced acute enterocolitis	Inflammatory bowel disease (mice)	Inhibition of antigen-specific $CD8^+$ T cells	18
Generated *in vitro* from mouse embryonic stem cells	Graft-versus-host disease (mice)	Prevention of disease following adoptive transfer of MDSCs	19
Induced by perioperative treatment with CD28-specific antibodies	Kidney allograft transplant (mice)	Maintenance of graft tolerance	20
Induced by endotoxin	Skin allograft transplant (mice)	Prolongation of graft survival following adoptive transfer of MDSCs	21

Abbreviations

ARG, arginase; bFGF, basic fibroblast growth factor; BCL-X_L, B cell lymphoma X_L; C5a, complement component 5a; CCR2, CC-chemokine receptor 2; cGMP, cyclic guanosine monophosphate; CMP, common myeloid progenitor; COX2, cyclooxygenase 2; CXCR, CXC-chemokine receptor; CX_3CR1, CX_3C-chemokine receptor 1; dsRNA, double-stranded RNA; EIF2A, eukaryotic translation initiation factor 2α; ERK2, extracellular-signal-regulated kinase 2; FLT3, FMS-like tyrosine kinase 3; FOXP3, Forkhead box P3; GCN2, also known as EIF2A kinase 4; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; H_2O_2, hydrogen peroxide; HSC, haematopoietic stem cell; HSP, heat shock protein; IFNγ, interferon-γ; IL, interleukin; IL-2R, IL-2 receptor; JAK, Janus kinase; LPS, lipopolysaccharide; M-CSF, macrophage colony-stimulating factor; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; MYD88, myeloid differentiation primary response protein 88; NF-κB, nuclear factor-κB; NO, nitric oxide; NOS, nitric oxide synthase; $ONOO^-$, peroxynitrite; PECAM1, platelet–endothelial cell adhesion molecule 1; PGE_2, prostaglandin E_2; PI3K, phosphoinositide 3-kinase; PROK2, prokineticin 2 (also known as BV8); RNS, reactive nitrogen species; ROS, reactive oxygen species; S100A8, S100 calcium-binding protein A8; SCF, stem cell factor (also known as KIT ligand); STAT, signal transducer and activator of transcription; TCR, T cell receptor; TGFβ, transforming growth factor-β; TLR, Toll-like receptor; TNF, tumour necrosis factor; T_{Reg} cell, regulatory T cell; TYK2, tyrosine kinase 2; VEGF, vascular endothelial growth factor; VEGFR1, VEGF receptor 1.

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The authors declare no competing financial interests.

Edited by Kirsty Minton and Olive Leavy; copyedited by Gemma Ryan; designed by Simon Bradbrook.

http://www.nature.com/nri/posters/mdscs
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