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Myeloid-derived suppressor cells in transplantation and cancer

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Abstract

Myeloid-derived suppressor cells (MDSC) are myeloid cells that suppress the immune response, a definition that reflects both their origin and their function. As negative regulators of the immune response, MDSC represent a novel therapeutic approach for manipulating the immune system toward tolerance or immunity. MDSC are present in cancer patients and tumor-bearing mice and are in part responsible for the inhibition of the cell-mediated immune response against the tumor. Our laboratories investigate the immunologic mechanisms of tumor acceptance mediated by MDSC, which can be exploited to prevent allograft rejection in transplantation. A better understanding of MDSC biology will open new avenues for therapeutic intervention, either by inhibiting their function (i.e. in cancer patients), or by enhancing their suppressive effects and promoting their expansion (i.e. in organ transplantation and alloimmune responses). In this review, we summarize some of the critical aspects of the immunoregulatory function of MDSC in cancer and transplantation and discuss their potential clinical applications.

Keywords

MDSC; Transplantation; Cancer

Introduction

Progressive tumor development is normally accompanied by defects in the immune system in the form of immunosuppression [1], which is mediated by the activation of suppressor cells induced by a growing tumor [2]. While there is considerable interest in defining alterations in the immune system that precede tumor growth and their development, little is known about the suppressive mechanisms that protect the solid tumor from the immune response. Myeloid cells with specific inhibitory activity have emerged as negative regulators of the immune response, and the term myeloid-derived suppressor cells (MDSC) has recently been proposed to define cells of myeloid origin with suppressor function [3].

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Although initially described in cancer patients, MDSC are also present in other inflammatory settings including solid organ transplantation. Pioneer studies from Bernard Vanhove demonstrated that transplantation tolerance is dependent on MDSC that accumulate in the allografts of tolerant recipients [4]. Since MDSC are in part responsible for protecting tumors against rejection despite the recognition of tumor-associated antigens, we hypothesize that a better understanding of the immunologic mechanisms of tumor acceptance mediated by MDSC can provide critical information to prevent allograft rejection in transplantation. Indeed, Argyris [5, 6] suggested that spleen cells from tumor-bearing mice secreted a "suppressor factor," which could be used to prolong skin allograft survival. Further, Muller and colleagues prolonged graft survival by transferring spleen cells from tumor-bearing mice into skin transplant recipients [7]. However, while there is an increasing interest in developing MDSC as a cell-based therapy, several concerns need to be addressed before MDSC can be taken into the clinic. Before proposing therapeutic targeting of MDSC, we must understand the mechanisms by which specific MDSC subsets mediate their suppressive function and their inhibitory effect. Here, we discuss the immune regulatory function of MDSC and comment on the similarities of MDSC in tumor-bearing mice, cancer patients, and transplant recipients.

MDSC subsets

A major concern regarding MDSC is the difficulty to define their specific lineage. The term MDSC describes their origin and function and includes a morphologically and functionally heterogeneous population of myeloid progenitor cells, dendritic cells (DC), and immature myeloid cells (IMC) at different stages of differentiation [8]. Given the wide range of cell types that may be included in this category, finding a phenotypic profile that characterizes all of them has been a difficult task (Table 1). In mice, all MDSC express the cell surface markers $CD11b^{+}Gr\text{-}1^{+}$ [9, 10]. CD11b is a subunit of the b2 integrin Mac-1, which is expressed in granulocytes, DC, monocytes, and macrophages, and regulates leukocyte adhesion and cell migration. The Gr-1 antigen is predominantly expressed on the surface of monocytes/macrophages and granulocytes and is recognized by the RB6-8C5 antibody, which binds to the cell surface molecules Ly6C and Ly6G [11]. The expression of Gr-1 antigen (Ly6C/Ly6G) and nuclear morphology have been used to characterize two major populations of MDSC: granulocytic MDSC (G-MDSC) expressing $CD11b^{+}$ $Ly6G^{+}$ $Ly6C^{int}$ $CD115^{lo}$, and monocytic MDSC (M-MDSC) expressing $CD11b^{+}$ $Ly6G^{-}$ $Ly6C^{+}$ $CD115^{+}$ [12–14]. In addition to Gr-1 and CD11b, other markers have been used to characterize specific subsets of MDSC. In tumor-bearing mice, $Gr\text{-}1^{+}$ $CD11b^{+}$ cells also express the immature myeloid antigens CD31 and ER-MP58 [9, 15]. Additional markers related to their suppressive function, activation or developmental stage include CD80, CD40, PD-L1, the cytokine receptor CD124 (alpha chain of IL-4 and IL-13 receptors), CD49d, F4/80, CD16/32, low expression of MHC class II and CD11c [12, 16–20]. Based on these cell surface molecules, the presence of MDSC in transplant recipient mice has been described [21–26]. However, the specific contribution of monocytic and granulocytic MDSC that develops in transplant recipients remains. Using CD11b, Ly6C, and Ly6G, our laboratories have identified different populations of MDSC. At least four different populations of myeloid cells with potential suppressive function can be identified by flow cytometry, which

include $Ly6G^{-}$ $Ly6C^{hi}$, $Ly6G^{-}$ $Ly6C^{lo}$, $Ly6G^{-}Ly6C^{int}$, and $Ly6G^{+}$ $Ly6C^{int}$ populations (Fig. 1).

It is important to clarify that the presence of myeloid cells expressing $CD11b^{+}Gr\text{-}1^{+}$ is not necessarily detrimental. Under steady-state conditions, $CD11b^{+}$ $Gr\text{-}1^{+}$ cells account for 20–30 % of bone marrow cells and 2–4 % of splenocytes, and these cells are not suppressive [8]. Therefore, before different myeloid subsets may be identified as MDSC, the specific suppressive function of these subpopulations must be investigated.

Unlike mouse MDSC, the human counterpart does not have a universal marker and their phenotype is less well defined. Both monocytic and granulocytic human MDSC express CD33 and CD11b [27]. M-MDSC are characterized by their additional expression of CD14+ and low/negative levels of HLA-DR [28–30], while G-MDSC express higher levels of CD15 [14, 31]. Other common markers include CD66b and VEGFR1 [32, 33], and CD34 in agreement with the immature phenotype of MDSC [34, 35]. More recently, it has been reported that the suppressive activity of human MDSC resides in a $CD11b^{lo}$ $CD16^{-}$ bone marrow myeloid cell population [36]. In transplantation, the presence of MDSC in human recipients has not yet been reported.

Suppressive mechanisms of MDSC

The most important function of MDSC is to inhibit the cytotoxic response mediated by T lymphocytes and NK cells [37–39]. G-MDSC and M-MDSC differ in their ability to suppress T-cell responses. Data from Dmitry Gabrilovich's laboratory demonstrated that tumor-derived G-MDSC inhibit T-cell responses though reactive oxygen species (ROS) [22, 25]. In addition, data from our laboratory and Vincenzo Bronte's laboratory demonstrated that M-MDSC inhibit T-cell responses through depletion of L-arginine, via both arginase-1 and iNOS [12, 19, 40, 41]. In transplantation, the critical role of iNOS was demonstrated by blocking iNOS with aminoguanidine in vivo, which resulted in rapid rejection of all kidney donor allografts in long-term tolerant recipients (>120 days post-transplant) [4]. Interestingly, production of iNOS in the transplanted allograft may be triggered in an antigen-specific manner. Otto and colleagues demonstrated that macrophages that accumulate in non-vascularized allografts produce iNOS following contact with antigen-specific CD4 T cells, in comparison with syngeneic control grafts [42]. In addition to the direct inhibitory effects of iNOS, large amounts of NO can also react with superoxide anion to form peroxynitrite, which is highly toxic [43]. In a tumor model, it has been shown that peroxynitrite alters the peptide recognition ability of T-cell receptor, so that T cells no longer respond to a specific antigen, providing a mechanism of tumor evasion [44]. Data from our laboratories indicated that MDSC are required for the induction of graft tolerance though iNOS-dependent mechanisms [24] and that IL-10 but not iNOS, is required for tumor tolerance and Treg induction [12]. Using recipient transgenic mice in which tolerance cannot be induced due to their deficiency in numbers of $Gr1^{+}$-expressing myeloid cells [45], we were able to induce tolerance following adoptive transfer of $Gr1^{+}$ myeloid precursors from the bone marrow under CD40 ligand blockade. However, $Gr1^{+}$ myeloid precursors from iNOS- or STAT-1-deficient mice failed to induce tolerance when adoptively

transferred. This suggests a critical role for IFN-γ signaling in the induction of MDSC-mediated transplantation tolerance (Fig. 2).

In addition to directly suppressing the immune response, MDSC have indirect mechanisms for actively suppressing T-cell-mediated cytotoxicity. Our groups have demonstrated that MDSC mediate the development of regulatory T cells (Treg) that suppress T-cell responses against tumor and transplanted grafts [12, 24, 44]. MDSC-dependent development of Treg seems to be mediated through IFN-γ-dependent pathways [24]. Although the protective role of IFN-γ in transplantation tolerance remains controversial, accumulating evidence indicates that a functioning IFN-γ signaling pathway is necessary to achieve indefinite allograft survival. Transplantation tolerance is not induced in IFN-γ-deficient recipient mice due to an exaggerated expansion of alloreactive effector T lymphocytes [46]. These tolerogenic effects of IFN-γ occur within the allograft, which may explain the necessity for M-MDSC cells in this anatomic compartment. In further support of the tolerogenic effects of IFN-γ at the transplanted site, it has been reported that IFN-γ and NO synthase gene expression are upregulated in infiltrating cells of tolerated heart allografts [47], which is associated with Treg cell development at the transplanted site [48]. Consistent with this finding, Kathryn Wood and colleagues demonstrated that development of alloantigen reactive Treg is impaired in the absence of IFN-γ and iNOS within the allograft [49]. Therefore, expression of IFN-γ and iNOS in the transplanted graft precedes Treg development and the induction of transplantation tolerance. Supporting this hypothesis, Vanhove and colleagues reported that iNOS-expressing MDSC stimulate IFN-γ secretion in Treg and are necessary for indefinite allograft survival [4]. However, we should clarify that the precise mechanism by which iNOS mediates Treg development has not yet been reported. It is possible that iNOS expression by MDSC may be selectively causing effector T-cell death, thus indirectly promoting Treg survival. On the other hand, we have shown that MDSC-mediated development of antigen-specific Treg in tumor-bearing mice requires IL-10, IL-4R, and arginase but not iNOS [12, 50].

MDSC development and therapeutic applications

Myeloid-derived suppressor cells develop under acute and chronic inflammatory conditions. In a mouse model of inflammation, acute-phase proteins were shown to mediate the development of MDSC in a STAT-3-dependent manner [51]. In a mouse model of chronic inflammation, Wang and colleagues demonstrated that the pro-inflammatory cytokine IL1-β activates MDSC that accumulate in the stomach of gastric tumor-bearing mice though NF-KB signaling pathways [52]. In transplantation, the ischemic donor allograft and the surgical procedure during engraftment induces various inflammation signaling processes that mediate the mobilization of bone marrow $CD11b^{+}Gr\text{-}1^{+}$ cells [24]. Therefore, cytokines and soluble factors that are associated with inflammatory responses through signaling pathways such as NF-κB, JAK, and STAT control the survival, proliferation, and differentiation of MDSC. It has become clear that the suppressive activity of MDSC requires not only factors that promote their expansion, but also factors that activate MDSC. These factors include inflammatory cytokines (e.g. IL-1β, IL-12, TNF-α, and IFN-γ), ligands of Toll-like receptors, and complement (C5a), which are produced by activated T cells, tumor stromal cells, or as a result of tumor cell death [13, 19, 53–57]. On the other hand, anti-inflammatory

cytokines (e.g. IL-10, IL-4, IL-13, IL-6, and TGF-β) can activate MDSC to mediate immune suppression. Additional factors that are involved in the development of MDSC include M-CSF, GM-CSF, G-CSF, SCF, S100A8/A9, PGE2, COX-2, and TSLP1 [58–64]. Activation of M-MDSC by these factors leads to the signaling of various pathways in differentiation of MDSC as summarized in Fig. 3.

Interleukins are involved in the development of MDSC. IL-1β increases ROS expression in MDSC, which enhances their suppressive activity [65–67], and promotes the secretion of IL-10 and IL-12 in the tumor environment [68]. In addition, signaling though IL-4 or IL-13 was shown to increase arginase-1 expression and the activation of MDSC [53, 69]. In transplantation, it has been reported that IL-13 in combination with G-CSF and GM-CSF generates MDSC expressing high levels of arginase-1 that inhibit graft versus host disease (GvHD) [70]. This is consistent with previous observations which demonstrated that IL-13 prolongs cardiac graft survival [71]. More recently, Thomson and colleagues have reported that IL-33 expands splenic MDSC expressing intermediate levels of Gr-1 and F4/80 that potently inhibit allogeneic T-cell responses and prolong graft survival [72]. In addition, IL-6-induced C/EBP beta transcription factor was shown to be critical for the induction of MDSC suppressive activity and, in combination with GM-CSF, generated MDSC that induced tolerance to islet allografts [73].

Prostaglandin E2 (PGE2) and cyclooxygenase-2 (COX-2) are inflammatory mediators produced by different tumors [74–76]. Cyclooxygenase (COX) 2 is the inducible isoform of rate-limiting enzymes involved in the synthesis of PGE2. PGE2 upregulates arginase-1 levels and suppressive activity in human MDSC [77], while blockade of COX-2 in bone marrow cell cultures prevents the development of MDSC [78]. Therefore, elevated levels of PGE2 promote tumor progression through non-immune mechanisms and through the induction of MDSC expansion that inhibits antitumor immunity [61, 62, 79]. Recent studies suggest that tumor-infiltrated MDSC frequently exhibit upregulated COX-2 expression and have enhanced PGE2 metabolism. These changes can skew GM-CSF-driven differentiation of M1-oriented myeloid APCs into M2-oriented arginase-expressing macrophages in the tumor microenvironment. Tumors impair intracellular PGE2 catabolism in myeloid cells through simultaneous stimulation of PGE2-forming enzyme, and inhibition of PGE2-degrading systems could be the potential mechanism for MDSC activation [78]. The proper control of MDSC differentiation may play an important role in how MDSC are able to modulate the immune response. In transplantation, upregulation of PEG2 is associated with prolonged skin allograft survival [80]. The positive feedback between COX-2 and PGE2 highlights a potential mechanism for the development of MDSC to manipulate immune responses in cancer and transplantation [81]. Since COX-2 blockade inhibits MDSC development and prevents tumor development [82], specific COX-2 blockade by celecoxib reduces the levels of PGE2 in vivo and prevents the expansion of MDSC [83]. Other strategies aim at blocking PGE2 production using COX-2 inhibitors, which reduce the expansion of MDSC [84] and inhibit tumor growth in mice [62].

Growth factors are also involved in the development of MDSC. Vascular endothelial growth factor (VEGF) is secreted by many tumors and mediates the formation and maintenance of vasculature. In addition to its well-characterized role in angiogenesis, VEGF inhibits

dendritic cell differentiation and promotes the accumulation of functional MDSC [58, 85, 86]. MDSC accumulation depends on VEGFR2 [87], which is increased following GM-CSF production [88]. HIF-1α is transcriptional factor involved in VEGF expression and regulates the development of MDSC [89]. In transplantation, hypoxia-induced VEGF enhances engraftment and prolongs islet allograft survival [90, 91]. Anti-VEGF treatment has shown promising results in tumor-bearing mice by reducing MDSC accumulation and preventing T-cell anergy and Treg development [92]. In addition, our laboratory has demonstrated that MDSC can be efficiently generated in vitro from ES cells or hematopoietic stem cells (HSC) in the presence of FLT3 ligand and VEGF that are able to prevent GvHD [93].

Inhibition of the paired immunoglobulin-like receptor B (PIR-B), also known as leukocyte immunoglobulin-like receptor subfamily B member 3 (LILRB3), prevents MDSC differentiation. MDSC genetically ablated for PIR-B (Lilrb3−/−) underwent a specific transition to M1-like cells when entering the periphery from bone marrow, resulting in decreased suppressive function, regulatory T-cell activation activity, primary tumor growth, and lung metastases. Activation of Toll-like receptor (TLR), signal transducers and activator of transcription 1 (STAT1), and nuclear factor-kappa B (NF-κB) signaling in Lilrb3−/−MDSC promoted the acquisition of an M1 phenotype [94]. In transplantation, MDSC can be generated in vitro using immunoglobulin-like transcript 2 (ILT2) to promote long-term allograft survival to skin allografts [26].

Final remarks

MDSC develop from bone marrow myeloid progenitors conditioned by tumor-derived cytokines and soluble factors, express the surface markers CD11b and Gr-1, and inhibit T-lymphocyte proliferation in cancer patients and tumor-bearing mice [95]. The understanding of MDSC development in tumor models provides an important means by which to control undesirable immune responses against transplant allografts. Bertie Argyris isolated a “suppressor factor” secreted from the spleen cells of tumor-bearing mice that was able to prolong skin allograft survival [5, 6]. More recently, Vinvenzo Bronte and our laboratory reported that adoptive transfer of MDSC was able to induce tolerance to autoimmune T cells against islet antigen, islet allograft and prevent graft versus host disease in bone marrow-transplanted mice [50, 73, 93]. Overall, these studies suggest that MDSC can be used as a cell-based therapy to prevent T-cell-mediated allograft rejection.

Different types of MDSC can be generated in vitro from mouse bone marrow in the presence of specific cytokines and growth factors [96, 97] and conditioned media [78, 98]. In addition, subsets of MDSC including monocytic ($Ly6G^{-}Ly6C^{+}$ $CD115^{+}$) and granulocytic ($Ly6G^{+}$ $Ly6C^{Int}$ $CD115^{-}$) MDSC, generated from mouse embryonic stem (ES) cells and hematopoietic stem cells, suppress T-cell proliferation by IL-10 and NO production [93]. However, the specific proportions and suppressive functions of varying MDSC subsets generated in vitro remain to be characterized. In addition, the similarities and differences between the different types of MDSC generated using different protocols, and the relationship between MDSC and other types of myeloid regulatory cells such as tumor-associated macrophages, alternatively activated macrophages (M2), or immature myeloid DC need to be fully established using specific cell markers and functional assays. In the

tumor microenvironment, TAM constitute the majority of tumor-infiltrating leukocytes. Two distinct TAM subpopulations have been defined. Classical or M1 macrophages are characterized by the expression of high amounts of iNOS and TNF-α, whereas alternatively activated M2 macrophages typically produce arginase-1 and IL-10 [18]. At the tumor site, TAM are predominantly M2-like macrophages, which are primarily responsible for suppressing T-cell-mediated antitumor responses and promoting tumor progression, metastasis, and angiogenesis [99–102], while M1 macrophages exhibit a tumoricidal effect [55, 56, 94, 103]. M1-like MDSC express CCR7, MHC class II, CD86, and iNOS, while M2-like MDSC express the mannose receptor (CD206) and IL-10 [104]. In addition, tumor-associated neutrophils (TAN) expressing $CD11b^{+}Ly6G^{+}$ have also been described in tumor-bearing mice [105]. In transplantation, lacto-N-fucopentaose III promotes the development of macrophages with high levels of PD-L1 that prolongs graft survival of both vascularized and non-vascularized allografts [106]. Lacto-N-fucopentaose III induces M2 macrophages that express high levels of arginase-1 and produce high levels of IL-10 and TGF-β [107]. In addition, since NO and ROS production are IFN-γ dependent [108, 109], blocking IFN-γ using neutralizing antibodies or disrupting IFN-γ pathway signaling using STAT1-deficient mice abolishes MDSC-mediated T-cell suppression [13]. Geissler and colleagues recently reported that differentiation of monocytes in the presence of IFN-γ results in the development of suppressive macrophages in vivo with T-cell suppressive function [110]. Similar results have been obtained with human cells in vitro, in which IFN-γ-mediated development of tolerogenic DCs from blood monocytes leads to the ability to promote Treg development [111]. More recently, the ONE study (a multinational clinical trial of immunomodulatory cell therapy in renal transplantation) demonstrated the clinical application of IFN-γ-induced regulatory macrophages in human kidney recipients [112]. Therefore, the efficacy of MDSC generated from a clinically applicable source depends on our ability to generate specific suppressive cell subsets, and their manipulation represents a novel therapeutic approach to achieving tolerance or immunity in the clinic. Furthermore, MDSC trafficking to the site of inflammation through chemokine-mediated migration may provide a potential tool for using MDSC to deliver therapeutic agents to these sites for immune suppression or tumor targeting or to prolong graft survival [113]. These concerns must be addressed before taking MDSC into the clinic.

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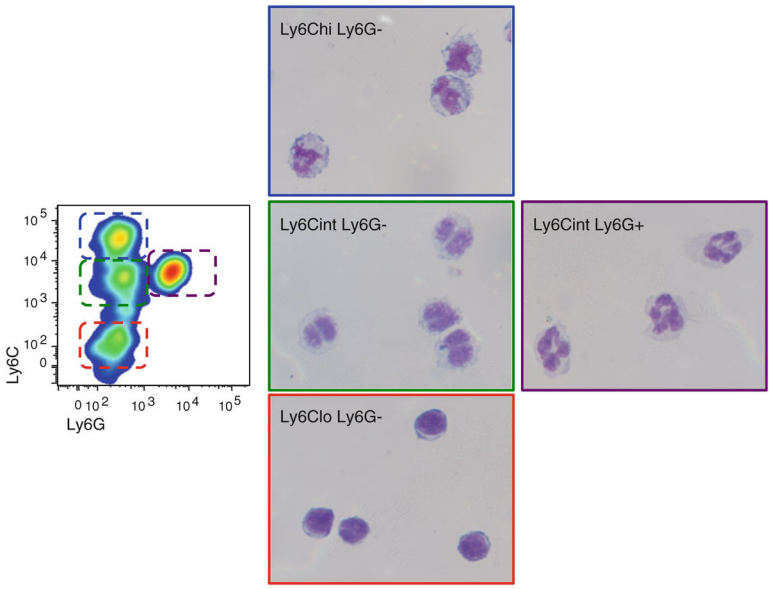

Fig. 1.

MDSC subsets. Cytospin preparations of CD11b-expressing Ly6C^{hi} Ly6G^{-}, Ly6C^{int} Ly6G^{-}, Ly-6C^{lo} Ly6G^{-}, and Ly6C^{int} Ly6G^{+} myeloid cells from tolerant allografts

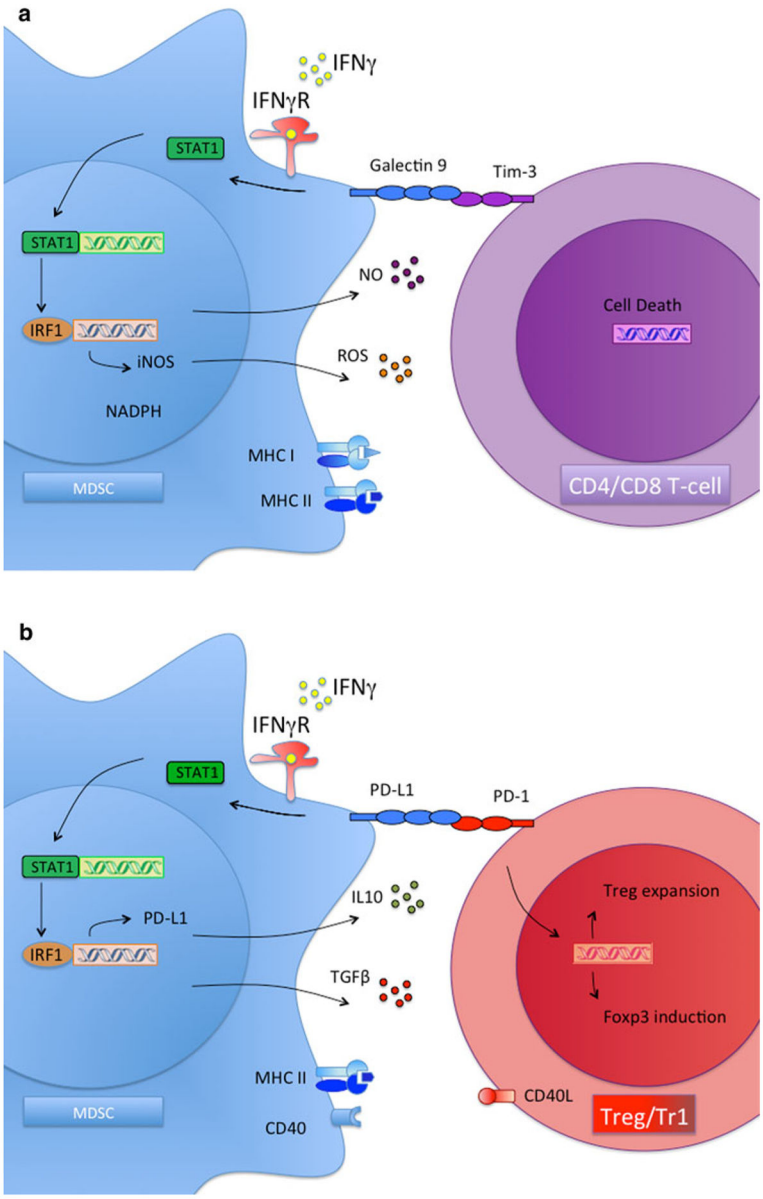

Fig. 2.

Suppressive mechanisms of MDSC. **a** MDSC-mediated T-cell suppression. IFN-gamma signaling mediates the induction of tolerance mediated by MDSC through activating STAT-1-dependent pathways, including iNOS activation and ROS production. **b** MDSC-mediated Treg development. IFN-gamma signaling mediates the induction of tolerance mediated by MDSC through activating STAT-1-dependent pathways, including PDL-1 expression and IL-10 plus TGF-β secretion

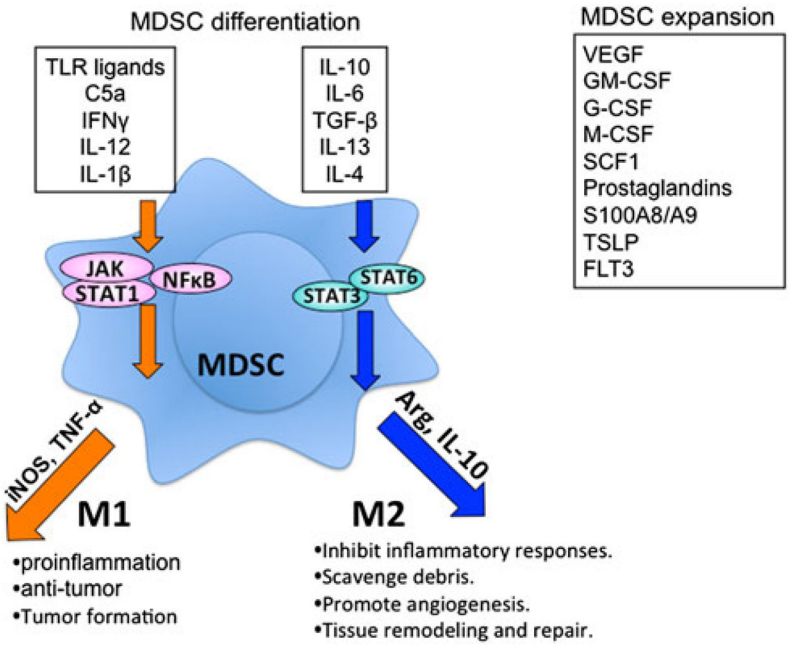

Fig. 3.

M-MDSC activation and differentiation in tumor microenvironment. M-MDSC can differentiate into M1-like phenotype (controlled by TLR ligands, C5a, INFγ, IL-12, and IL-1β), which have antitumor effect through the production of iNOS. Alternatively, M-MDSC can differentiate into M2-like phenotype (controlled by IL-10, IL-6, TGF-β, IL-13, and IL-4), which promotes tumor growth, tissue remodeling and angiogenesis through producing IL-10 and arginase. In addition, the expansion of MDSC population can be controlled by VEGF, GM-CSF, G-CSF, M-CSF, SCF1, prostaglandins, S100A8/A9, and FLT3

Table 1

MDSC subsets

MDSC subset	Cell markers	Reference(s)
Mouse G-MDSC	$CD11b^+$, $Ly6C^{int}$, $Ly6G^+$	[14]
Mouse M-MDSC	$CD11b^+$, $CD115^+$, $Ly6C^+$, $Ly6G^-$	[12–14, 24]
Mouse N1-like MDSC	$CD11b^+$, $Ly6G^+$, $ICAM1^+$, ROS^+, $TNF\alpha^+$	[17]
Mouse N2-like MDSC	$CD11b^+$, $Ly6G^+$, $CCL2^+$, $CCL5^+$, ARG^+	[105]
Mouse M1-like MDSC	$CD11b^+$, $Ly6C^+$, $iNOS^+$, $TNF\alpha^+$, $CCR7^+$, $CXCL10^+$	[18, 104]
Mouse M2-like MDSC	$CD11b^+$, $Ly6C^+$, $F4/80^+$, $CD206^+$, ARG^+, $C124^+$	[94]
Human G-MDSC	$CD11b^+$, $CD33^+$, $CD15^+$	[31]
Human M-MDSC	$CD11b^+$, $CD33^+$, $CD14^+$, $CD16^+$, MHC^{lo}	[29]
Human bone marrow MDSC	$CD11b^{lo}$, $CD16^-$	[36]
Rat MDSC	$CD11b^+$, $NKRP1^+$, $CD172a^+$, $His48^+$, $CD80/86^+$	