EXPERT REVIEWS

The roles of myeloid-derived suppressor cells in transplantation

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$CD11b^+Gr1^+$ myeloid-derived suppressor cells (MDSCs) are an important regulatory innate cell population and have significant inhibitory effect on T cell-mediated responses. In addition to their negative role in cancer development, MDSCs also exert strong regulatory effects on transplantation and autoimmunity. In many transplantation models, such as bone marrow transplant, renal transplant, heart transplant and skin transplant settings, MDSCs accumulate and have inhibitory effect on graft rejection. However, the inducing factors, detailed phenotype and functional molecular mediators of MDSCs are significantly different in various transplant models. With their strong suppressive activity, MDSCs could become a potential clinical therapy during transplantation tolerance induction and the combination of the MDSCs with other immunoregulatory cells or immunosuppressive drugs is an intriguing protocol in the future. In this review, we will summarize MDSC expansion, activation and induction in different transplantation models and discuss the effects of immunoregulatory cells and immunosuppressive drugs on MDSCs in transplant settings.

Keywords: immunosuppressant • myeloid-derived suppressor cells • tolerance • transplantation

Myeloid-derived suppressor cells (MDSCs) were initially reported in solid tumors for their ability to suppress immune responses [1]. Up to now, MDSCs are known to accumulate in various conditions such as infection, inflammation, autoimmunity and transplantation. In mice, MDSCs are defined as $CD11b^+Gr1^+$ cells, and in humans as $Lin^-HLA\text{-}DR^-$, $CD11b^+$ and $CD33^+$ cells, with variable expression of CD14, CD15 and selected other markers. These cells are a highly heterogeneous cell population and consist of hematopoietic cell precursors at various stages of homeostatic differentiation to mature macrophages, dendritic cells and granulocytes [2]. In particular, MDSCs can be divided into at least two groups, monocytic (M-MDSCs) and granulocytic (G-MDSCs). The two subsets are distinguished phenotypically by the presence or absence of CD14 in humans [3] and expression of Ly6C and Ly6G in mice. Functionally, M-MDSCs express high levels of nitric oxide (NO) and low levels of reactive oxygen species (ROS) while G-MDSCs express high levels ofROS and low levels of NO. Both of themexpress arginase 1 (Arg1) [4,5]. MDSC-mediated suppression of T-cell functions via several mechanisms. First, they express high levels of both Arg1 and inducible nitric oxide synthase (iNOS), resulting in depletion of L-arginine in the microenvironments, which is essential for T-cell proliferation [6]. Second, ROS also contributes the immunosuppressive function of MDSCs via catalyzing the nitration of T cell receptor, which consequently inhibits the T-cell-peptide/MHC interaction [7]. Despite iNOS, Arg1 and ROS, other mechanisms involved in MDSC-mediated immunosuppression have been reported. Endotoxin-induced MDSCs inhibit allo-immune responses via heme oxygenase-1 (HO-1) in conjunction with IL-10 [8]. Cancer-expanded MDSCs induce anergy of NK cells through membrane-bound TGF-β1 [9]. In cancer models, MDSCs have also been shown to either express the enzyme indoleamine 2,3 dioxygenase (IDO) themselves [10,11] or induce other cells to express IDO, which reduces local tryptophan and generation of cytotoxic metabolites to block initiation of antigen-specific immune response and antitumor cytotoxicity of activated T cells [12]. Importantly, MDSCs also

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Table 1. Myeloid-derived suppressor cells in different transplantation models.

Species	Models	Phenotype	Inducing factors	Suppressive function	Ref.
Mouse	Irradiation BMT	$CD11b^+Gr1^+$	Induced inflammation	iNOS	[102]
Mouse	Parent-in-F1 BMT	$CD11b^+Gr1^+$	Endogenous expansion	iNOS, Arg1, HO-1	[27]
Human	Allo-HSCT	$CD14^+HLA\text{-}DR^{low/neg}IDO^+$	G-CSF, IL-6	IDO	[29]
Mouse	GVHD	$CD11b^{high}Gr1^{low}$	GCSF/Flt3	IL-10, Treg induction	[31]
Mouse	GVHD	$CD11b^+Gr1^+$	SHIP deficiency	Altered Ag processing	[33]
Mouse	GVHD	$CD11b^+Gr1^+$	G-CSF	IDO-independent	[32]
Mouse	GVHD	$CD11b^+Ly6G^{low}Ly6C^+$	IL-13	Arg1	[20]
Rat	Renal transplant	$CD3^-classII^-CD11b^+$ $CD80/86^+CD172a^+$	Anti-CD28 Ab	iNOS	[35]
Human	Renal transplant	$CD33^+HLA\text{-}DR^-CD11b^+CD14^{+/-}$	?	IL-10, Treg induction	[36]
Human	Renal transplant	$CD33^+HLA\text{-}DR^-CD11b^+$	?	Treg induction and Th17 inhibition	[37]
Mouse	Cardiac transplant	$CD11b^+Gr1^+CD115^+$	Anti-CD40L mAb	iNOS, Treg induction	[40]
Mouse	Cardiac transplant	$CD11b^{hi}Gr1^{intermed}ST2^+$	IL-33	?	[41]
Mouse	Cardiac transplant	$CD11b^+Gr1^{low/int}$	IL-6 deficiency in donor	?	[42]
Mouse	Cardiac transplant	$CD11b^+Gr1^+$	ECDI-SPs	IDO, iNOS	[43]
Mouse	Skin transplant	$CD11b^+Gr1^+$	HLA-G-ILT2	Arg1	[44]
Mouse	Skin transplant	$CD11b^+Gr1^+$	Lipopolysaccharide induction *in vivo*	IL-10, HO-1	[8]
Mouse	Skin transplant	$CD11b^+Gr1^+$	G-CSF and IL-2C	Inhibition of the ζ chain on T cells	[47]
Mouse	Skin transplant	$CD11b^+Gr1^+$	Smad3 deficient	iNOS	[49]
Mouse	Islets transplant	$CD11b^+Gr1^+Ly6C^{hi}$	Hepatic stellate cells co-transplant	iNOS, Arg1, Treg induction	[82]

allo-HSCT: Allogeneic hematopoietic stem cell transplantation; BMT: Bone marrow transplantation; ECDI-SPs: Ethylcarbodiimide; GVHD: Graft-versus-host disease; HO-1: Heme oxygenase-1; IDO: Dioxygenase; iNOS: Inducible nitric oxide synthase; SHIP: Phosphatidylinositol-3,4,5-trisphosphate 5-phosphatase.

impact the attraction and activation of regulatory T-cell (Treg cell) subsets in general, and especially the induction of Treg cells *in vivo* [13,14]. The factors triggering MDSC expansion and activation are well studied in tumor models, including growth factors such as SCF, VEGF, GM-CSF, G-CSF and M-CSF [15]; cytokines such as IFN-γ, IL-1β, IL-6, IL-10, IL-12 and IL-13 [6]; calcium binding proteins S100A8, S100A9 [16], complement component 3 (C3) [17], cyclooxygenase-2 and prostaglandin E2 [18]. However, the factors involved in the accumulation of MDSCs in transplantation tolerance induction still need to be identified.

It is well established that MDSCs exert a local immunosuppressive effect in transplanted organs during induction of tolerance to kidney, cardiac and skin grafts (Table 1). Adoptive transfer of MDSCs, which is induced via CpG and lipopolysaccharide (LPS) *in vitro*, can suppress the pathogenesis of graft-versus-host disease (GVHD) and skin graft rejection *in vivo* [8]. Such protective effects of adoptively transferred MDSCs have also been reported recently for MDSCs generated *in vitro* from embryonic and hematopoietic stem cells [19,20]. Although adoptive transfer experiments have demonstrated that these cells could induce transplantation tolerance *in vivo*, the intrinsic expansion of MDSCs may be more important in clinical therapy. On the other hand, the combination of MDSCs with immunoregulatory cells or immunosuppressive agents has currently become an intriguing therapy regimen in transplanted patients as well as in certain allergic and autoimmune conditions in clinics. Thus, studies on the effect of immunosuppressive cells or drugs on MDSCs will be of clinical significance. Here we try to summarize our recent understanding on the

expansion and activation of MDSCs in transplantation models and to notify the effect of transplantation tolerance induction protocols and immunosuppressive cells or drugs on MDSC biology.

MDSCs in bone marrow transplantation

In the 1980s, MDSCs were found in the spleen of clinical bone marrow transplantation recipients and named 'natural suppressor cells'. These cells significantly inhibited T-cell proliferation under the stimulation of allo-antigens or mitogen [21–24]. In mouse models, accumulation of MDSCs was observed in the blood and spleens of both allogeneic and syngeneic recipient. It is suggested that expansion of MDSCs probably was the result of radiation-induced myelosuppression [21,24]. In fact, total body radiation treatment initiates proinflammatory cytokine release, including IFN-γ, G-CSF and IL-1β, which induce the accumulation and activation of MDSCs [25,26]. Recently, some experiments demonstrated that in nonirradiation models, such as parent-in-F1 mouse models [27,28], MDSC accumulation still occurred and indicated that MDSCs can expand as a physiological bystander phenomenon in the course of bone marrow chimera induction.

In patients who accepted allogeneic hematopoietic stem cell transplantation, $CD14^+HLA\text{-}DR^{low/neg}IDO^+$ M-MDSCs were indentified and inhibited proliferative capacity or CD3ζ-chain expression of T cells in an IDO-dependent way [29]. Allogeneic transplantation will initiate GVHD, and the relationship between GVHD and MDSCs is not fully understood. MDSC mobilization reduced GVHD incidence or severity. An early study found that low incidence of GVHD after transplantation of allogeneic G-peripheral blood mononuclear cells (G-CSF mobilized peripheral blood mononuclear cells) was partially due to mobilization of large portion of immunosuppressive M-MDSCs [30]. These cells inhibited alloreactive T-cell expansion *in vitro* by increasing IL-10 production [31] and inhibited acute GVHD lethality through an IDO-independent mechanism [32]. Kerr *et al.* have linked higher numbers of MDSCs in $SHIP^{-/-}$ recipient mice with reduced GVHD lethality compared with wild-type recipients [33]. Adoptive transfer of IL-13-induced MDSCs into recipients significantly inhibited GVHD lethality via an Arg1-dependent mechanism [20]. These results indicated that MDSCs could regulate GVHD development *in vivo*. More detailed studies investigated the relationship between MDSCs and GVHD development. It is demonstrated that the incidence of GVHD is not necessary for increase of MDSCs but significantly enhances the number and function of MDSCs. Additionally, MDSC accumulation positively correlated with the severity of GVHD [34].

MDSCs in solid organ transplantation

Kidney transplantation

Anti-CD28 monoclonal antibody (mAb)-induced kidney allograft tolerance in rat triggers the accumulation of plastic adherent $CD11b^+CD80/86^+$ MDSCs in the peripheral blood. These cells inhibit alloreactive T-cell proliferation and induce T-cell apoptosis in an iNOS-dependent way. Although adoptive transfer of these MDSCs isolated from the blood or the bone marrow did not significantly prolong kidney allograft survival, they still prevented the proliferation of allogeneic T cells *in vivo* [35]. In humans, $CD11b^+CD33^+HLA\text{-}DR^-$ MDSCs are increased in renal transplanted recipients while the *in vitro* immunosuppressive function is predominantly due to $CD14^+$ M-MDSCs. More importantly, these MDSCs are capable of expanding Treg cells *in vitro*, and their accumulation over time after transplantation linearly correlated with an increase of Treg cells *in vivo* [36]. Recently, clinical significance of MDSCs in renal transplantation with acute T-cell-mediated rejection has been analyzed. Allograft function was significantly increased in patients with high levels of MDSCs in which the percentage of MDSCs in peripheral blood mononuclear cells is over 10. Furthermore, isolated MDSCs from transplanted recipients are capable of expanding Treg cells and inhibiting production of IL-17 *in vitro* [37]. Thus, MDSCs were present in kidney-transplanted recipients and play a protective role in graft rejection. Additionally, renal transplant recipients have a significantly increased risk of cancer. A recent report suggested that residual tumor resection patients have significantly elevated circulating levels of functional $HLA\text{-}DR^-CD3^-CD57^-$ MDSCs and a systemic increase in the circulating MDSC/dendritic cell ratio. MDSCs enriched from renal transplant recipients, when co-cultured with activated normal donor's T cells, significantly suppressed extracellular IL-10 levels and can, when activated with formyl-methionyl-leucyl-phenylalanine, inhibit T-cell proliferation [38]. This suggests that these MDSCs are in fact *in vitro* formyl-methionyl-leucyl-phenylalanine-activated neutrophils, known to process suppressive function [39], rather than MDSCs with inherent inhibitory properties.

Cardiac transplantation

In cardiac rejection models, the costimulatory blockade treatment such as CD40 ligand-specific mAb mobilizes the bone marrow $CD11b^+CD115^+Gr1^+$ M-MDSCs. These cells migrated from the bone marrow into the transplanted organs and prevented the initiation of adaptive immune responses that are dependent on IFN-γR-iNOS signaling. Cell depletion experiments *in vivo* demonstrated that MDSCs are necessary for the induction of indefinite allograft survival [40]. In a chronic cardiac rejection model, IL-33, which induces Th2 cytokines, can significantly prolong the graft survival. After IL-33 treatment, graft-infiltrating $CD11b^{high}Gr1^{high}$ granulocytes decreased and $CD11b^{high}Gr1^{intermediate}$ MDSCs increased. Meanwhile, IL-17A production was decreased and a direct induction of $CD4^+Foxp3^+$ Treg cells was observed [41]. Blockade of IL-6 signal pathway in donors by gene deletion increases infiltration of $CD11b^+Gr1^{low}$ and $CD11b^+Gr1^{int}$ MDSCs with strong immunosuppressive activity in the heart graft [42]. Preemptive infusion of apoptotic donor splenocytes treated with the chemical crosslinker ethylcarbodiimide induced the expansion of MDSCs for cardiac allograft protection. These MDSCs produce a high level of IFN-γ and exhibit an enhanced

responsiveness to IFN-γ by expressing higher levels of downstream effector molecules IDO and iNOS [43].

Skin transplantation

The regulatory role of MDSCs was more significantly demonstrated in skin transplant models than other transplant models. Induced MDSCs *in vitro* or *in vivo* via different methods can effectively prolong the graft survival. Early experiment found that the number and function of MDSCs were significantly enhanced by immunoglobulin-like transcript 2 (ILT2) receptor and its ligands *in vivo* during allo-skin graft transplantation. These ILT2-MDSCs expressed lower levels of MHC class I and higher level of IL-4Rα. Importantly, MDSCs generated by ILT2 receptor and its ligands significantly prolonged allo-skin graft survival in recipient mice [44]. Moreover, transfer LPS-induced MDSCs in untreated recipients also significantly prolonged skin allograft survival. Interestingly, these LPS-induced MDSCs mediate suppression neither via iNOS nor Arg1. They produced large amounts of IL-10 and expressed HO-1, revealing a new MDSCs-associated suppression mechanism relevant for transplantation [8]. Recently, it was reported that *in vivo* co-administration of G-CSF (for MDSCs) [45] and IL-2 complex (IL-2C, for Treg cells) [46] induced more potent MDSCs that prolonged donor skin survival [47]. The increased levels of Treg cells are beneficial for MDSC induction in a pre-sensitized cardiac transplant model [48]. In addition, we found one endogenous factor that regulates MDSCs during skin transplantation. Wu *et al.* demonstrated that Smad3 negatively regulates MDSC development in an allo-skin-grafted mouse model. The enhanced MDSCs in smad3-deficient mice resulted in prolonged allo-skin graft rejection via an NO-dependent pathway [49].

Islet transplantation

Islet transplantation is cellular transplant and immunosuppression always has the side effects outweighing the benefits. Thus, it is crucial to develop immune regulatory cells *in vivo* and avoid intensive immunosuppression. It is reported that allogeneic islets co-transplanted with immunosuppressive hepatic stellate cells (HpSCs) achieve long-term survival in mice via inhibition of T-cell response and marked expansion of Treg cells and MDSCs [50]. HpSC-induced MDSCs *in vitro* expressed high Arg1, iNOS and TGF-β and effectively protects islet allografts via attenuation of T-cell response by enhancement of antigen-specific Treg cells, which was mediated by B7-H1 pathway [14]. Further study demonstrated that iNOS is critical for the immunosuppressive function of HpSCs-induced MDSCs during islet transplantation [51].

MDSCs in xenotransplantation

The role of MDSCs in xenotransplantation is still unclear. The *in vitro* experiment results demonstrated that activated human $CD33^+$ $CD14^+HLA\text{-}DR^-$ MDSCs, derived from peripheral blood monocytes cultured with GM-CSF plus IL-4, dramatically induce apoptosis of xenogeneic cytotoxic T lymphocytes (CTLs) via an IDO-dependent manner and aggressively phagocytose apoptotic CTLs [52]. Thus, MDSCs may have potential as a therapeutic strategy for dealing with xenograft rejection.

The location of MDSCs in transplanted recipients

In tumor models, MDSCs in spleen and tumor of tumor-bearing animals are phenotypically and functionally different. Compared with splenic MDSCs, tumor-infiltrating MDSCs possess a stronger suppressive capacity and various suppressive mechanisms [53]. In the transplantation models, the location of MDSCs *in vivo* where a contact between effector T cells and MDSCs could occur is still unclear. In the kidney transplant model, MDSCs in the blood, spleen and lymph nodes had identical phenotypes but only these derived from blood had suppressive activity *in vitro* [35]. In the cardiac transplantation model, $CD11b^+Gr1^+$ monocytes from the allograft of tolerogen-treated recipients greatly suppressed T-cell proliferation in an antigen-nonspecific manner, whereas the cells from the bone marrow and the spleen of the same recipients did not inhibit T-cell proliferation [40]. In the co-transplantation of HpSCs-induced allo-islet transplantation tolerance model, the $CD11b^+$ cells isolated from the grafts elicited lower T-cell proliferative response with low IFN-γ production and generated low-specific CTL activity *in vitro* [17]. IL-6 deficiency in grafts significantly increases infiltration of MDSCs with strong immunosuppressive activity in the transplanted grafts [42]. It has been demonstrated that the infiltration into grafts is important for the immunosuppressive function of MDSCs. Thus, MDSCs infiltrating into grafts may prove more potent in suppression T cells [53].

The mechanisms for the MDSC induction in transplantation

During allogeneic hematopoietic stem cell transplantation, inducing factors that promote the accumulation of MDSCs may include radio-chemotherapeutic regimens, which cause inflammation, regenerative myelopoiesis, which favors the efflux of immature cell progenitors from the bone marrow during early engraftment and cytopenia results in a compensatory release of various cytokines including myelopoietic growth factors [54]. In solid organ transplantation settings, induction of MDSCs is mainly correlated with inflammation and T-cell response.

Inflammation condition

At the early stage of the solid organ transplantation process, ischemia/reperfusion injury triggers the cascade of inflammation [55]. Proinflammatory cytokines and soluble factors that are associated with inflammatory responses through signaling pathways such as NF-κB, JAK and signal transducer and activator of transcription (STAT) critically control the survival, proliferation and differentiation of MDSCs [56]. For example, the inflammatory process triggered by ischemia/reperfusion causes mitochondria DNA escaping from flamed heart, which binds to Toll-like receptor 9 to induce IL-1β and IL-6 production by

cardiomyocytes [57]. These processes favor the induction of MDSCs during heart transplantation [58]. The attenuation of ischemia/reperfusion injury significantly reduces the infiltration of MDSCs in the graft [59]. Therefore, an inflammatory microenvironment favors the induction of MDSC differentiation in transplantation.

Th1/Th2 CD4$^+$ T cells

Depleted of CD4$^+$ T cells or rendered unable to produce IFN-γ abrogated MDSCs in TGF-β1-deficient mice, thereby demonstrating that Th1 cells have the ability to induce MDSC accumulation [60]. Additionally, production of IFN-γ from Th1 cells is important for enhancement of MDSC function. Early experiments found that transplantation tolerance is hard to be induced in IFN-γ-deficient recipient mice, indicating the protective role of IFN-γ in transplantation tolerance [61]. In fact, IFN-γ production by antigen-activated T cells will enhance the suppressive function of MDSCs in STAT1-dependent and -independent manners [4]. Blocking IFN-γ secretion by T cells also abrogates MDSCs-mediated suppression, mainly via the block of iNOS upregulation [62]. The iNOS was critical to the immunosuppression mediated by MDSCs in cardiac and kidney transplantation models. Moreover, Th1 cells promote IDO expression in MDSCs. IDO is a tryptophan metabolizing enzyme that has been reported to play an important role in tolerance induction in cardiac transplant models [63–66]. MDSCs have been previously shown to express IDO as a mechanism of suppressing host immunity in cancer and allogeneic hematopoietic stem cell transplantation [29,67]. A previous paper indicated that CTLA-4 expressing on the activated T cells may interact with CD80 expressing on MDSCs and induce IDO production by MDSCs [68–70]. However, studies in tumors found that CTLA-4 expressing on MDSCs was critical for regulation of Arg1 activity [71] and blockade of CTLA-4 has more impact on the function of MDSCs than blockade of CD80 [53].

Th2-type reaction can induce Arg1 expression in MDSCs, which synergize with NO to give rise to peroxynitrites and inhibit protein tyrosine phosphorylation via nitration of tyrosine residues and drive the apoptosis of Ag-primed T cells [72]. Th2-type cytokine IL-13 in combination with G-CSF and GM-CSF generates MDSCs expressing high level of Arg1 that inhibits GVHD [20]. During chronic cardiac rejection, IL-33 treatment increases systemic levels of IL-13 and promotes the development of a Th2-type immune response, which favors MDSCs accumulation in grafts [41]. In a mammary adenocarcinoma model, IL-4–expressing CD4$^+$Th2 cells promoted expansion of MDSCs and tumor-associated macrophages [73]. Trauma-induced STAT6-dependent MDSC accumulation was dependent on Th2-type cytokine release [74].

Th17 cells

The Th17 cells, which act as one of the key effectors of inflammation, contribute to all forms of allograft rejection. During transplantation, the impact of IL-17 is mainly to initiate an immune response by recruitment of immune cells to sites of injury, maturation of antigen-presenting cells. Moreover, the developmental plasticity of Treg cells and Th17 cells is a major hurdle to Treg cell-based cellular therapies for transplantation [75]. Interestingly, the relationship of MDSCs and Th17 cells is still controversial. MDSCs from mice with experimental autoimmune encephalomyelitis promoted Th17 cell differentiation via IL-1 signal and depletion of MDSCs reduced the frequency of Th17 cells *in vivo* [76]. However, a negative correlation between increased circulating MDSCs and Th17 cells was found in the peripheral blood of patients with rheumatoid arthritis [77]. On the other hand, IL-17 can increase the suppressive activity of MDSCs *in vitro* through the upregulation of Arg1, IDO and cyclooxygenase-2 [78]. Consistent with that report, an *in vivo* study showed that MDSCs from IL-17R$^{-/-}$ tumor-bearing mice did not have an inhibitory effect on T-cell proliferation and expressed lower levels of Arg1, matrix metalloproteinase 9 and S100A8/A9 [79]. These results suggested that Th17 cells may enhance MDSCs during transplantation.

Immunoregulatory cells

MDSCs mediated Treg cell induction and attraction mentioned earlier. However, the effect of Treg cells on MDSCs is not well documented. The studies in tumor models showed that Treg cell depletion reduced the production of IL-10 and the expression of B7-H1, B7-H3 and B7-H4 on MDSCs from melanoma-bearing mice and modify a less immunosuppressive phenotype of MDSCs [80]. The MDSC suppressive function was abrogated from Treg cell-depleted mice bearing ovarian carcinoma [70]. Moreover, in malignant brain tumors, Treg cell depletion abrogated the MDSCs infiltration and increased the macrophage and neutrophil infiltration into the brain [81]. The concerted immunosuppressive activity of Treg cells and MDSCs was also found in transplantation. In allo-skin transplantation, the induction of Treg cells significantly increases the number and function of MDSCs [47]. Boost of Treg cells remarkably caused an increase of CD11b$^+$Gr1$^{-/low}$ frequency in the graft, peripheral blood and spleen [48]. Besides Treg cells, other immunosuppressive cells also have benefits on MDSCs. HpSCs, which are well known for storing vitamin A and participating in fibrogenesis, are immunosuppressive [82]. Co-transplantation of HpSCs with allogeneic islets can achieve long-term survival of islet allografts in mice. One of the important mechanisms is that HpSCs promote the generation of MDSCs *in vivo* and *in vitro* [51,83]. Induction of MDSCs by HpSCs is dependent on an intact IFN-γ signaling pathway and complement activation factors B and D, which then enhanced C3 cleavage and led to the differentiation of MDSCs with potent immunosuppressive function [17]. Mesenchymal stem cells are known as immune regulatory cells and offer therapeutic potential for achieving transplantation tolerance, especially in protecting islet grafts from both rejection and autoimmune attack [84]. It is reported that human Mesenchymal stem cells can expand human CD14$^-$CD11b$^+$CD33$^+$ MDSCs via hepatocyte growth factor/c-Met and STAT3 [85]. Mesenchymal stem cells can also tune the

Table 2. The effect of immunosuppressive reagents on myeloid-derived suppressor cells.

Drugs	Models	Effect	Mechanisms
Glucocorticoid	*In vitro* induction, trauma	↑	IL-10, CD124
Cyclophosphamide	Inflammation, tumor	↑	Accumulation, NO, reactive oxygen species
Cyclophosphamide	Tumor	↓	Expansion, differentiation
Rapamycin	Tumor	↓	Inhibition of FKBP51
Rapamycin	Immunological hepatic injury	↑	Inhibition of mTOR
FTY720	Small bowel transplantation	↓	Infiltration into grafts
FTY720	Immunological hepatic injury	↑	Recruitment, inducible nitric oxide synthase, via inhibition of S1P1
Anti-CD200 mAb	Renal, cardiac transplantation	↑	Population
Anti-CD20 mAb	Type I diabetes	↑	Expansion, IL-10, NO

NO: Nitric oxide.

development of monocyte-derived dendritic cells toward a myeloid-derived suppressive phenotype through growth-regulated oncogene chemokines [86]. These results indicated that combination of immunosuppressive cells with MDSCs would have synergistic effects on tolerance induction.

The immunosuppressive drugs on MDSCs

The effects of immunosuppressive drugs on MDSCs have been addressed recently (Table 2). Glucocorticoid promotes MDSC expansion *in vitro* and *in vivo* [87–89]. Dexamethasone, a representative glucocorticoid, potentiates MDSC function in prolonging allograft survival through NO [90]. Cyclophosphamide treatment in chronic inflammation or tumor-bearing mice stimulates accumulation and suppressive function of MDSCs [91,92]. However, in the mouse 4T1 mammary carcinoma model, the treatment of low dose of cyclophosphamide combined with anti-TGF-β mAb markedly decreased the number of splenic $CD11b^+Gr1^+$ cells and increased their expression of MHC II and CD80 [93]. Rapamycin reduced the suppressive function of MDSCs in a dose-dependent manner and partially due to the blockade of FKBP51 activity [94]. Additionally, rapamycin inhibition of mammalian target of rapamycin complex 1 in granulocytes resulted in rapid differentiation, indicating its negative role on MDSCs [95]. However, in an immunological hepatic injury mouse model, rapamycin treatment increases the recruitment and iNOS expression of MDSCs via inhibition of mTOR [96]. The effects of antimetabolites such as mycophenolate mofetil and leflunomide on MDSCs are still unclear. It has been observed that cyclosporin A, FK506, leflunomide, mycophenolate mofetil, pentoxifylline and linomide can directly modulate cytokine and/or LPS-induced NO production in various cell types *in vitro*, probably by interfering with iNOS gene transcription or catalytic activity of iNOS enzyme [97]. Thus, these drugs may have inhibitory effect on MDSC function. Recently, a paper reported that cyclosporin A can increase $CD11b^+Gr1^+$ monocytes to develop into fibrocytes *in vitro* and *in vivo* [98]. In the small bowel transplantation model, FTY720 treatment significantly decreased $CD11b^{+/intermediate}Gr1^+$ cells in grafts [99] and FTY720 delivery in inflamed tissue resulted in a reduction in proinflammatory cytokine secretion and an increase in regenerative cytokine secretion [100]. In addition, potential immunosuppressive antibodies have effects on MDSCs in different animal models. Anti-CD200 mAb improved renal and cardiac graft survival by an increased production of Treg cells and MDSCs [101]. B cells-depleting anti-CD20 mAb treatment in type I diabetes induced the expansion of MDSCs that suppress diabetogenic $CD4^+$ and $CD8^+$ T-cell function via IL-10 and NO [102].

Expert commentary & five-year view

MDSCs are a highly heterogeneous cell subpopulation belonging to the innate immune system. The expansion and activation of MDSCs *in vivo* depend on models and the local microenvironments [53]. The inhibitory effects of MDSCs were mediated by many pathways such as iNOS, Arg1, IDO, HO-1 and anti-inflammatory cytokines. MDSCs are certainly involved in the delayed graft rejection and transplantation immune tolerance induction, which made MDSCs become potential clinical therapy to control the ensuing graft rejection of the recipient's immune system and to establish transplantation tolerance induction. Thus, establishment of a protocol for the amplification of MDSCs *ex vivo* would provide a significant boost for clinical application of MDSCs. However, up to now, the current systems for the *ex vivo* differentiation of MDSCs are inefficient and fail to achieve significant levels of amplification [103]. In fact, before the clinical application of MDSCs, their specific surface markers, stability, lifespan and molecular effector pathways/mechanisms need to be fully identified. Moreover, the efficiency, specificity and safety for MDSCs-mediated treatment remain to be determined with experimental and preclinical studies.

Recently, immunologists and clinicians have put great efforts into the study of MDSCs in many respects, including, but not limited to, identifying the specific markers for MDSC subpopulation; understanding the induction pathways for MDSCs; uncovering the effector molecules for MDSCs-mediated immunosuppression and establishing efficient induction systems to expand MDSCs. We believe that deeply understanding the molecular mechanisms for the biological properties of MDSCs

would significantly advance the clinical application of MDSCs in transplanted patients.

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Key issues

- Myeloid-derived suppressor cells (MDSCs) display $CD11b^+Gr1^+$ phenotype, which belongs to a highly heterogeneous cell subpopulation within the innate immune system. MDSCs were roughly divided into two subsets including monocytic-MDSCs and granulocytic-MDSCs.
- Many factors including VEGF, GM-CSF, G-CSF, M-CSF, IFN-γ, IL-1β, IL-6, IL-10, IL-12, IL-13, calcium binding proteins S100A8/S100A9, complement C3 and prostaglandin E2 could induce the expansion and activation of MDSCs.
- The immunosuppressive effects of MDSCs were mediated by many pathways such as iNOS, Arg1, IDO, HO-1 and anti-inflammatory cytokines. MDSCs in different models or its different subpopulations may use distinct inhibitory approaches to downregulate immune response.
- MDSCs are certainly involved in the delayed graft rejection and transplantation immune tolerance induction, which made MDSCs become potential clinical therapy to control the ensuing graft rejection and to establish transplantation tolerance induction. The lack of specific surface markers and the poor understanding on the effector pathways and mechanisms currently limit their application in clinics.

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