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Brief Reviews

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Reciprocal Relationship between Myeloid-Derived Suppressor Cells and T Cells

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Myeloid-derived suppressor cells (MDSCs) are a heterogeneous group of myeloid cells that play a major role in the regulation of immune responses in many pathological conditions. These cells have a common myeloid origin, relatively immature state, common genetic and biochemical profiles, and, most importantly, the ability to inhibit immune responses. Although initial studies of MDSCs were almost exclusively performed in tumor-bearing mice or cancer patients, in recent years, it became clear that MDSCs play a critical role in the regulation of different types of inflammation that are not directly associated with cancer. In this review we discuss the nature of the complex relationship between MDSCs and the different populations of CD4$^+$ T cells. ***The Journal of Immunology*****, 2013, 191: 17–23.**

Myeloid-derived suppressor cells (MDSCs) play a major role in the regulation of immune responses in cancer and many pathological conditions associated with chronic inflammation. These cells have a common myeloid origin, relatively immature state, common genetic and biochemical features, and, most importantly, the ability to inhibit immune responses. MDSCs consist of two main subsets: polymorphonuclear cells (PMN-MDSCs) and monocytic (M-MDSCs) cells (1, 2). The phenotype of these populations is now well defined in mice, and recently these cells were defined in cancer patients as well (3). PMN-MDSCs consist of relatively immature and pathologically activated neutrophils (4), whereas M-MDSCs consist of pathologically activated inflammatory monocytes. A small proportion of MDSCs is represented by precursors of myeloid cells, with the ability to form colonies in semisolid medium. It appears that, at least in cancer, M-MDSCs may play a central role in the development of immune suppressive myeloid cells. In the tumor site, they differentiate to tumor-associated macrophages with potent immunosuppressive activity, and in the periphery they may give rise to PMN-MDSCs (5, 6). The phenotype of MDSCs, their mechanisms of expansion, and the specific mechanisms by which they exert their suppressive effects are described in many reviews (3, 7–10). Initial studies of MDSCs were almost exclusively performed in tumor-bearing mice or in cancer patients. Cancer still remains the main focus of MDSC research. However, in recent years, it became increasingly clear that MDSCs play a critical role in the regulation of different types of inflammation not directly associated with cancer. It also became clear that the interaction of MDSCs with different populations of CD4$^+$ T cells is not one-directional and goes beyond the simple direct immunosuppressive activity of MDSCs on T cells. These issues are discussed in this review.

Suppressive activity of MDSCs on T cells in pathologic conditions not associated with cancer

Ample evidence favors the important functional role of MDSCs in various pathologic conditions associated with noncancerous inflammation. The priming of mice with CFA resulted in an expansion of MDSCs. These cells could subsequently be stimulated by activated T cells to produce reactive oxygen species (ROS) and NO (11). *Mycobacterium bovis* bacillus Calmette–Guérin (BCG) vaccination recruited NO-producing MDSCs. These cells were unable to kill BCG or the nonpathogenic *Mycobacterium smegmatis*, and they impaired T cell priming in the draining lymph node. The elimination of MDSCs by all-*trans* retinoid acid increased the number of IFN-γ–producing CD4$^+$ T cells after vaccination with BCG (12). In individuals who received hepatitis B virus vaccine, GM-CSF augmented the preservation of peripheral blood MDSCs, which could contribute to the lack of improved vaccine responses (13).

Most chronic infections cause an expansion of M-MDSCs. Goñi et al. (14) found that during *Trypanosoma cruzi* infection, suppression was mediated through IFN-γ–dependent NO secretion by MDSCs. In lupus-prone MRL-*Fas*^{lpr} mice, MDSCs had a suppressive effect on CD4$^+$ T cell proliferation, which was restored by an arginase 1 (Arg1) inhibitor (15). The MyD88-dependent expansion of MDSCs induced T cell suppression and Th2 polarization in sepsis (16). The administration of cerulean, which induces gallbladder contraction and the release of insulin, to MyD88$^{-/-}$ mice resulted in

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Abbreviations used in this article: Arg1, arginase 1; BCG, bacillus Calmette–Guérin; EAE, experimental autoimmune encephalomyelitis; GVHD, graft-versus-host disease; MDSC, myeloid-derived suppressor cell; M-MDSC, monocytic myeloid-derived suppressor cell; NOS2, NO synthase 2; PMN-MDSC, polymorphonuclear cell myeloid-derived suppressor cell; PNT, peroxynitrite; RA, rheumatoid arthritis; ROS, reactive oxygen species; Treg, regulatory T cell.

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severe pancreatitis, whereas this effect was much smaller in MyD88$^{+/+}$ mice. The number of IL-10–expressing MDSCs in cerulean-treated MyD88$^{-/-}$ mice was significantly smaller than in the control MyD88$^{+/+}$ mice, which was associated with a reciprocal increase in the infiltration of CD4$^+$ T cells (17).

In an inflammatory bowel disease model, the repeated transfer of Ag-specific T cells led to an increase in the frequency of NO synthase 2 (*Nos2*)– and *Arg1*-expressing MDSCs in spleen and intestine. The cotransfer of MDSCs with specific CD8$^+$ T cells into mice ameliorated enterocolitis and suggested a direct immunoregulatory effect of MDSCs on the induction of inflammatory bowel disease by Ag-specific T cells (18). In inflammatory bowel disease induced by resveratrol, MDSCs also attenuated T cell proliferation and reduced the IFN-γ and GM-CSF production by lamina propria–derived T cells (19).

Multiple sclerosis is a demyelinating disease associated with an inflammatory immune response in the CNS. In a Theiler's murine encephalomyelitis virus mouse model of multiple sclerosis, the depletion of M-MDSCs increased the virus-specific CD4$^+$ and CD8$^+$ T cell responses during the early virus infection, which were associated with an increased expression of IFN-γ and IL-17 and a decreased expression of IL-10 in the CNS (20). The in vivo transfer of MDSCs ameliorated the experimental autoimmune encephalomyelitis (EAE), significantly decreased demyelination, and delayed disease onset through the inhibition of encephalitogenic Th1 and Th17 immune responses (21).

MDSCs were shown to counter proinflammatory immune cells in the liver and adipose tissue during obesity. In obese mice, MDSCs suppressed proliferation of CD8$^+$ T cells, induced their apoptosis, and skewed the differentiation of macrophages into insulin-sensitizing, alternatively activated M2 macrophages (22). Lysosomal acid lipase cleaves cholesteryl esters and triglycerides to generate free fatty acids and cholesterol in lysosomes. Lysosomal acid lipase deficiency causes an expansion of MDSCs, the loss of T cells, and an impairment of T cell function (23). MDSCs were essential for the IL-6–mediated protection of liver injury caused by an anti-CD137 Ab via inhibition of CD8$^+$ T cell proliferation and IFN-γ expression (24).

MDSCs were implicated in the regulation of immune response during organ transplantation and graft-versus-host disease (GVHD). The data suggested that the expansion of MDSCs, together with regulatory T cells (Tregs), may be an important factor in the survival of cardiac allografts (25). The administration of recombinant G-CSF or IL-2 in mice resulted in the accumulation of MDSCs and Tregs in the peripheral lymphoid organs. This treatment significantly delayed MHC class II disparate allogeneic donor skin rejection (26). GVHD is the significant cause of morbidity and mortality following allogeneic bone marrow transplantation. It was shown that in minor histocompatibility, mismatched bone marrow transplantation is associated with the accumulation of MDSCs in blood, which peaked at week 3 and returned to the physiological level at week 12 (27). MDSCs, generated in vitro or in vivo, alleviated GVHD in murine allogeneic bone marrow transplantation models (28–30). The addition of functional MDSCs to the donor graft alleviated GVHD, whereas removal of MDSCs in vivo exacerbated GVHD. MDSC accumulation has been positively correlated with the severity of GVHD (31).

Recent reports have also implicated MDSCs in viral diseases. Patients with chronic hepatitis C virus showed a significant correlation between the MDSC levels, disease progression, and the response of patients to antiviral therapy. MDSCs suppressed T cell function in an Arg1-dependent manner (32). HIV and SIV infections induced a population phenotypically similar to M-MDSCs that expressed higher levels of STAT3 and NOS2 and a suppressed expansion of CD8$^+$ T cells (33). In a large study of HIV-1–seropositive subjects compared with healthy controls, the presence of M-MDSCs in peripheral blood correlated with prognostic HIV-1 disease markers, including the HIV-1 load and CD4$^+$ T cell loss. M-MDSCs from HIV-1$^+$ subjects suppressed T cell responses in both HIV-1–specific and Ag-nonspecific manners (34). In a recent study, infections with an acute Armstrong or a chronic clone 13 strain of the lymphocytic choriomeningitis virus led to two distinct phases of innate immune response. Seven days after infection, there was an increase in immunosuppressive M-MDSCs and PMN-MDSCs in lymphoid organs and blood. This expansion was sustained only in the chronic clone 13 infection, whereas it occurred only transiently in acute Armstrong infection (35).

Thus, the role of MDSCs as an important negative regulator of immune responses is extended beyond cancer and observed in many pathological conditions. Although the immunosuppressive activity of MDSCs is the most prominent feature of these cells, ample evidence points to their role in the regulation of different populations of CD4$^+$ T cells. Importantly, it appears that T cells can, in turn, regulate MDSC expansion and activity as well (Fig. 1). In this review, we discuss the interaction between MDSCs and specific subsets of CD4$^+$ T cells.

Interaction between MDSCs and Th1/Th2 CD4$^+$ T cells

In an early study, Terabe et al. (36) demonstrated that MDSCs can be activated to produce TGF-β in response to IL-13 in tumor-bearing mice. More recently, in a mammary adenocarcinoma model, IL-4–expressing CD4$^+$ Th2 cells promoted expansion of MDSCs and tumor-associated macrophages. This enhanced pulmonary metastasis through activation of the epidermal growth factor receptor signaling in malignant mammary epithelial cells (37). Immune-mediated liver injury in hepatitis is caused by activated IFN-γ–producing Th1 cells. The accumulation of Th1 cells in liver was associated with the accumulation of MDSCs and suppression of T cell proliferation. TGF-β1–deficient mice acutely develop liver inflammation caused by Th1 cells. The rapid accumulation of MDSCs in TGF-β1–deficient liver was abrogated when mice were either depleted of CD4$^+$ T cells or rendered unable to produce IFN-γ, demonstrating that Th1 cells can induce MDSC accumulation (38). In humans, LPS has been associated with protection from allergic diseases such as asthma. However, in mouse models of allergic asthma, a low dose of LPS promoted Th2 responses and allergic disease, whereas a high dose has been associated with suppression of allergic airway inflammation. The adoptive transfer of LPS-induced CD11b$^+$Gr-1^{int}F4/80$^+$ cells suppressed allergen-induced airway inflammation, suggesting that these cells may have regulatory functions in asthma. These cells were found to blunt the ability of the lung dendritic cells to upregulate GATA-3 or to promote STAT5 activation in primed Th2 cells (39).

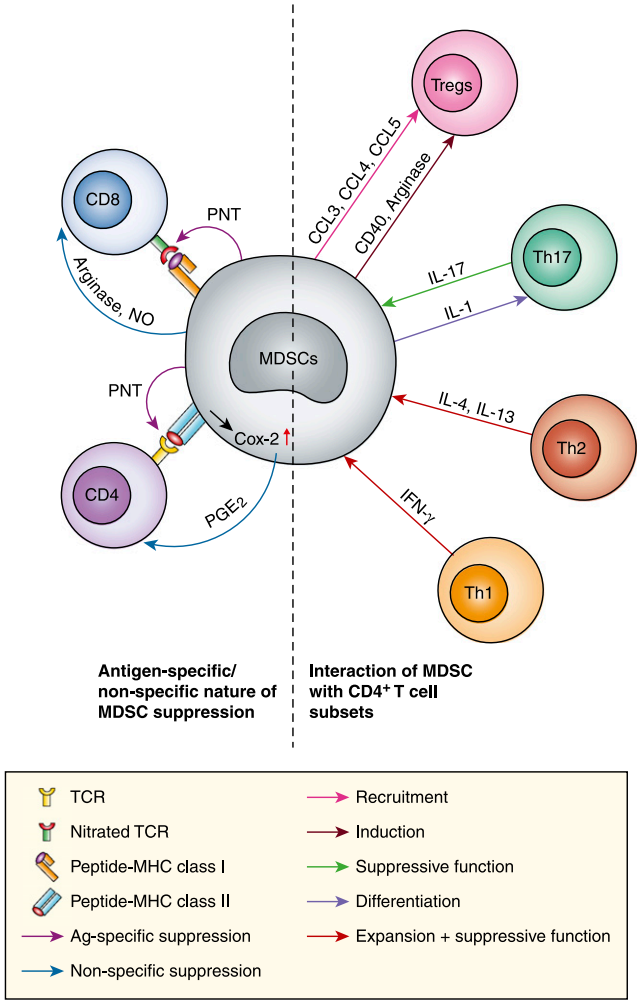

FIGURE 1. Complex interaction between MDSCs and different populations of T cells.

TLR7 was shown to modulate the accumulation of MDSCs during influenza A virus infections in mice. A lack of TLR7 signaling led to a Th2-biased response and an accumulation of MDSCs in the lungs (40). Trauma induced STAT6-dependent MDSC accumulation in spleens. This process was dependent on Th2-type cytokine release (41). Taken together, these data suggest that in contrast to Th1 cells, Th2 cells are directly involved in the expansion and activation of MDSCs, apparently via STAT6 (Fig. 1). The exact role of the specific cytokines (IL-4, IL-13, or others) and the molecular pathways responsible for this phenomenon remain to be elucidated.

Interaction between MDSCs and Tregs

The interaction between MDSCs and Tregs in cancer is well documented. In an initial study, Huang et al. (42) showed that Gr-1$^+$CD115$^+$F4/80$^+$ MDSCs induced the expansion of Foxp3$^+$CD25$^+$ Tregs in vitro. Additionally, the adoptive transfer of CD115$^+$Gr-1$^+$ MDSCs induced IL-10– and IFN-γ–dependent Foxp3$^+$CD25$^+$ Tregs in vivo and suppressed the antitumor response in a mouse colon carcinoma model (42). Another study from the same group demonstrated that CD40 expression by MDSCs was required for MDSC-mediated Treg induction and tolerance (43). The Lewis lung cancer model showed increased MDSC and Foxp3$^+$ Treg accumulation in the tumor tissue. After in vivo depletion of MDSCs, the number of tumor-infiltrating Tregs was significantly decreased, and this reduced tumor growth and prolonged survival of tumor-bearing mice (44). The Arg1-dependent induction of Tregs by MDSCs was found in a B cell lymphoma model (45). MDSCs may attract Tregs via various chemokines. Tumor-infiltrating M-MDSCs had significantly higher levels of CCL3, CCL4, and CCL5 as compared with the other subsets of MDSCs in lymphoma-bearing mice. Tregs from CCR5 knockout mice had a diminished ability to migrate toward chemokines secreted by M-MDSCs (46). It was suggested that infiltration of tumors by Tregs could be coordinated by mast cells and MDSCs. One study showed that mast cells could mobilize MDSCs to tumor and induce the production of IL-17 by MDSCs. IL-17 increased the level of CCL18 and CCL22 in tumor microenvironment, which attracted Tregs to tumor (47). Conversely, Treg depletion downregulated the production of IL-10 and the expression of PD-L1 in MDSCs from melanoma-bearing mice and promoted the MDSC conversion into a less immunosuppressive phenotype (48). The depletion of CD4$^+$CD25$^+$ Tregs abrogated the suppression activity of CD80$^+$Gr-1$^+$ MDSCs from mice bearing ovarian carcinoma (49).

There are some data suggesting interaction between MDSCs and Tregs in cancer patients. CD14$^+$HLA-DR$^{-/low}$ MDSCs from hepatocellular carcinoma patients induce functional CD4$^+$CD25$^+$Foxp3$^+$ Tregs when cocultured with autologous T cells. The induction of Tregs was cell contact–dependent and was abrogated when MDSCs and T cells were separated (50).

There are now some indications that MDSCs and Tregs can interact in conditions other than cancer. M-MDSCs accumulated in lungs of mice with evolving experimental allergic airway inflammation were able to downregulate T cell activation, recruit Tregs, and dramatically decrease Ag-induced airway hyperresponsiveness (51). The MDSC-mediated expansion of Tregs and T cell suppression required MHC-dependent Ag presentation in a murine type 1 diabetes model in which the animals received CD4- hemagglutinin-TCR transgenic T cells. A significant reduction in the incidence of diabetes was observed in recipients receiving MDSCs plus influenza hemagglutinin, but not OVA peptide. The protective effects of MDSCs required an induction of anergy in autoreactive T cells and the development of Tregs (52). The administration of MDSCs in mice with pancreatic islet transplants was associated with attenuation of CD8$^+$ T cells in grafts and a marked expansion of Tregs in a B7-H1–dependent manner (53).

Interaction between MDSCs and Th17 cells

The exact contribution of Th17 cells to tumor progression is not clear. Th17 cells were implicated in both tumorigenesis and in the eradication of established tumors. For instance, Th17 cells elicited neovascularization and promoted angiogenesis and tumor growth (54). Increased Th17 cell density within the tumors in patients with hepatocellular carcinoma correlated with microvessel density and poor prognosis (55). In contrast, it was reported that tumor-specific Th17 cells could mediate the destruction of advanced B16 melanoma (56). It appears that Th17 cells may play opposite roles depending on the stage of cancer. It has been shown that

MDSCs could induce Th17 cell polarization from naive $CD4^+$ T cells. The generation of Th17 cells by MDSCs was independent of MDSC/T cell contact but dependent on the cytokines secreted by MDSCs (57). Novitskiy et al. (58) found that the incubation of MDSCs with IL-17 increased the suppressive activity of MDSCs through the upregulation of Arg1, IDO, and cyclooxygenase-2. Consistent with that report, another study showed that MDSCs from IL-$17R^{-/-}$ tumor-bearing mice expressed lower levels of Arg1, matrix metalloproteinase 9, and S100A8/A9 than from wild-type tumor-bearing mice, and they did not have an inhibitory effect on T cell proliferation (59). One study demonstrated rather different results. MDSCs reduced Th17 responses in an HLA-G^+ xenotumor model. HLA-G induced the expansion of MDSCs and formation of the Th2-type cytokine environment rather than Th1 or Th17. However, no data were provided indicating whether those MDSCs were directly involved in the Th17 cytokine profile in the HLA-G^+ tumor model (60).

MDSCs could drive a Th17 response that consequently contributes to the pathogenesis of experimental EAE. MDSCs from mice with EAE promoted Th17 cell differentiation under Th17-polarizing conditions. Th17 cell differentiation was mediated by IL-1 from MDSCs and required an IL-1 receptor on T cells. The depletion of MDSCs by gemcitabine reduced the frequency of Th17 cells in vivo and ameliorated EAE (61). Flagellin-induced MDSCs efficiently suppressed polyclonal T cell proliferation in a dose-dependent manner and substantially dampened released IL-17 protein by Th17 cells (62). However, in a clinical study, a negative correlation between increased circulating MDSCs and Th17 cells was found in the peripheral blood of patients with rheumatoid arthritis (RA). Compared with healthy controls, both the prevalence of circulating MDSCs and plasma Arg1 increased significantly in RA patients. However, no significant difference was observed in the mRNA level of *NOS2* between RA patients and healthy controls. The frequency of Th17 cells in RA patients was significantly higher than in healthy controls but correlated negatively with the frequency of MDSCs and plasma Arg1 (63).

Ag-specific versus nonspecific suppression of T cell responses by MDSCs

The complex nature of interaction between MDSCs and T cells contributed to the controversy associated with the role of Ags in the MDSC-mediated suppression of T cell responses. The fact that MDSCs can inhibit different types of T cell responses is widely accepted. It was demonstrated that MDSCs can inhibit Ag-specific $CD8^+$ or $CD4^+$ T cell responses (42, 64, 65). The suppression of MDSCs was mediated by cell-to-cell contact between MDSCs and T cells (64). Peroxynitrite (PNT) production by MDSCs during direct contact with T cells resulted in the nitration of the TCR and CD8 molecules, which induced conformational changes in these molecules and a loss of binding of the T cells. Ultimately, T cells are rendered nonresponsive to Ag-specific stimulation (66). PNT scavenger completely eliminated the MDSC-induced T cell tolerance, suggesting that ROS, and peroxynitrite in particular, could be responsible for MDSC-mediated $CD8^+$ T cell tolerance. MDSCs are also reported to inhibit nonspecific immune responses. MDSCs from bone marrow or spleen from tumor-bearing mice significantly suppressed CD3/CD28-induced T cell proliferation (67–69). Human prostatic adenocarcinomas were reported to be infiltrated by terminally differentiated unresponsive cytotoxic T lymphocytes (70). A higher presence of nitrotyrosine in prostatic tumor–infiltrating lymphocytes suggested a local production of PNT. Thus, local PNT production could represent one of the important mechanisms by which tumors escape immune response.

The Ag-specific nature of MDSC-mediated immune suppression could be regulated by several factors: the type of MDSC involved, the local microenvironment, the state of T cell activation, and the retrograde signaling provided to MDSCs from T cells.

Type of MDSCs may influence the nature of immune suppression

There is now enough evidence demonstrating that PMN-MDSCs and M-MDSCs use different mechanisms of immune suppression (71). The immunosuppressive activity of M-MDSCs is largely dependent on a high level of production of NO and different immunosuppressive cytokines and intermediates. There is a large body of literature indicating that these cells exert their suppressive activity in an Ag-independent manner (34, 72–74). In contrast, PMN-MDSCs are largely dependent on ROS, which require closer and more prolonged cell–cell contact and which are better provided during Ag-specific interaction (1, 2, 75, 76). This may explain the fact that PMN-MDSCs, in contrast to M-MDSCs, were implicated in Ag-specific T cell suppression. However, the type of MDSCs cannot fully explain the nature of immune suppression because several reports demonstrated that PMN-MDSCs could also inhibit the Ag nonspecific immune responses (74–79).

Local microenvironment may define the nature of immune suppression by MDSCs

Several recent reports have demonstrated that MDSCs may exhibit different activities in peripheral lymphoid organs and in tumor tissues. We found that splenic MDSCs suppress only Ag-specific T cell response, whereas tumor MDSCs exerted a profound suppressive effect on both Ag-specific and nonspecific T cell responses. Splenic MDSCs displayed a significantly higher level of ROS than did tumor MDSCs, whereas tumor MDSCs had much higher levels of NO and Arg1 than did splenic MDSCs (6). A similar phenomenon exists in the peripheral blood and tumor MDSCs from patients with head and neck cancer. The data suggested that the tumor microenvironment converted MDSCs into nonspecific suppressor cells by upregulating Arg1 activity or NO production via HIF-1α (6). Recently Lesokhin et al. also demonstrated that $CD11b^+$ MDSCs (mainly $CCR2^+CD11b^+$ M-MDSCs) from tumor tissues, but not from the spleens, were able to suppress the Ag nonspecific proliferation of $CD8^+$ T cells induced by CD3/CD28 Abs in mouse melanoma model (74).

Activated T cells could be more sensitive to Ag-specific suppression

It was suggested that the state of T cell activation may determine the Ag-specific nature of immune suppression mediated by MDSCs (7). In most of the studies that investigated the nature of $CD8^+$ T cell tolerance induced by MDSCs, T cells were activated by specific peptides. Therefore, this hypothesis needs to be formally tested. However, in recent

study, the nonspecific activation of $CD4^+$ T cells did not affect the Ag-specific suppression of these cells by MDSCs (80).

T cells may change the nature of MDSC-mediated immune suppression

$CD8^+$ T cell tolerance caused by MDSCs was mediated via MHC class I (66). MDSCs could induce Ag-specific $CD4^+$ T cell tolerance via MHC class II (80). Because in most mouse tumor models expression of MHC class II on MDSCs was low (80), this mechanism apparently is operational only in few experimental systems. Similar variability in MHC class II expression was described in some human studies (81–84). This may explain some of the contradictory data regarding the effect of MDSCs on $CD4^+$ T cell function. Ag-specific $CD4^+$ T cells (but not $CD8^+$ T cells) could dramatically enhance the immunosuppressive activity of MDSCs by converting them into powerful nonspecific suppressor cells. This effect was mediated through crosslinking of MHC class II on MDSC with subsequent upregulation of cyclooygenase-2 expression and PGE_2 production by MDSC (80), which were previously implicated in MDSC-mediated immune suppression (85–87). We suggest that activated Ag-specific $CD4^+$ T cells may enhance the immunosuppressive activity of MDSCs and convert these cells into nonspecific suppressors, a mechanism that normally might serve as a negative feedback loop to control hyperactivated immune responses (Fig. 1). In cancer, this mechanism is hijacked by tumor cells and contributes to heightened immune suppression associated with tumor progression.

Conclusions

Recent years have brought understanding that MDSCs may play a critical role in regulation of immune responses, not only in cancer but also in many other pathologic conditions. It is clear that the interaction of MDSCs with T cells is not a one-directional where MDSCs inhibit T cell proliferation, cytokine production, or tumor cell killing. T cells can affect MDSC function in a major way by promoting their expansion and suppressive activity. Many questions regarding the molecular mechanisms of the complex interaction between MDSCs and T cells have remained unanswered. Understanding the nature of this interaction may help to develop more precise targeted therapy for many diseases.

Disclosures

The authors have no financial conflicts of interest.

References

1. Movahedi, K., M. Guilliams, J. Van den Bossche, R. Van den Bergh, C. Gysemans, A. Beschin, P. De Baetselier, and J. A. Van Ginderachter. 2008. Identification of discrete tumor-induced myeloid-derived suppressor cell subpopulations with distinct T cell-suppressive activity. *Blood* 111: 4233–4244.
2. Youn, J. I., S. Nagaraj, M. Collazo, and D. I. Gabrilovich. 2008. Subsets of myeloid-derived suppressor cells in tumor-bearing mice. *J. Immunol.* 181: 5791–5802.
3. Gabrilovich, D. I., S. Ostrand-Rosenberg, and V. Bronte. 2012. Coordinated regulation of myeloid cells by tumours. *Nat. Rev. Immunol.* 12: 253–268.
4. Youn, J.-I., M. Collazo, I. N. Shalova, S. K. Biswas, and D. I. Gabrilovich. 2012. Characterization of the nature of granulocytic myeloid-derived suppressor cells in tumor-bearing mice. *J. Leukoc. Biol.* 91: 167–181.
5. Youn, J. I., V. Kumar, M. Collazo, Y. Nefedova, T. Condamine, P. Cheng, A. Villagra, S. Antonia, J. C. McCaffrey, M. Fishman, et al. 2013. Epigenetic silencing of retinoblastoma gene regulates pathologic differentiation of myeloid cells in cancer. *Nat. Immunol.* 14: 211–220.
6. Corzo, C. A., T. Condamine, L. Lu, M. J. Cotter, J. I. Youn, P. Cheng, H. I. Cho, E. Celis, D. G. Quiceno, T. Padhya, et al. 2010. HIF-1α regulates function and differentiation of myeloid-derived suppressor cells in the tumor microenvironment. *J. Exp. Med.* 207: 2439–2453.
7. Solito, S., V. Bronte, and S. Mandruzzato. 2011. Antigen specificity of immune suppression by myeloid-derived suppressor cells. *J. Leukoc. Biol.* 90: 31–36.
8. Ostrand-Rosenberg, S., and P. Sinha. 2009. Myeloid-derived suppressor cells: linking inflammation and cancer. *J. Immunol.* 182: 4499–4506.
9. Raber, P., A. C. Ochoa, and P. C. Rodríguez. 2012. Metabolism of L-arginine by myeloid-derived suppressor cells in cancer: mechanisms of T cell suppression and therapeutic perspectives. *Immunol. Invest.* 41: 614–634.
10. Monu, N. R., and A. B. Frey. 2012. Myeloid-derived suppressor cells and anti-tumor T cells: a complex relationship. *Immunol. Invest.* 41: 595–613.
11. Dietlin, T. A., F. M. Hofman, B. T. Lund, W. Gilmore, S. A. Stohlman, and R. C. van der Veen. 2007. Mycobacteria-induced $Gr\text{-}1^+$ subsets from distinct myeloid lineages have opposite effects on T cell expansion. *J. Leukoc. Biol.* 81: 1205–1212.
12. Martino, A., E. Badell, V. Abadie, V. Balloy, M. Chignard, M. Y. Mistou, B. Combadière, C. Combadière, and N. Winter. 2010. *Mycobacterium bovis* bacillus Calmette-Guérin vaccination mobilizes innate myeloid-derived suppressor cells restraining in vivo T cell priming via IL-1R-dependent nitric oxide production. *J. Immunol.* 184: 2038–2047.
13. Anthony, D. D., T. Umbleja, J. A. Aberg, M. Kang, K. Medvik, M. M. Lederman, M. G. Peters, M. J. Koziel, and E. T. Overton. 2011. Lower peripheral blood $CD14^+$ monocyte frequency and higher $CD34^+$ progenitor cell frequency are associated with HBV vaccine induced response in HIV infected individuals. *Vaccine* 29: 3558–3563.
14. Goñi, O., P. Alcaide, and M. Fresno. 2002. Immunosuppression during acute *Trypanosoma cruzi* infection: involvement of Ly6G $(Gr1^+)CD11b^+$ immature myeloid suppressor cells. *Int. Immunol.* 14: 1125–1134.
15. Iwata, Y., K. Furuichi, K. Kitagawa, A. Hara, T. Okumura, S. Kokubo, K. Shimizu, N. Sakai, A. Sagara, Y. Kurokawa, et al. 2010. Involvement of $CD11b^+$ $GR\text{-}1^{low}$ cells in autoimmune disorder in MRL-Fas^{lpr} mouse. *Clin. Exp. Nephrol.* 14: 411–417.
16. Delano, M. J., P. O. Scumpia, J. S. Weinstein, D. Coco, S. Nagaraj, K. M. Kelly-Scumpia, K. A. O'Malley, J. L. Wynn, S. Antonenko, S. Z. Al-Quran, et al. 2007. MyD88-dependent expansion of an immature $GR\text{-}1^+CD11b^+$ population induces T cell suppression and Th2 polarization in sepsis. *J. Exp. Med.* 204: 1463–1474.
17. Koike, Y., T. Kanai, K. Saeki, Y. Nakamura, M. Nakano, Y. Mikami, Y. Yamagishi, N. Nakamoto, H. Ebinuma, and T. Hibi. 2012. MyD88-dependent interleukin-10 production from regulatory $CD11b^+Gr\text{-}1^{high}$ cells suppresses development of acute cerulein pancreatitis in mice. *Immunol. Lett.* 148: 172–177.
18. Haile, L. A., R. von Wasielewski, J. Gamrekelashvili, C. Kruger, O. Bachmann, A. M. Westendorf, J. Buer, R. Liblau, M. P. Manns, F. Korangy, and T. F. Greten. 2008. Myeloid-derived suppressor cells in inflammatory bowel disease: a new immunoregulatory pathway. *Gastroenterology* 135: 871–881.e5.
19. Singh, U. P., N. P. Singh, B. Singh, L. J. Hofseth, D. D. Taub, R. L. Price, M. Nagarkatti, and P. S. Nagarkatti. 2012. Role of resveratrol-induced $CD11b^+$ $Gr\text{-}1^+$ myeloid derived suppressor cells (MDSCs) in the reduction of $CXCR3^+$ T cells and amelioration of chronic colitis in $IL\text{-}10^{-/-}$ mice. *Brain Behav. Immun.* 26: 72–82.
20. Bowen, J. L., and J. K. Olson. 2009. Innate immune $CD11b^+Gr\text{-}1^+$ cells, suppressor cells, affect the immune response during Theiler's virus-induced demyelinating disease. *J. Immunol.* 183: 6971–6980.
21. Ioannou, M., T. Alissafi, L. Boon, D. Boumpas, and P. Verginis. 2013. In vivo ablation of plasmacytoid dendritic cells inhibits autoimmunity through expansion of myeloid-derived suppressor cells. *J. Immunol.* 190: 2631–2640.
22. Xia, S., H. Sha, L. Yang, Y. Ji, S. Ostrand-Rosenberg, and L. Qi. 2011. $Gr\text{-}1^+$ $CD11b^+$ myeloid-derived suppressor cells suppress inflammation and promote insulin sensitivity in obesity. *J. Biol. Chem.* 286: 23591–23599.
23. Qu, P., C. Yan, J. S. Blum, R. Kapur, and H. Du. 2011. Myeloid-specific expression of human lysosomal acid lipase corrects malformation and malfunction of myeloid-derived suppressor cells in $lal^{-/-}$ mice. *J. Immunol.* 187: 3854–3866.
24. Cheng, L., J. Wang, X. Li, Q. Xing, P. Du, L. Su, and S. Wang. 2011. Interleukin-6 induces $Gr\text{-}1^+CD11b^+$ myeloid cells to suppress $CD8^+$ T cell-mediated liver injury in mice. *PLoS ONE* 6: e17631.
25. Turnquist, H. R., Z. Zhao, B. R. Rosborough, Q. Liu, A. Castellaneta, K. Isse, Z. Wang, M. Lang, D. B. Stolz, X. X. Zheng, et al. 2011. IL-33 expands suppressive $CD11b^+$ $Gr\text{-}1^{int}$ and regulatory T cells, including $ST2L^+$ $Foxp3^+$ cells, and mediates regulatory T cell-dependent promotion of cardiac allograft survival. *J. Immunol.* 187: 4598–4610.
26. Adeegbe, D., P. Serafini, V. Bronte, A. Zoso, C. Ricordi, and L. Inverardi. 2011. In vivo induction of myeloid suppressor cells and $CD4^+Foxp3^+$ T regulatory cells prolongs skin allograft survival in mice. *Cell Transplant.* 20: 941–954.
27. Billiau, A. D., S. Fevery, O. Rutgeerts, W. Landuyt, and M. Waer. 2003. Transient expansion of $Mac1^+Ly6\text{-}G^+Ly6\text{-}C^+$ early myeloid cells with suppressor activity in spleens of murine radiation marrow chimeras: possible implications for the graft-versus-host and graft-versus-leukemia reactivity of donor lymphocyte infusions. *Blood* 102: 740–748.
28. Highfill, S. L., P. C. Rodriguez, Q. Zhou, C. A. Goetz, B. H. Koehn, R. Veenstra, P. A. Taylor, A. Panoskaltsis-Mortari, J. S. Serody, D. H. Munn, et al. 2010. 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* 116: 5738–5747.
29. Joo, Y. D., S. M. Lee, S. W. Lee, W. S. Lee, S. M. Lee, J. K. Park, I. W. Choi, S. G. Park, I. Choi, and S. K. Seo. 2009. Granulocyte colony-stimulating factor-induced immature myeloid cells inhibit acute graft-versus-host disease lethality through an indoleamine dioxygenase-independent mechanism. *Immunology* 128 (Suppl.): e632–e640.

30. Zhou, Z., D. L. French, G. Ma, S. Eisenstein, Y. Chen, C. M. Divino, G. Keller, S. H. Chen, and P. Y. Pan. 2010. Development and function of myeloid-derived suppressor cells generated from mouse embryonic and hematopoietic stem cells. *Stem Cells* 28: 620–632.
31. Wang, D., Y. Yu, K. Haarberg, J. Fu, K. Kaosaard, S. Nagaraj, C. Anasetti, D. Gabrilovich, and X. Z. Yu. 2013. Dynamic change and impact of myeloid-derived suppressor cells in allogeneic bone marrow transplantation in mice. *Biol. Blood Marrow Transplant.* 19: 692–702.
32. Cai, W., A. Qin, P. Guo, D. Yan, F. Hu, Q. Yang, M. Xu, Y. Fu, J. Zhou, and X. Tang. 2013. Clinical significance and functional studies of myeloid-derived suppressor cells in chronic hepatitis C patients. *J. Clin. Immunol.* 33: 798–808.
33. Gama, L., E. N. Shirk, J. N. Russell, K. I. Carvalho, M. Li, S. E. Queen, J. Kalil, M. C. Zink, J. E. Clements, and E. G. Kallas. 2012. Expansion of a subset of $CD14^{high}CD16^{neg}CCR2^{low/neg}$ monocytes functionally similar to myeloid-derived suppressor cells during SIV and HIV infection. *J. Leukoc. Biol.* 91: 803–816.
34. Qin, A., W. Cai, T. Pan, K. Wu, Q. Yang, N. Wang, Y. Liu, D. Yan, F. Hu, P. Guo, et al. 2013. Expansion of monocytic myeloid-derived suppressor cells dampens T cell function in HIV-1-seropositive individuals. *J. Virol.* 87: 1477–1490.
35. Norris, B. A., L. S. Uebelhoer, H. I. Nakaya, A. A. Price, A. Grakoui, and B. Pulendran. 2013. Chronic but not acute virus infection induces sustained expansion of myeloid suppressor cell numbers that inhibit viral-specific T cell immunity. *Immunity* 38: 309–321.
36. Terabe, M., S. Matsui, J. M. Park, M. Mamura, N. Noben-Trauth, D. D. Donaldson, W. Chen, S. M. Wahl, S. Ledbetter, B. Pratt, et al. 2003. Transforming growth factor-β production and myeloid cells are an effector mechanism through which CD1d-restricted T cells block cytotoxic T lymphocyte-mediated tumor immunosurveillance: abrogation prevents tumor recurrence. *J. Exp. Med.* 198: 1741–1752.
37. DeNardo, D. G., J. B. Barreto, P. Andreu, L. Vasquez, D. Tawfik, N. Kolhatkar, and L. M. Coussens. 2009. $CD4^+$ T cells regulate pulmonary metastasis of mammary carcinomas by enhancing protumor properties of macrophages. *Cancer Cell* 16: 91–102.
38. Cripps, J. G., J. Wang, A. Maria, I. Blumenthal, and J. D. Gorham. 2010. Type 1 T helper cells induce the accumulation of myeloid-derived suppressor cells in the inflamed *Tgfb1* knockout mouse liver. *Hepatology* 52: 1350–1359.
39. Arora, M., S. L. Poe, A. Ray, and P. Ray. 2011. LPS-induced $CD11b^+Gr1^{int}F4/80^+$ regulatory myeloid cells suppress allergen-induced airway inflammation. *Int. Immunopharmacol.* 11: 827–832.
40. Jeisy-Scott, V., W. G. Davis, J. R. Patel, J. B. Bowzard, W. J. Shieh, S. R. Zaki, J. M. Katz, and S. Sambhara. 2011. Increased MDSC accumulation and Th2 biased response to influenza A virus infection in the absence of TLR7 in mice. *PLoS ONE* 6: e25242.
41. Munera, V., P. J. Popovic, J. Bryk, J. Pribis, D. Caba, B. M. Matta, M. Zenati, and J. B. Ochoa. 2010. Stat 6-dependent induction of myeloid derived suppressor cells after physical injury regulates nitric oxide response to endotoxin. *Ann. Surg.* 251: 120–126.
42. Huang, B., P. Y. Pan, Q. Li, A. I. Sato, D. E. Levy, J. Bromberg, C. M. Divino, and S. H. Chen. 2006. $Gr\text{-}1^+CD115^+$ immature myeloid suppressor cells mediate the development of tumor-induced T regulatory cells and T-cell anergy in tumor-bearing host. *Cancer Res.* 66: 1123–1131.
43. Pan, P. Y., G. Ma, K. J. Weber, J. Ozao-Choy, G. Wang, B. Yin, C. M. Divino, and S. H. Chen. 2010. Immune stimulatory receptor CD40 is required for T-cell suppression and T regulatory cell activation mediated by myeloid-derived suppressor cells in cancer. *Cancer Res.* 70: 99–108.
44. Zhang, Y., Q. Liu, M. Zhang, Y. Yu, X. Liu, and X. Cao. 2009. Fas signal promotes lung cancer growth by recruiting myeloid-derived suppressor cells via cancer cell-derived PGE_2. *J. Immunol.* 182: 3801–3808.
45. Serafini, P., S. Mgebroff, K. Noonan, and I. Borrello. 2008. Myeloid-derived suppressor cells promote cross-tolerance in B-cell lymphoma by expanding regulatory T cells. *Cancer Res.* 68: 5439–5449.
46. Schlecker, E., A. Stojanovic, C. Eisen, C. Quack, C. S. Falk, V. Umansky, and A. Cerwenka. 2012. Tumor-infiltrating monocytic myeloid-derived suppressor cells mediate CCR5-dependent recruitment of regulatory T cells favoring tumor growth. *J. Immunol.* 189: 5602–5611.
47. Yang, Z., B. Zhang, D. Li, M. Lv, C. Huang, G. X. Shen, and B. Huang. 2010. Mast cells mobilize myeloid-derived suppressor cells and Treg cells in tumor microenvironment via IL-17 pathway in murine hepatocarcinoma model. *PLoS ONE* 5: e8922.
48. Fujimura, T., S. Ring, V. Umansky, K. Mahnke, and A. H. Enk. 2012. Regulatory T cells stimulate B7-H1 expression in myeloid-derived suppressor cells in ret melanomas. *J. Invest. Dermatol.* 132: 1239–1246.
49. Yang, R., Z. Cai, Y. Zhang, W. H. Yutzy, IV, K. F. Roby, and R. B. Roden. 2006. CD80 in immune suppression by mouse ovarian carcinoma-associated $Gr\text{-}1^+$ $CD11b^+$ myeloid cells. *Cancer Res.* 66: 6807–6815.
50. Hoechst, B., L. A. Ormandy, M. Ballmaier, F. Lehner, C. Krüger, M. P. Manns, T. F. Greten, and F. Korangy. 2008. A new population of myeloid-derived suppressor cells in hepatocellular carcinoma patients induces $CD4^+CD25^+Foxp3^+$ T cells. *Gastroenterology* 135: 234–243.
51. Deshane, J., J. W. Zmijewski, R. Luther, A. Gaggar, R. Deshane, J. F. Lai, X. Xu, M. Spell, K. Estell, C. T. Weaver, et al. 2011. Free radical-producing myeloid-derived regulatory cells: potent activators and suppressors of lung inflammation and airway hyperresponsiveness. *Mucosal Immunol.* 4: 503–518.
52. Yin, B., G. Ma, C. Y. Yen, Z. Zhou, G. X. Wang, C. M. Divino, S. Casares, S. H. Chen, W. C. Yang, and P. Y. Pan. 2010. Myeloid-derived suppressor cells prevent type 1 diabetes in murine models. *J. Immunol.* 185: 5828–5834.
53. Chou, H. S., C. C. Hsieh, R. Charles, L. Wang, T. Wagner, J. J. Fung, S. Qian, and L. L. Lu. 2012. Myeloid-derived suppressor cells protect islet transplants by B7-H1 mediated enhancement of T regulatory cells. *Transplantation* 93: 272–282.
54. Numasaki, M., J. Fukushi, M. Ono, S. K. Narula, P. J. Zavodny, T. Kudo, P. D. Robbins, H. Tahara, and M. T. Lotze. 2003. Interleukin-17 promotes angiogenesis and tumor growth. *Blood* 101: 2620–2627.
55. Zhang, J. P., J. Yan, J. Xu, X. H. Pang, M. S. Chen, L. Li, C. Wu, S. P. Li, and L. Zheng. 2009. Increased intratumoral IL-17-producing cells correlate with poor survival in hepatocellular carcinoma patients. *J. Hepatol.* 50: 980–989.
56. Muranski, P., A. Boni, P. A. Antony, L. Cassard, K. R. Irvine, A. Kaiser, C. M. Paulos, D. C. Palmer, C. E. Touloukian, K. Ptak, et al. 2008. Tumor-specific Th17-polarized cells eradicate large established melanoma. *Blood* 112: 362–373.
57. Chatterjee, S., S. Das, P. Chakraborty, A. Manna, M. Chatterjee, and S. K. Choudhuri. 2013. Myeloid derived suppressor cells (MDSCs) can induce the generation of Th17 response from naive $CD4^+$ T cells. *Immunobiology* 218: 718–724.
58. Novitskiy, S. V., M. W. Pickup, A. E. Gorska, P. Owens, A. Chytil, M. Aakre, H. Wu, Y. Shyr, and H. L. Moses. 2011. TGF-β receptor II loss promotes mammary carcinoma progression by Th17 dependent mechanisms. *Cancer Discov.* 1: 430–441.
59. He, D., H. Li, N. Yusuf, C. A. Elmets, J. Li, J. D. Mountz, and H. Xu. 2010. IL-17 promotes tumor development through the induction of tumor promoting microenvironments at tumor sites and myeloid-derived suppressor cells. *J. Immunol.* 184: 2281–2288.
60. Agaugué, S., E. D. Carosella, and N. Rouas-Freiss. 2011. Role of HLA-G in tumor escape through expansion of myeloid-derived suppressor cells and cytokinic balance in favor of Th2 versus Th1/Th17. *Blood* 117: 7021–7031.
61. Yi, H., C. Guo, X. Yu, D. Zuo, and X. Y. Wang. 2012. Mouse $CD11b^+Gr\text{-}1^+$ myeloid cells can promote Th17 cell differentiation and experimental autoimmune encephalomyelitis. *J. Immunol.* 189: 4295–4304.
62. Rieber, N., A. Brand, A. Hector, U. Graepler-Mainka, M. Ost, I. Schäfer, I. Wecker, D. Neri, A. Wirth, L. Mays, et al. 2013. Flagellin induces myeloid-derived suppressor cells: implications for *Pseudomonas aeruginosa* infection in cystic fibrosis lung disease. *J. Immunol.* 190: 1276–1284.
63. Jiao, Z., S. Hua, W. Wang, H. Wang, J. Gao, and X. Wang. 2013. Increased circulating myeloid-derived suppressor cells correlated negatively with Th17 cells in patients with rheumatoid arthritis. *Scand. J. Rheumatol.* 42: 85–90.
64. Gabrilovich, D. I., M. P. Velders, E. M. Sotomayor, and W. M. Kast. 2001. Mechanism of immune dysfunction in cancer mediated by immature $Gr\text{-}1^+$ myeloid cells. *J. Immunol.* 166: 5398–5406.
65. Sinha, P., V. K. Clements, and S. Ostrand-Rosenberg. 2005. Interleukin-13-regulated M2 macrophages in combination with myeloid suppressor cells block immune surveillance against metastasis. *Cancer Res.* 65: 11743–11751.
66. Nagaraj, S., K. Gupta, V. Pisarev, L. Kinarsky, S. Sherman, L. Kang, D. L. Herber, J. Schneck, and D. I. Gabrilovich. 2007. Altered recognition of antigen is a mechanism of $CD8^+$ T cell tolerance in cancer. *Nat. Med.* 13: 828–835.
67. Kusmartsev, S. A., Y. Li, and S.-H. Chen. 2000. $Gr\text{-}1^+$ myeloid cells derived from tumor-bearing mice inhibit primary T cell activation induced through CD3/CD28 costimulation. *J. Immunol.* 165: 779–785.
68. Watanabe, S., K. Deguchi, R. Zheng, H. Tamai, L. X. Wang, P. A. Cohen, and S. Shu. 2008. Tumor-induced $CD11b^+Gr\text{-}1^+$ myeloid cells suppress T cell sensitization in tumor-draining lymph nodes. *J. Immunol.* 181: 3291–3300.
69. Connolly, M. K., J. Mallen-St Clair, A. S. Bedrosian, A. Malhotra, V. Vera, J. Ibrahim, J. Henning, H. L. Pachter, D. Bar-Sagi, A. B. Frey, and G. Miller. 2010. Distinct populations of metastases-enabling myeloid cells expand in the liver of mice harboring invasive and preinvasive intra-abdominal tumor. *J. Leukoc. Biol.* 87: 713–725.
70. Bronte, V., T. Kasic, G. Gri, K. Gallana, G. Borsellino, I. Marigo, L. Battistini, M. Iafrate, T. Prayer-Galetti, F. Pagano, and A. Viola. 2005. Boosting antitumor responses of T lymphocytes infiltrating human prostate cancers. *J. Exp. Med.* 201: 1257–1268.
71. Youn, J. I., and D. I. Gabrilovich. 2010. The biology of myeloid-derived suppressor cells: the blessing and the curse of morphological and functional heterogeneity. *Eur. J. Immunol.* 40: 2969–2975.
72. Nausch, N., I. E. Galani, E. Schlecker, and A. Cerwenka. 2008. Mononuclear myeloid-derived "suppressor" cells express RAE-1 and activate natural killer cells. *Blood* 112: 4080–4089.
73. Cuervo, H., N. A. Guerrero, S. Carbajosa, A. Beschin, P. De Baetselier, N. Gironès, and M. Fresno. 2011. Myeloid-derived suppressor cells infiltrate the heart in acute *Trypanosoma cruzi* infection. *J. Immunol.* 187: 2656–2665.
74. Lesokhin, A. M., T. M. Hohl, S. Kitano, C. Cortez, D. Hirschhorn-Cymerman, F. Avogadri, G. A. Rizzuto, J. J. Lazarus, E. G. Pamer, A. N. Houghton, et al. 2012. Monocytic $CCR2^+$ myeloid-derived suppressor cells promote immune escape by limiting activated CD8 T-cell infiltration into the tumor microenvironment. *Cancer Res.* 72: 876–886.
75. Lechner, M. G., D. J. Liebertz, and A. L. Epstein. 2010. Characterization of cytokine-induced myeloid-derived suppressor cells from normal human peripheral blood mononuclear cells. *J. Immunol.* 185: 2273–2284.
76. Choi, J., B. Suh, Y. O. Ahn, T. M. Kim, J. O. Lee, S. H. Lee, and D. S. Heo. 2012. $CD15^+/CD16^{low}$ human granulocytes from terminal cancer patients: granulocytic myeloid-derived suppressor cells that have suppressive function. *Tumour Biol.* 33: 121–129.
77. Ko, J. S., A. H. Zea, B. I. Rini, J. L. Ireland, P. Elson, P. Cohen, A. Golshayan, P. A. Rayman, L. Wood, J. Garcia, et al. 2009. Sunitinib mediates reversal of myeloid-derived suppressor cell accumulation in renal cell carcinoma patients. *Clin. Cancer Res.* 15: 2148–2157.
78. Raychaudhuri, B., P. Rayman, J. Ireland, J. Ko, B. Rini, E. C. Borden, J. Garcia, M. A. Vogelbaum, and J. Finke. 2011. Myeloid-derived suppressor cell accumulation and function in patients with newly diagnosed glioblastoma. *Neuro-oncol.* 13: 591–599.

79. Ioannou, M., T. Alissafi, I. Lazaridis, G. Deraos, J. Matsoukas, A. Gravanis, V. Mastorodemos, A. Plaitakis, A. Sharpe, D. Boumpas, and P. Verginis. 2012. Crucial role of granulocytic myeloid-derived suppressor cells in the regulation of central nervous system autoimmune disease. *J. Immunol.* 188: 1136–1146.
80. Nagaraj, S., A. Nelson, J. I. Youn, P. Cheng, D. Quiceno, and D. I. Gabrilovich. 2012. Antigen-specific $CD4^+$ T cells regulate function of myeloid-derived suppressor cells in cancer via retrograde MHC class II signaling. *Cancer Res.* 72: 928–938.
81. Poschke, I., D. Mougiakakos, J. Hansson, G. V. Masucci, and R. Kiessling. 2010. Immature immunosuppressive $CD14^+HLA\text{-}DR^{-/low}$ cells in melanoma patients are $Stat3^{hi}$ and overexpress CD80, CD83, and DC-sign. *Cancer Res.* 70: 4335–4345.
82. Filipazzi, P., R. Valenti, V. Huber, L. Pilla, P. Canese, M. Iero, C. Castelli, L. Mariani, G. Parmiani, and L. Rivoltini. 2007. Identification of a new subset of myeloid suppressor cells in peripheral blood of melanoma patients with modulation by a granulocyte-macrophage colony-stimulation factor-based antitumor vaccine. *J. Clin. Oncol.* 25: 2546–2553.
83. Solito, S., E. Falisi, C. M. Diaz-Montero, A. Doni, L. Pinton, A. Rosato, S. Francescato, G. Basso, P. Zanovello, G. Onicescu, et al. 2011. A human promyelocytic-like population is responsible for the immune suppression mediated by myeloid-derived suppressor cells. *Blood* 118: 2254–2265.
84. Zea, A. H., P. C. Rodriguez, M. B. Atkins, C. Hernandez, S. Signoretti, J. Zabaleta, D. McDermott, D. Quiceno, A. Youmans, A. O'Neill, et al. 2005. Arginase-producing myeloid suppressor cells in renal cell carcinoma patients: a mechanism of tumor evasion. *Cancer Res.* 65: 3044–3048.
85. Xiang, X., A. Poliakov, C. Liu, Y. Liu, Z. B. Deng, J. Wang, Z. Cheng, S. V. Shah, G. J. Wang, L. Zhang, et al. 2009. Induction of myeloid-derived suppressor cells by tumor exosomes. *Int. J. Cancer* 124: 2621–2633.
86. Rodriguez, P. C., C. P. Hernandez, D. Quiceno, S. M. Dubinett, J. Zabaleta, J. B. Ochoa, J. Gilbert, and A. C. Ochoa. 2005. Arginase I in myeloid suppressor cells is induced by COX-2 in lung carcinoma. *J. Exp. Med.* 202: 931–939.
87. Donkor, M. K., E. Lahue, T. A. Hoke, L. R. Shafer, U. Coskun, J. C. Solheim, D. Gulen, J. Bishay, and J. E. Talmadge. 2009. Mammary tumor heterogeneity in the expansion of myeloid-derived suppressor cells. *Int. Immunopharmacol.* 9: 937–948.