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Reciprocal relationship between myeloid-derived suppressor cells and T cells

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Abstract

Myeloid-derived suppressor cells (MDSC) 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 MDSC were almost exclusively performed in tumor-bearing mice or cancer patients, in recent years, it became clear that MDSC play a critical role in the regulation of different types of inflammation which are not directly associated with cancer. This review discusses the nature of the complex relationship between MDSC and the different populations of $CD4^+$ T cells.

Myeloid-derived suppressor cells (MDSC) 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 also defined in cancer patients, as well (3). PMN-MDSC consist of relatively immature and pathologically activated neutrophils (4), whereas M-MDSC - pathologically activated inflammatory monocytes. A small proportion of MDSCs is represented by precursors of myeloid cells, with the ability to form colonies in semi-solid medium. It appears that, at least in cancer, M-MDSC may play a central role in the development of immune suppressive myeloid cells. In tumor site, they differentiate to tumor-associated macrophages ($M\Psi$) with potent immune suppressive activity and, in the periphery, may give rise to PMN-MDSC (5, 6). The MDSC phenotype, mechanisms of expansion and the specific mechanisms, by which MDSC exert their suppressive effects, are described in many reviews (3, 7–10). Initial studies of MDSC were, almost exclusively, performed in tumor-bearing mice or cancer patients. Cancer still remains the main focus of MDSC research. However, in recent years, it became increasingly clear that MDSC 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 MDSC with different populations of $CD4^+$ T cells is not a one-way street and goes beyond the simple direct immune suppressive activity of MDSC on T cells. These issues will be discussed in this review.

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Suppressive activity of MDSC 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 non-cancerous inflammation. The priming of mice, with complete Fruend's adjuvant, resulted in an expansion of MDSCs. These cells could, subsequently, be stimulated by activated T cells to produce reactive oxygen species (ROS) and nitric oxide (NO) (11). *M. bovis* bacillus Calmette-Guerin (BCG) vaccination recruited NO producing MDSCs. These cells were unable to kill BCG or the non-pathogenic *M. smegmatis*, and impaired T cell priming in the draining lymph node. The elimination of MDSCs, by all-trans retinoid acid (ATRA), increased the number of IFN-γ-producing $CD4^+$ T cells, after vaccination with BCG (12). In individuals who received Hepatitis B virus (HBV) 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. Oscar Goni et al. found that, during *T. cruzi* infection, suppression was mediated through IFN-γ-dependent NO secretion by MDSCs (14). 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 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 (IBD) model, the repeated transfer of antigen-specific T cells led to an increase in the frequency of nitric oxide synthase 2 (*nos2*) and *arg1*-expressing MDSCs in spleen and intestine. The co-transfer of MDSCs, with specific $CD8^+$ T cells, into mice ameliorated enterocolitis and suggested a direct immune regulatory effect of MDSCs on the induction of IBD by antigen-specific T cells (18). In IBD, 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 central nervous system (CNS). In a Theiler's murine encephalomyelitis virus (TMEV) 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, 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, significantly decreased demyelination, and delayed disease onset through the inhibition of encephalitogenic Th1 and Th17 immune responses (21).

MDSCs were shown to counter pro-inflammatory immune cells in the liver and adipose tissue, during obesity. In obese mice, MDSCs suppressed the proliferation, induced apoptosis of $CD8^+$ T cells and skewed the differentiation of macrophages into insulin-sensitizing, alternatively activated M2 macrophages (22). Lysosomal acid lipase (LAL) cleaves cholesteryl esters and triglycerides to generate free fatty acids and cholesterol in lysosomes. LAL 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 antibody, via inhibition of $CD8^+$ T cells proliferation, and IFN-γ expression (24).

MDSC were implicated in the regulation of immune response, during organ transplantation and graft versus host diseases (GVHD). The data suggested that the expansion of MDSC, 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, after allogeneic bone marrow transplantation (BMT). It was shown that, in minor histocompatibility, mismatched BMT is associated with the accumulation of MDSC in blood, which peaked at week 3 and returned to the physiological level at week 12 (27). MDSC, generated *in vitro* or *in vivo*, alleviated GVHD in murine allogeneic BMT models (28–30). The addition of functional MDSCs to the donor graft alleviated GVHD; whereas, removal of MDSCs *in vivo* exacerbated GVHD. MDSC accumulation positively correlated with the severity of GVHD (31).

Recent reports have also implicated MDSC in viral diseases. Patients with chronic Hepatitis C virus (HCV) showed a significant correlation between the MDSC levels, disease progression, and the patients' response to antiviral therapy. MDSCs suppressed T cell function in an Arg1-dependent manner (32). Human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV) infections induced a population, phenotypically similar to M-MDSC, 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 antigen-nonspecific manners (34). In a recent study, infections, with an acute Armstrong (ARM) or a chronic Clone 13 (C13) strain of the lymphocytic choriomeningitis virus, led to two distinct phases of innate immune response. Seven days after infection, there was an increase in the immune suppressive M-MDSC and PMN-MDSC in lymphoid organs and blood. This expansion was sustained only in the chronic C13 infection; whereas, it occurred only transiently in acute ARM infection (35).

Thus, the role of MDSC, as an important negative regulator of immune responses, is extended beyond cancer and observed in many pathological conditions. Although the immune suppressive activity of MDSC 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 (Figure). Herein, we discuss the interaction between MDSC and specific subsets of $CD4^+$ T cells.

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

In an early study, Terabe et al. demonstrated that MDSC can be activated to produce TGFβ, in response to IL-13 in tumor-bearing mice (36). More recently, in a mammary adenocarcinoma model, IL-4-expressing $CD4^+$ Th2 cells promoted expansion of MDSCs and tumor associated macrophages (TAM). 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. TGFβ1 deficient mice acutely develop liver inflammation caused by Th1 cells. The rapid accumulation of MDSC in TGFβ1 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 MDSCs accumulation (38). In humans, lipopolysaccharide (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 $CD11b^{+}Gr1^{int}F4/80^{+}$ 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). 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 MDSC 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 MDSC, apparently via STAT6 (Figure). The exact role of the specific cytokines (IL-4, IL-13 or others) and the molecular pathways, responsible for this phenomenon, remains to be elucidated.

Interaction between MDSC and regulatory T cells

The interaction between MDSC and Tregs in cancer is well documented. In an initial study, Huang et al showed that $Gr\text{-}1^{+}CD115^{+}F4/80^{+}$ MDSCs induced the expansion of $Foxp3^{+}CD25^{+}$ Tregs *in vitro* (42). In addition, the adoptive transfer of $CD115^{+}Gr\text{-}1^{+}$ 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 MDSCs-mediated Treg induction and tolerance (43). The Lewis lung cancer model showed increased MDSCs and $Foxp3^{+}$ Tregs accumulation in the tumor tissue. After *in vivo* depletion of MDSCs, the number of tumor infiltrating Tregs was significantly decreased and this reduced the 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 to 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 cell and MDSCs. 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, Tregs depletion down-regulated the production of IL-10 and the expression of PD-L1 in MDSCs, from melanoma-bearing mice, and promoted the MDSCs conversion into a less immunosuppressive phenotype (48). The depletion of $CD4^{+}CD25^{+}$ Tregs abrogated the suppression activity of $CD80^{+}Gr\text{-}1^{+}$ MDSCs from mice bearing ovarian carcinoma (49).

There are some data suggesting interaction between MDSC and Tregs in cancer patients. $CD14^{+}$ $HLA\text{-}DR^{-/low}$ MDSCs, from hepatocellular carcinoma patients, induce functional $CD4^{+}CD25^{+}Foxp3^{+}$ Tregs when co-cultured 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 MDSC 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 down-regulate T-cell activation, recruit Tregs, and dramatically decrease antigen-induced airway hyper-responsiveness (51). The MDSCs-mediated expansion of Tregs and T-cell suppression required MHC-dependent antigen presentation in a murine type 1 diabetes model, in which the animals received CD4-HA-

TCR transgenic T cells. A significant reduction in the incidence of diabetes was observed in recipients receiving MDSCs plus influenza hemagglutinin (HA), but not ovalbumin (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 MDSC and Th17 cells

The exact contribution of Th17 cells to tumor progression is not clear. Th17 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 naïve $CD4^+$ T cells. The generation of Th17 cells, by MDSCs, was independent on MDSCs-T cell contact, but dependent on the cytokines secreted by MDSCs (57). Novitskiy et al found that the incubation of MDSCs, with IL-17, increased the suppressive activity of MDSCs through the up-regulation of Arg1, indoleamine 2,3-dioxygenase (IDO), and cyclooxygenase (COX)-2 (58). Consistent with that report, another study showed that MDSCs, from IL-$17R^{-/-}$ tumor-bearing mice, expressed lower levels of Arg1, matrix metalloproteinases 9 (MMP9), and S100A8/A9, than from wild type tumor-bearing mice, and did not have an inhibitory effect on T cell proliferation (59). One study demonstrated rather different results. MDSC reduced Th17 responses in an HLA-G^+ xenotumor model. HLA-G induced the expansion of MDSC and formation of the Th2-type cytokine environment rather than Th1 or Th17. However, no data were provided indicating whether those MDSC 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 autoimmune encephalomyelitis (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 of MDSCs and Th17 cells was found in the peripheral blood of patients with rheumatoid arthritis (RA). Compared with healthy controls (HC), 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 HC. The frequency of Th17 cells in RA patients was significantly higher than in HC, but correlated negatively with the frequency of MDSCs and plasma Arg1 (63).

Antigen-specific vs. non-specific suppression of T-cell responses by MDSC

The complex nature of interaction between MDSC and T cells contributed to the controversy associated with the role of antigens in the MDSC mediated suppression of T-cell responses. The fact that MDSC can inhibit different types of T-cell responses is widely accepted. It was demonstrated that MDSC can inhibit antigen-specific $CD8^+$ or $CD4^+$ T-cell responses (64–66). The suppression of MDSC was mediated by cell-to-cell contact between MDSC and T cells (65). Peroxynitrite (PNT) production by MDSCs, during direct contact with T cells,

resulted in the nitration of the T-cell receptor and CD8 molecules, which induced conformational changes in these molecules and a loss of binding of the T cells. Ultimately, T cells are rendered non-responsive to antigen-specific stimulation (67). 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 non-specific immune responses. MDSCs, from BM or spleen from tumor-bearing mice, significantly suppressed the CD3/CD28-induced T cell proliferation (68–70). Human prostatic adenocarcinomas were reported to be infiltrated by terminally differentiated unresponsive cytotoxic T lymphocytes (71). 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 tumor escape immune response.

The antigen-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 MDSC from T cells.

Type of MDSC may influence the nature of immune suppression

There is now enough evidence demonstrating that PMN-MDSC and M-MDSC use different mechanisms of immune suppression (72). The immune suppressive activity of M-MDSC is largely dependent on a high level of production of NO and different immune suppressive cytokines and intermediates. There is a large body of literature indicating that these cells exert their suppressive activity in antigen-independent manner (73–76). In contrast, PMN-MDSC are largely dependent on ROS, which requires closer and more prolonged cell-cell contact, which is be better provided during antigen-specific interaction (1, 2, 77, 78). This may explain the fact that PMN-MDSCs, in contrast to M-MDSCs, were implicated in antigen-specific T-cell suppression. However, the type of MDSCs cannot fully explain the nature of immune suppression since several reports demonstrated that PMN-MDSC could also inhibit the antigen non-specific immune responses (79–81).

Local microenvironment may define the nature of immune suppression by MDSC

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 antigen-specific T cell response; whereas, tumor MDSCs exerted a profound suppressive effect on both antigen-specific and non-specific T cell responses. Splenic MDSCs displayed a significantly higher level of ROS than tumor MDSCs; whereas, tumor MDSCs had much higher levels of NO and Arg1 than 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 non-specific suppressor cells by up-regulating Arg1 activity or NO production via HIF-1α (6). Recently Lesokhin et al also demonstrated that $CD11b^+$ MDSC (mainly $CCR2^+CD11b^+$ M-MDSCs) from tumor tissues, but not from the spleens, were able to suppress the antigen non-specific proliferation of $CD8^+$ T cells, induced by CD3/CD28 antibodies in mouse melanoma model (75).

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

It was suggested that the state of T-cell activation may determine the antigen-specific nature of immune suppression mediated by MDSC (7). In most of the studies that investigated the nature of $CD8^+$ T-cell tolerance induced by MDSC, T cells were activated by specific peptides. Therefore, this hypothesis needs to be formally tested. However, in recent study, the non-specific activation of $CD4^+$ T cells did not affect the antigen-specific suppression of these cells by MDSC (82).

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

$CD8^+$ T-cell tolerance, caused by MDSC was mediated *via* MHC class I (83). MDSC could induce antigen-specific $CD4^+$ T-cell tolerance *via* MHC class II (82). Since, in most mouse tumor models, expression of MHC class II on MDSC was low (82), this mechanism, apparently, is operational only in few experimental systems. Similar variability in MHC class II expression was described in some human studies (84–87). This may explain some of the contradictory data regarding the effect of MDSC on $CD4^+$ T-cell function. Antigen-specific $CD4^+$ T cells (but not $CD8^+$ T cells) could dramatically enhance the immune suppressive activity of MDSC, by converting them into powerful non-specific suppressor cells. This effect was mediated through cross-linking of MHC class II on MDSC with subsequent up-regulation of Cox-2 expression and prostaglandin E2 production by MDSC (82), which were previously implicated in MDSC mediated immune suppression (88–90). We suggest that activated antigen-specific $CD4^+$ T cells may enhance the immune suppressive activity of MDSC and convert these cells into non-specific suppressors, a mechanism that normally might serve as a negative feedback loop to control hyperactivated immune responses (Figure). 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 MDSC 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 MDSC with T cells is not a one-way street, where MDSC 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 MDSC and T cells have remained unanswered. Understanding of the nature of this interaction may help to develop more precise targeted therapy for many diseases.

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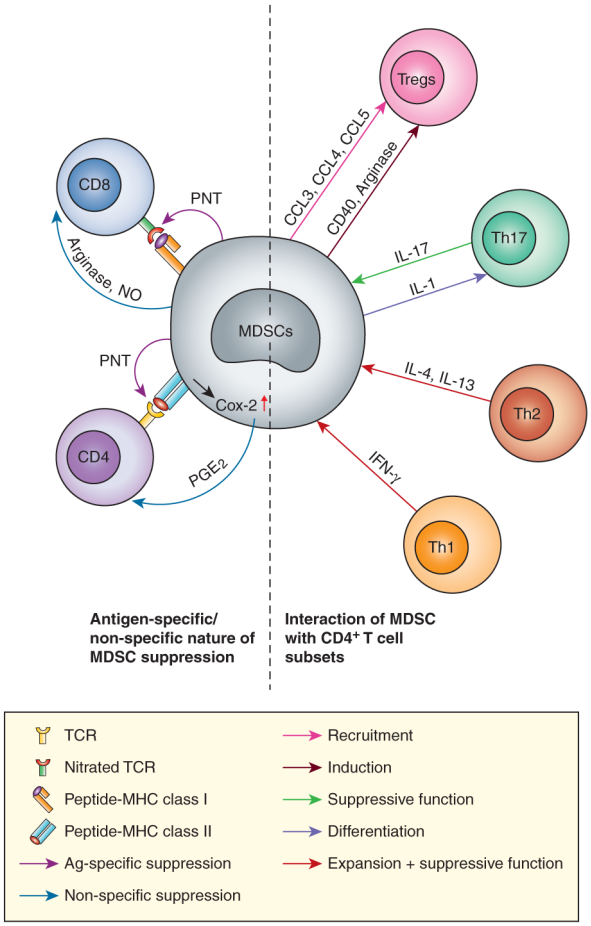

Figure. Complex interaction between MDSC and different populations of T cells
See description in the text.