

Myeloid-derived suppressor cells

Vincenzo Bronte and Dmitry Gabrilovich

nature
REVIEWS

IMMUNOLOGY

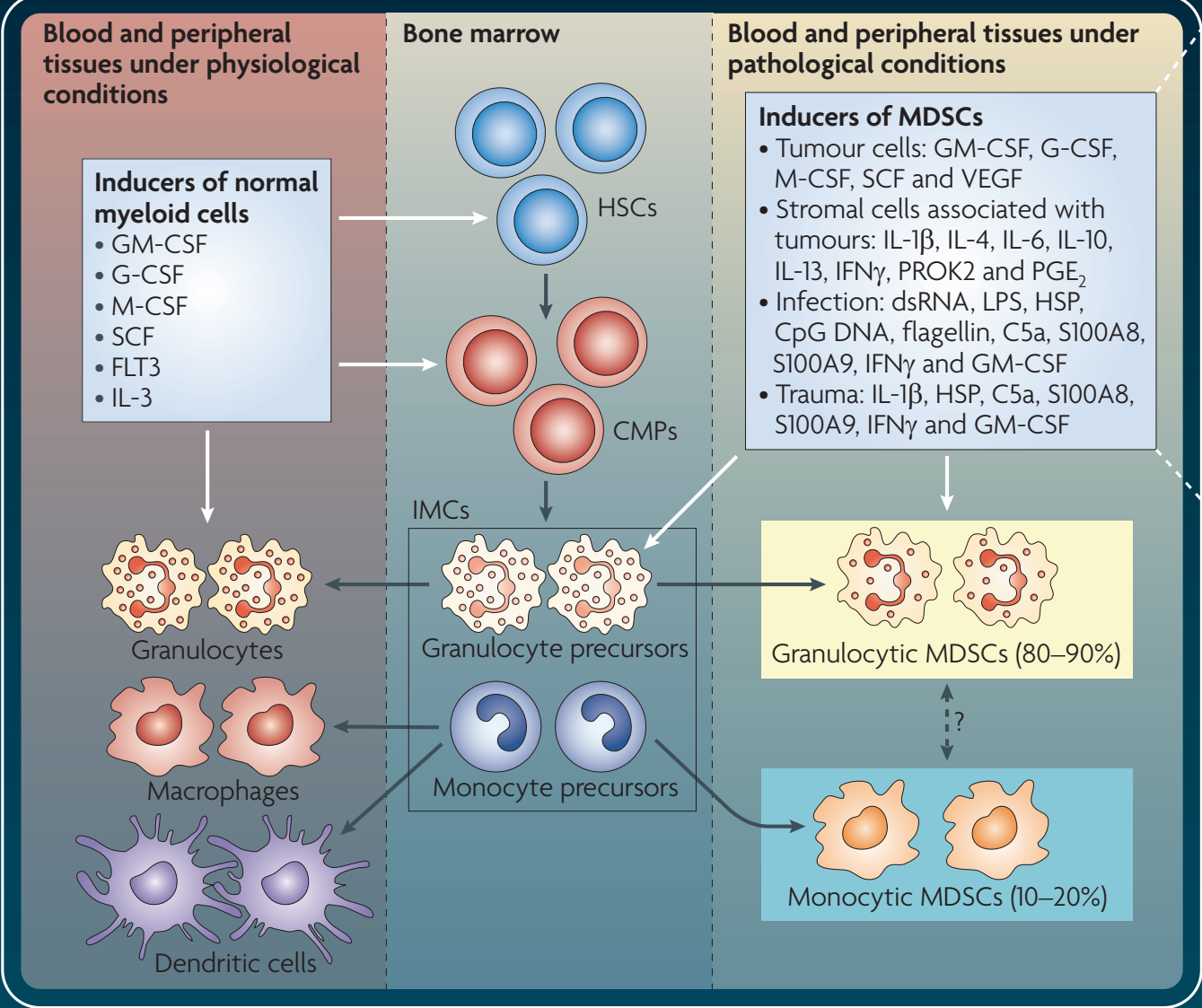


To protect the host from the harmful effects of excessive immune stimulation during acute and chronic infections, and to limit the generation of autoimmune responses towards tissue antigens released by trauma, the bone marrow is stimulated to release immature myeloid cells (IMCs) into the blood. These 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.

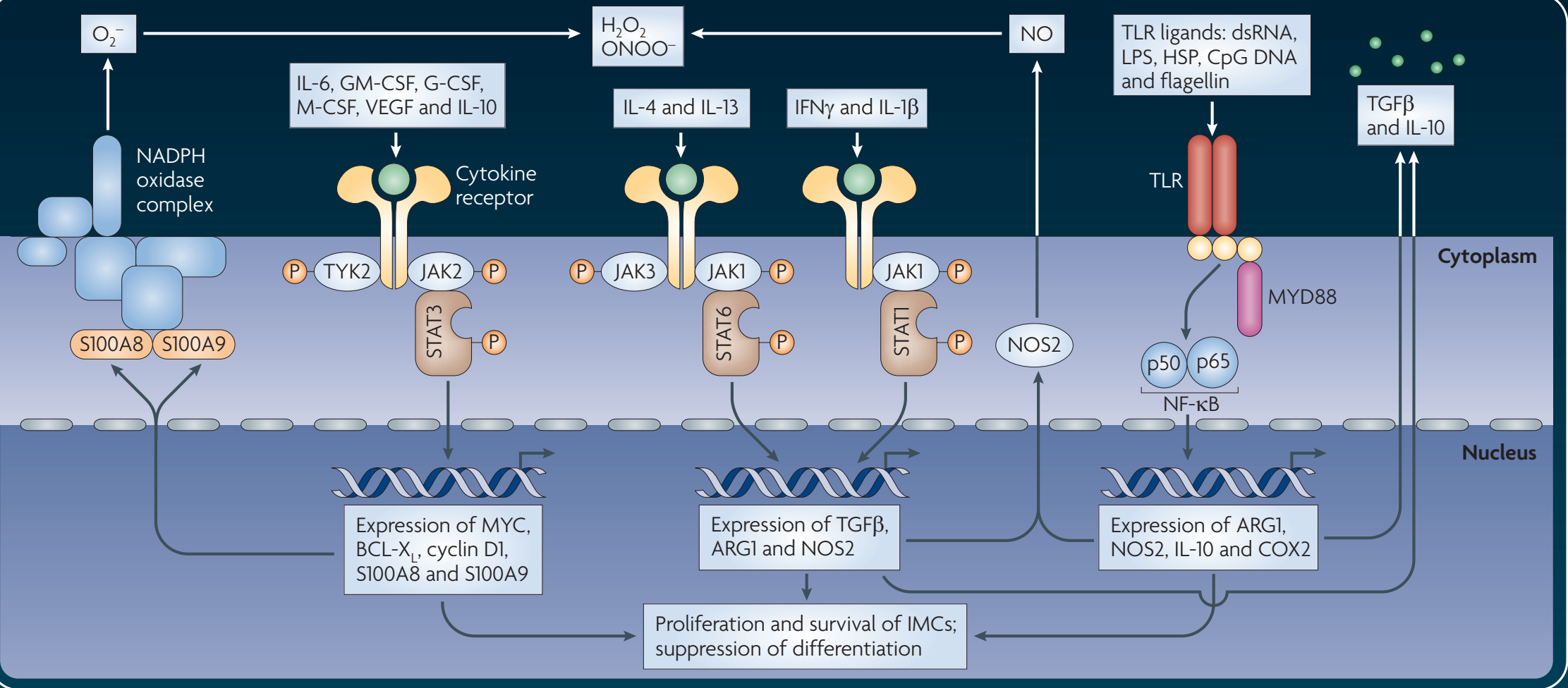
Generation and accumulation

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.

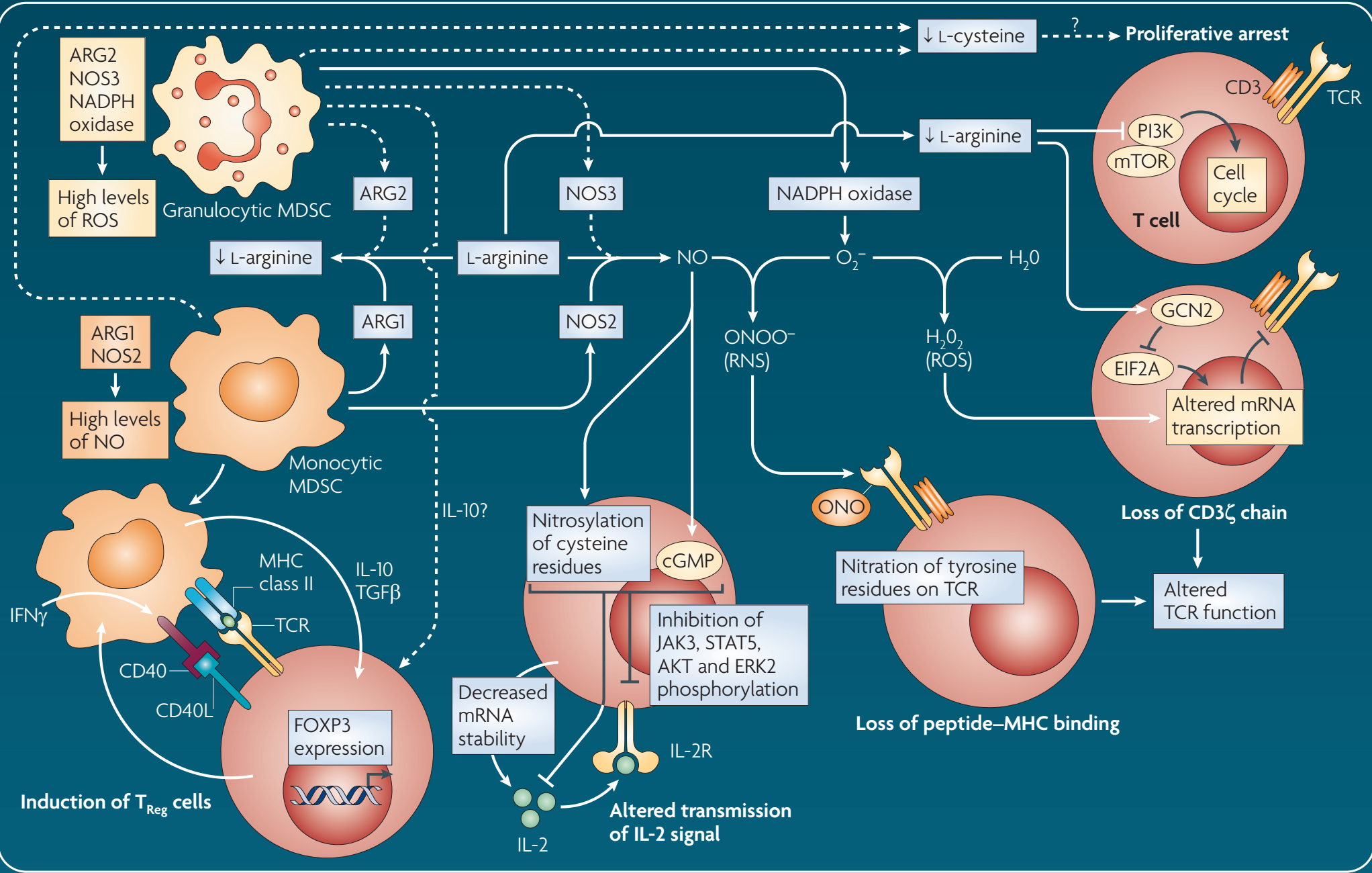


MDSC markers

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	CXCR1	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 H₂O₂ 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.



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)	Inhibition of proliferation	7
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

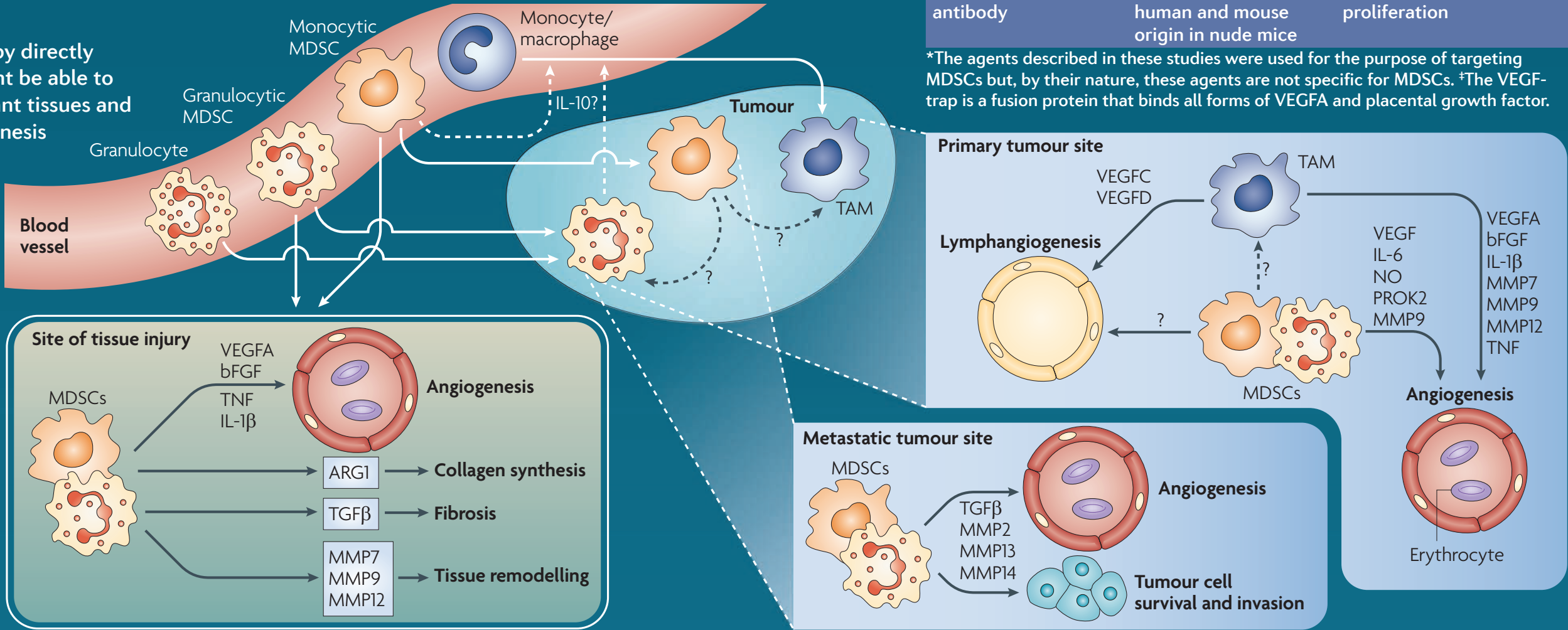
*The agents described in these studies were used for the purpose of targeting MDSCs but, by their nature, these agents are not specific for MDSCs. †The VEGF-trap is a fusion protein that binds all forms of VEGFA and placental growth factor.

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.

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, CXCR-chemokine receptor; CX₂CR1, CX₂-chemokine receptor 1; dsRNA, double-stranded RNA; EIF2A, eukaryotic translation initiation factor 2a; 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; H₂O₂, hydrogen peroxide; HSC, haematopoietic stem cell; HSP, heat shock protein; IFN_γ, 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- κ B, nuclear factor- κ B; NO, nitric oxide; NOS, nitric oxide synthase; ONOO[–], peroxynitrite; PECAM1, platelet-endothelial cell adhesion molecule 1; PGE₂, prostaglandin E₂; 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; TGF β , 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.

Affiliations

Vincenzo Bronte is at the Istituto Oncologico Veneto, Via Gattamelata 64, 35128 Padova, Italy. Dmitry Gabrilovich is at the H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, MRC 2067, 12902 Magnolia Drive, Tampa, Florida 33612, USA. e-mails: enzo.bronte@unipd.it; dmitry.gabrilovich@moffitt.org

The authors declare no competing financial interests.

Edited by Kirsty Minton and Olive Leavy; copyedited by Gemma Ryan; designed by Simon Bradbrook. © (2010) Macmillan Publishers Ltd. All rights reserved.

<http://www.nature.com/nri/posters/mdscs>
References available online.

BioLegend (www.biolegend.com)

BioLegend is your resource for world-class quality antibodies and other reagents for biomedical research, provided at an outstanding value. Founded in 2002, BioLegend is located in the heart of the biotechnology community in San Diego, California. Our experienced leaders were co-founders of PharMingen, now BD Biosciences. Our product areas include cell immunophenotyping, cytokines and chemokines, adhesion, cancer research, T regulatory cells, stem cells, innate immunity, cell-cycle analysis, apoptosis, and T helper subsets. All of BioLegend's reagents are supported by superior customer service and come with a 100% quality guarantee. Our aggressive product development program, through technology licensing, collaborations, and internal hybridoma development, produces strategic reagents for use in a variety of applications including flow cytometry, ELISA, immunoprecipitation, Western blotting, immunofluorescence microscopy, immunohistochemistry, custom Luminex assays, and *in vitro* or *in vivo* functional assays. BioLegend offers the broadest selection of fluorochrome conjugates for multi-color flow cytometry. BioLegend offers a wide array of custom assays and services, including development of multicolor flow cytometry panels to meet our customers' specific needs. BioLegend is the preferred vendor for flow cytometry reagents at Harvard University, and we are a proud sponsor of just about every immunology society in the world.

References

1. Sinha, P., Clements, V. K., Fulton, A. M. & Ostrand-Rosenberg, S. Prostaglandin E2 promotes tumor progression by inducing myeloid-derived suppressor cells. *Cancer Res.* **67**, 4507–4513 (2007).
2. Melani, C., Sangaletti, S., Barazzetta, F. M., Werb, Z. & Colombo, M. P. Amino-biphosphonate-mediated MMP-9 inhibition breaks the tumor–bone marrow axis responsible for myeloid-derived suppressor cell expansion and macrophage infiltration in tumor stroma. *Cancer Res.* **67**, 11438–11446 (2007).
3. Serafini, P. *et al.* Phosphodiesterase-5 inhibition augments endogenous antitumor immunity by reducing myeloid-derived suppressor cell function. *J. Exp. Med.* **203**, 2691–2702 (2006).
4. Pan, P. Y. *et al.* Reversion of immune tolerance in advanced malignancy: modulation of myeloid-derived suppressor cell development by blockade of stem-cell factor function. *Blood* **111**, 219–228 (2008).
5. De Santo, C. *et al.* Nitroaspirin corrects immune dysfunction in tumor-bearing hosts and promotes tumor eradication by cancer vaccination. *Proc. Natl Acad. Sci. USA* **102**, 4185–4190 (2005).
6. Nagaraj, S. *et al.* Anti-inflammatory triterpenoid blocks immune suppressive function of myeloid-derived suppressor cells and improves immune response in cancer. *Clin. Cancer Res.* (in the press).
7. Kusmartsev, S. *et al.* All-trans-retinoic acid eliminates immature myeloid cells from tumor-bearing mice and improves the effect of vaccination. *Cancer Res.* **63**, 4441–4449 (2003).
8. Mirza, N. *et al.* All-trans-retinoic acid improves differentiation of myeloid cells and immune response in cancer patients. *Cancer Res.* **66**, 9299–9307 (2006).
9. Lathers, D., Clark, J., Achille, N. & Young, M. Phase 1B study to improve immune responses in head and neck cancer patients using escalating doses of 25-hydroxyvitamin D3. *Cancer Immunol. Immunother.* **53**, 422–430 (2004).
10. Suzuki, E., Kapoor, V., Jassar, A. S., Kaiser, L. R. & Albelda, S. M. Gemcitabine selectively eliminates splenic Gr-1⁺/CD11b⁺ myeloid suppressor cells in tumor-bearing animals and enhances antitumor immune activity. *Clin. Cancer Res.* **11**, 6713–6721 (2005).
11. Sinha, P., Clements, V. K., Bunt, S. K., Albelda, S. M. & Ostrand-Rosenberg, S. Cross-talk between myeloid-derived suppressor cells and macrophages subverts tumor immunity toward a type 2 response. *J. Immunol.* **179**, 977–983 (2007).
12. Fricke, I. *et al.* Vascular endothelial growth factor-trap overcomes defects in dendritic cell differentiation but does not improve antigen-specific immune responses. *Clin. Cancer Res.* **13**, 4840–4848 (2007).
13. Kusmartsev, S. *et al.* Oxidative stress regulates expression of VEGFR1 in myeloid cells: link to tumor-induced immune suppression in renal cell carcinoma. *J. Immunol.* **181**, 346–353 (2008).
14. Diaz-Montero, C. M. *et al.* Increased circulating myeloid-derived suppressor cells correlate with clinical cancer stage, metastatic tumor burden, and doxorubicin-cyclophosphamide chemotherapy. *Cancer Immunol. Immunother.* **58**, 49–59 (2009).
15. Yang, L. *et al.* Abrogation of TGF β signaling in mammary carcinomas recruits Gr-1⁺CD11b⁺ myeloid cells that promote metastasis. *Cancer Cell* **13**, 23–35 (2008).
16. van Cruijsen, H. *et al.* Sunitinib-induced myeloid lineage redistribution in renal cell cancer patients: CD1c⁺ dendritic cell frequency predicts progression-free survival. *Clin. Cancer Res.* **14**, 5884–5892 (2008).
17. Shojaei, F. *et al.* Bv8 regulates myeloid-cell-dependent tumour angiogenesis. *Nature* **450**, 825–831 (2007).
18. Haile, L. A. *et al.* Myeloid-derived suppressor cells in inflammatory bowel disease: a new immunoregulatory pathway. *Gastroenterology* **135**, 871–881 (2008).
19. Zhou, Z. *et al.* Development and function of myeloid-derived suppressor cells generated from mouse embryonic and hematopoietic stem cells. *Stem Cells* 13 Jan 2010 (doi:10.1002/stem.301).
20. Dugast, A. S. *et al.* Myeloid-derived suppressor cells accumulate in kidney allograft tolerance and specifically suppress effector T cell expansion. *J. Immunol.* **180**, 7898–7906 (2008).
21. De Wilde, V. *et al.* Endotoxin-induced myeloid-derived suppressor cells inhibit alloimmune responses via heme oxygenase-1. *Am. J. Transplant.* **9**, 2034–2047 (2009).