# The role of myeloid-derived suppressor cells in haematology: hype or reality?

M. Beckers, MD, PhD[1], D. Dierickx, MD, PhD[1], T. Devos, MD, PhD[1], S. Fevery, MD, PhD[2], B. Sprangers, MD, PhD[3]

**One of the hallmarks of failure of elimination of malignant cells by activated T-cells is the immunosuppressive environment of the tumour. Myeloid-derived suppressor cells contribute to this immunosuppressive environment by inhibition of the adaptive and innate immune system. In this article we describe the current knowledge of the role of myeloid-derived suppressor cells in the progression of haematological malignancies.**
*(Belg J Hematol 2016;7(6):213-6)*

## Introduction

Immune based therapies are taking central stage in the treatment of haematological malignancies. The principle of influencing the immune system of the patient to treat cancer is attractive, however many obstacles need to be overcome. One of these is the so-called 'immune-tolerance to tumours'. It appears that one of the key-players inhibiting anti-tumour immunity is myeloid-derived suppressor cells (MDSC). These cells were already identified in mice in the previous century as a heterogeneous population of immature myeloid cells with immune-suppressive characteristics. Based on the expression of surface markers and their immune-suppressive characteristics MDSC can be divided in two groups: monocytic (MO-MDSC) and granulocytic (PMN-MDSC). In humans, MO-MDSC are $CD11b^+$ $CD14^+$ $CD15^-$ $CD33^+$ HLA-$DR^{low}$ and PMN-MDSC are $CD11b^+$ $CD14^-$ $CD15^+$ $CD33^+$ HLA-$DR^{low/-}$.[1]

## MDSC expansion and function

Both the pro-inflammatory environment of the tumour and the tumour cells themselves induce MDSC by secreting several factors (*Figure 1*). Most of these factors activate several signalling pathways within MDSC leading to an expansion of MDSC. MDSC suppress both the adaptive and innate immune system by direct cell-cell contact and by cytokine production. This leads to an inhibition of proliferation and activation of T-cells, induction of regulatory T-cells (Tregs) and impairment of natural killer (NK) cells. Besides influencing the immune system of the host, MDSC have a direct effect on the tumour-microenvironment by interfering with vascular endothelial growth factor (VGEF), interaction with tumour-associated macrophages (shift of M1-like subtype to M2-like subtype) and they may contribute to epithelial-mesenchymal transition (EMT). Other effects of MDSC are inhibition of homing of T-cells to lymph nodes and sites of inflammation.[2-4]

## MDSC in haematological malignancies

In solid tumours, MDSC are extensively studied and they play an important role in promoting tumour growth and immune suppression. The role of MDSC has been less studied in haematological malignancies. In newly diagnosed and refractory multiple myeloma (MM) patients, MDSC defined as $CD11b^+CD14^-$HLA-$DR^{-/low}CD33^+CD15^+$ are increased in the peripheral blood and bone marrow.[5] In MM, MDSC promote tumour growth in the MM microenvironment. The immune suppressive capacities of MDSC in the MM-bone marrow environment are mediated by arginine and NO synthases.[5] Importantly, lenalidomide and bortezomib, commonly used in the treatment of MM, do not abrogate MDSC number and function. This may hamper the effectiveness of immune-based therapy in

[1]Department of Haematology, [2]Department of Experimental Transplantation, [3]Department of Nephrology, University Hospitals Leuven, Leuven, Belgium.
*Please send all correspondence to:* M. Beckers, MD, PhD, Department of Haematology, University Hospital Leuven, Herestraat 49, 3000 Leuven, Belgium, tel: +32 16 34 68 80, fax: +32 16 34 68 81, email: marielle.beckers@uzleuven.be.
**Conflict of interest:** The authors have nothing to disclose and indicate no potential conflict of interest.
**Keywords:** haematological malignancies, immune system, MDSC, stem cell transplantation.

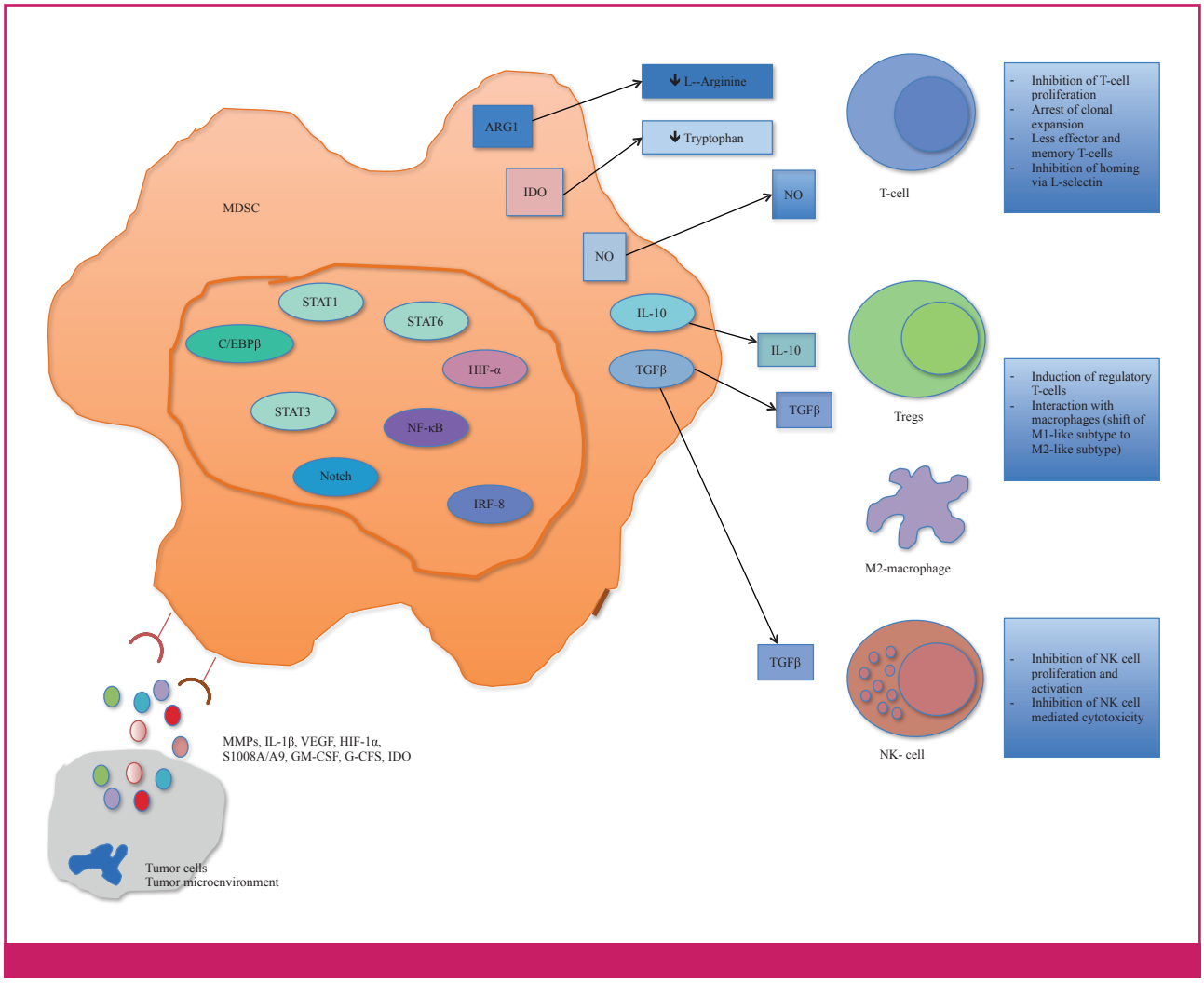


**Figure 1.** MDSC expansion and function.

*MMPs: matrix metalloproteases; IL-1β: interleukin-1beta; VEGF: vascular endothelial growth factor; HIF-1α: hypoxia-inducible factor-1 alpha; GM-CSF: granulocyte/macrophage-colony-stimulating factor; G-CSF: granulocyte colony-stimulating factor; IDO: indoleamine 2, 3-dioxygenase; STAT: signal transducer and activator of transcription; IRF-8: interferon regulatory factor-8; NF-κB: nuclear factor kappa B; C/EBPβ: CCAAT/enhancer binding protein β; ARG1: arginine-1; NO: nitric oxide; TGFβ: tumour growth factor-beta; IL-10: interleuking-10; Tregs: regulatory T-cells; NK: natural killer.*

MM. Others have found similar results of MDSC being present in the peripheral blood and bone marrow of MM patients at time of diagnosis.[6-8] Favoloro *et al.* observed an increase of mostly PMN-MDSC ($CD33^+CD11b^+CD14^-CD15^+HLA\text{-}DR^{low/-}$) in patients with progressive MM.[9]

Little is known about the role of MDSC in other haematological malignancies. Recently it was shown that in patients with acute myeloid leukaemia MDSC ($CD33^+CD11b^+HLA\text{-}DR^{low/-}$) were increased in the bone marrow at time of diagnosis. Furthermore, the decline of MDSC after the initial induction therapy was highest in those patients with complete remission. The patients with high minimal residual disease ($MRD>1x10^{-2}$) had high MDSC levels.[10] It is speculated that this phenomenon may reflect a favourable immune suppressive microenvironment provided by MDSC where leukaemia cells can survive. In the bone marrow of patients with myelodysplastic syndrome, MDSC ($Lin^-CD33^+HLA\text{-}DR^-$) do not only possess immunosuppressive characteristics but also suppress hematopoiesis.[11,12] By the S100A9/CD33 pathway, MDSC contributes to the development of MDS.[11] In chronic lymphocytic leukaemia (CLL) patients, increased levels of MDSC ($CD14^+HLA\text{-}DR^{low}$) were found and it was shown that they suppressed T-cell activation and induced Tregs through IDO.[13] Whether CLL cancer cells can induce MDSC is unknown despite the fact that CLL patients with high MDSC levels

do have more circulating malignant cells. Increased levels of MDSC are also observed in chronic myeloid leukaemia (CML) patients.[14,15] Based on the expression of BCR-ABL these MDSC (both MO-MDSC and PMN-MDSC) originate from the malignant clone in the study by Giallongo *et al*.[15] Treatment of CML with imatinib and dasatinib lead to a decline of MDSC.[16]

In diffuse large B-cell lymphoma (DLBCL) MO-MDSC ($CD14^+HLA\text{-}DR^{-/low}$) were significantly higher in patients when compared to healthy controls.[17] In poor risk patients groups, the level of MO-MDSC were significantly higher than in the good risk group.[18] Similar results were found in patients with Hodgkin lymphoma (HL). In a study by Romano *et al*., significant higher numbers of PMN-MDSC ($CD11b^+CD33^+CD14^-HLA\text{-}DR^-Lin^-$), MO-MDSC ($CD14^+HLA\text{-}DR^{low/-}$) and i-MDSC ($CD34^+CD11b^+CD33^+CD14^-HLA\text{-}DR^-$) were present at diagnosis in HL patients.[19] HL patients with high $CD34^+$ MDSC levels ($\geq 0.0045 \times 10^9$ cells/l) at diagnosis had a shorter PFS compared to those patients with low $CD34^+$ MDSC count. In the peripheral blood of patients with extranodal NK/T-cell lymphoma, MDSC ($HLA\text{-}DR^-CD33^+CD11b^+$) were increased and associated with disease free survival and overall survival.[20]

As such, MDSC appear to be associated with several haematological malignancies. However, they also play a role in commonly used therapies within haematology such as allogeneic stem cell transplantation and immunotherapy. One of the factors responsible for morbidity and mortality after allogeneic stem cell transplantation (allo-SCT) is graft-versus-host disease (GvHD). In the immediate, post-transplant period, MO-MDSC ($CD14^+HLA\text{-}DR^{low/-}$) and PMN-MDSC ($CD33^+CD15^+CD66b^+$) are increased in peripheral blood.[21,22] This is explained by the presence of inflammatory stimuli caused by the conditioning regimen (cytokine storm). Various factors are described that contribute to the immunosuppressive state, such as IDO and arginase, which may play a role in the occurrence of GvHD.[21,23] Lv *et al*. and others reported low levels of MO-MDSC at onset of aGvHD. In those patients who responded to steroid therapy a rapid increase of MO-MDSC occurred.[24] High levels of MDSC are required at the time of transplantation to reduce aGvHD. Mice models show that adoptive transfer of MDSC prevent GvHD without compromising the graft-versus-tumour effect. However, MDSC do not have an effect on ongoing GvHD when administered later than the activation and proliferation of allogeneic T-cells *in vivo*.[25] Others postulate that, in contrast to tumour-induced MDSC that are known to represent a mechanism used by tumours to escape immune-surveillance, the MDSC in the context of allo-SCT may play a beneficial role.[26]

Nowadays, the use of checkpoint inhibitors (anti-PD-1/PD-L1 and anti-CTLA-4) and novel cellular therapies (CAR-T cells) are increasingly used for treating haematological malignancies such as Hodgkin lymphoma, CLL and acute lymphoblastic leukaemia. However, the efficacy of these therapies may be reduced by the presence of MDSC. In mice-models, PD-L1 expression on MDSC may be induced by the hypoxic environment via HIF-$\alpha$ and STAT 3 via IL-10 secretion by activated T-cells.[27,28] Controversial data exist on the expression of PD-L1 on MDSC in humans. In MM patients PD-L1 positive MDSC are observed.[29] However, Favoloro *et al*. did not find PD-L1 expression on MDSC in MM patients.[9] Some data show that PD-L1 blockade alone may not be sufficient enough to alter MDSC-mediated immunosuppression.[29] Therefore, it may be necessary to combine these therapies with other therapies that diminish MDSC numbers and/or alter the immunosuppressive capacities of MDSC. In MM patients, PD-1/PD-L1 blockade combined with lenalidomide lead to enhanced anti-multiple myeloma responses versus PD-1/PD-L1 blockade alone.[29] In a mice model with liver metastases CAR-T efficacy was increased in combination with MDSC depletion.[30] Currently, it is unknown if MDSC influence the efficacy of CAR-T in haematological malignancies.

## Conclusion

The role of MDSC in haematological malignancies is just starting to be clarified. MDSC inhibit both the innate and adoptive immune system by secretion of various factors. By doing so, MDSC are important in tumour immunology and transplantation tolerance. Targeting MDSC may become crucial in the efficacy of immune based therapy, checkpoint inhibitors and cellular therapies.

## References

1. Montero AJ, Diaz-Montero CM, Kyriakopoulos CE, et al. Myeloid-derived suppressor cells in cancer patients: a clinical perspective. J Immunother. 2012; 35(2):107-15.

2. Parker KH, Beury DW, Ostrand-Rosenberg S. Myeloid-Derived Suppressor Cells: critical cells driving immune suppression in the tumour microenvironment. Adv Cancer Res. 2015;128:95-139.

3. Motallebnezhad M, Jadidi-Niaragh F, Qamsari ES, et al. The immunobiology of myeloid-derived suppressor cells in cancer. Tumour Biol. 2016;37(2):1387-406.

4. Ugel S, De Sanctis F, Mandruzzato S, et al. Tumor-induced myeloid deviation: when myeloid-derived suppressor cells meet tumour-associated macrophages.

## Key messages for clinical practice

1. MDSC play an important role in the immunosuppressive environment of tumours.
2. MDSC are involved in the pathogenesis of several haematological malignancies.
3. MDSC may interfere with new immunotherapies like checkpoint inhibitors.
4. In the context of allogeneic stem cell transplantation, MDSC may play a beneficial role.

J Clin Invest. 2015;125(9):3365-76.

5. Görgün GT, Whitehill G, Anderson JL, et al. Tumor-promoting immune-suppressive myeloid-derived suppressor cells in the multiple myeloma micro-environment in humans. Blood. 2013;121(15):2975-87.

6. Brimnes MK, Vangsted AJ, Knudsen LM, et al. Increased level of both CD4+FOXP3+ regulatory T cells and CD14+HLA-DR-/low myeloid-derived suppressor cells and decreased level of dendritic cells in patients with multiple myeloma. Scand J Immunol. 2010;72(6):540-7.

7. Castella B, Foglietta M, Sciancalepore P, et al. Anergic bone marrow Vγ9Vδ2 T cells as early and long-lasting markers of PD-1-targetable microenvironment-induced immune suppression in human myeloma. Oncoimmunology. 2015;4(11):e1047580.

8. Ramachandran IR, Martner A, Pisklakova A, et al. Myeloid-derived suppressor cells regulate growth of multiple myeloma by inhibiting T cells in bone marrow. J Immunol. 2013;190(7):3815-23.

9. Favaloro J, Liyadipitiya T, Brown R, et al. Myeloid derived suppressor cells are numerically, functionally and phenotypically different in patients with multiple myeloma. Leuk Lymphoma. 2014;55(12):2893-900.

10. Sun H, Li Y, Zhang ZF, et al. Increase in myeloid-derived suppressor cells (MDSCs) associated with minimal residual disease (MRD) detection in adult acute myeloid leukaemia. Int J Hematol. 2015;102(5):579-86.

11. Chen X, Eksioglu EA, Zhou J, et al. Induction of myelodysplasia by myeloid-derived suppressor cells. J Clin Invest. 2013;123(11):4595-611.

12. Gleason MK, Ross JA, Warlick ED, et al. CD16xCD33 bispecific killer cell engager (BiKE) activates NK cells against primary MDS and MDSC CD33+ targets. Blood. 2014;123(19):3016-26.

13. Jitschin R, Braun M, Büttner M, et al. CLL-cells induce IDOhi CD14+HLA-DRlo myeloid-derived suppressor cells that inhibit T-cell responses and promote Tregs. Blood. 2014;124(5):750-60.

14. Christiansson L, Söderlund S, Svensson E, et al. Increased level of myeloid-derived suppressor cells, programmed death receptor ligand 1/programmed death receptor 1, and soluble CD25 in Sokal high risk chronic myeloid leukaemia. PLoS One. 2013;8(1):e5518.

15. Giallongo C, Parrinello N, Brundo MV, et al. Myeloid derived suppressor cells in chronic myeloid leukaemia. Front Oncol. 2015;5:107.

16. Christiansson L, Söderlund S, Mangsbo S, et al. The tyrosine kinase inhibitors imatinib and dasatinib reduce myeloid suppressor cells and release effector lymphocyte responses. Mol Cancer Ther. 2015;14(5):1181-91.

17. Tadmor T, Fell R, Polliack A, et al. Absolute monocytosis at diagnosis correlates with survival in diffuse large B-cell lymphoma-possible link with monocytic myeloid-derived suppressor cells. Hematol Oncol. 2013;31(2):65-71.

18. Wu C, Wu X, Zhang X, et al. Prognostic significance of peripheral monocytic myeloid-derived suppressor cells and monocytes in patients newly diagnosed with diffuse large b-cell lymphoma. Int J Clin Exp Med. 2015;8(9):15173-81.

19. Romano A, Parrinello NL, Vetro C, et al. Circulating myeloid-derived suppressor cells correlate with clinical outcome in Hodgkin Lymphoma patients treated up-front with a risk-adapted strategy. Br J Haematol. 2015;168(5):689-700.

20. Zhang H, Li ZL, Ye SB, et al. Myeloid-derived suppressor cells inhibit T cell proliferation in human extranodal NK/T cell lymphoma: a novel prognostic indicator. Cancer Immunol Immunother. 2015;64(12):1587-99.

21. Mougiakakos D, Jitschin R, von Bahr L, et al. Immunosuppressive CD14+HLA-DRlow/neg IDO+ myeloid cells in patients following allogeneic hematopoietic stem cell transplantation. Leukemia. 2013;27(2):377-88.

22. Guan Q, Blankstein AR, Anjos K, et al. Functional Myeloid-Derived Suppressor Cell Subsets Recover Rapidly after Allogeneic Hematopoietic Stem/Progenitor Cell Transplantation. Biol Blood Marrow Transplant. 2015;21(7):1205-14.

23. Highfill SL, Rodriguez PC, Zhou Q, et al. Bone marrow myeloid-derived suppressor cells (MDSCs) inhibit graft-versus-host disease (GVHD) via an arginase-1-dependent mechanism that is up-regulated by interleukin-13. Blood. 2010;116(25):5738-47.

24. Lv M, Zhao XS, Hu Y, et al. Monocytic and promyelocytic myeloid-derived suppressor cells may contribute to G-CSF-induced immune tolerance in haplo-identical allogeneic hematopoietic stem cell transplantation. Am J Hematol. 2015;90(1):E9-E16.

25. Wang D, Yu Y, Haarberg K, et al. Dynamic change and impact of myeloid-derived suppressor cells in allogeneic bone marrow transplantation in mice. Biol Blood Marrow Transplant. 2013;19(5):692-702.

26. Luyckx A, Schouppe E, Rutgeerts O, et al. G-CSF stem cell mobilization in human donors induces polymorphonuclear and mononuclear myeloid-derived suppressor cells. Clin Immunol. 2012;143(1):83-7.

27. Noman MZ, Desantis G, Janji B, et al. PD-L1 is a novel direct target of HIF-1α, and its blockade under hypoxia enhanced MDSC-mediated T cell activation. J Exp Med. 2014;211(5):781-90.

28. Pinton L, Solito S, Damuzzo V, et al. Activated T cells sustain myeloid-derived suppressor cell-mediated immune suppression. Oncotarget. 2016;7(2):1168-84.

29. Görgün G, Samur MK, Cowens KB, et al. Lenalidomide enhances immune checkpoint blockade-induced immune response in multiple myeloma. Clin Cancer Res. 2015;21(20):4607-18.

30. Burga RA, Thorn M, Point GR, et al. Liver myeloid-derived suppressor cells expand in response to liver metastases in mice and inhibit the anti-tumour efficacy of anti-CEA CAR-T. Cancer Immunol Immunother. 2015;64(7):817-29.