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Myeloid derived suppressor cells in transplantation

Jason R Lees, Agnes M Azimzadeh and Jonathan S Bromberg

Myeloid derived suppressor cells (MDSC) are a heterogeneous population of hematopoietic derived cell precursors that can suppress immune responses in a variety of inflammatory settings. Here we review recent studies detailing expansion of phenotypically and functionally disparate MDSC. Findings related to MDSC accumulation, activation, and mechanisms utilized in immune suppression are presented. Further, we discuss recent reports that suggest MDSC are expanded during transplantation and that modulation of MDSC can participate in preventing graft rejection.

Address

Department of Surgery, University of Maryland School of Medicine, Baltimore, MD, United States

Corresponding author: Bromberg, Jonathan S
(JBromberg@smail.umaryland.edu)

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Introduction

The methods currently used to prevent transplant rejection are associated with deleterious effects including systemic immune suppression and concomitant infection, development of metabolic disorders, and chronic drug administration and toxicity. These limitations of established immunosuppressive strategies inform current interest in the understanding and modulation of homeostatic mechanisms for preventing or limiting inflammatory responses to grafted tissue.

In tumor settings, myeloid derived suppressor cells (MDSC) accumulation has been demonstrated to participate in the suppression of immune responses to tumor antigens (1–5). In addition to the tumor environment, expansion of MDSC is now also widely recognized in a variety of inflammatory settings, both acute and chronic. The apparent MDSC accumulation found in disparate inflammatory settings suggests that increased MDSC numbers may be a common anti-inflammatory control mechanism for the maintenance of homeostasis. Further, MDSC can regulate inflammatory responses through

multiple mechanisms resulting in modulation of both innate and adaptive immunity.

Here we review the current literature regarding MDSC and immunosuppression in the context of organ transplantation. While existing studies are limited in number and scope, the apparent anti-inflammatory activity of MDSC in a variety of physiological settings, and early successes with MDSC in several transplantation models, suggest that these cells may provide novel ways of preventing graft tissue rejection.

MDSC definition

MDSC are a heterogeneous cell population, defined functionally by immune suppressive activity and phenotypically by expression of characteristics associated with hematopoietic cell precursors at various stages of homeostatic differentiation to mature macrophages, dendritic cells (DCs), and granulocytes [1]. The different progenitor cells that form this population demonstrate a broad range of morphology and functional capacity. In particular, MDSC can be divided into at least two groups, monocytic and granulocytic, based on morphological and functional features. While the phenotypically immature state is maintained by the majority of MDSC, a small percentage of cells within the monocytic and granulocytic MDSC populations can differentiate into the cognate mature myeloid cell following growth factor-induced stimulation [1,2] (Table 1).

Despite the apparent range of cell types and/or maturation stages included within the MDSC population, similarities among them have emerged, including several elements common to both mice and humans. In both species, MDSC are marked by high expression of CD11b (Mac-1) a common myeloid cell surface marker, as well as low or absent expression of MHC class II molecules, with continued expression of MHC class I molecules. Human MDSC are further identified by expression of CD33 (Siglec-3).

Phenotypically, monocytic, and granulocytic subsets are distinguished by the presence or absence, respectively, of CD14 [3] in humans; and expression of Ly6C or Ly6G [4,5], respectively, in mice. As both Ly6C and Ly6G epitopes are bound by some anti-GR-1 antibodies, GR-1 positivity is often used as an overall marker for MDSC in mice, with relative intensity of GR-1 staining indicative of monocytic (intermediate) and granulocytic (high) subsets [5]. A recent report demonstrated that CD49d expression also differentiates the monocytic and granulocytic subsets of mouse MDSC, with monocytic cells

Table 1

Phenotype of monocytic and granulocytic MDSC subsets in mice and humans.

	Mouse	Human
Granulocytic	MHC class II ^{low} CD11b ⁺ GR1 ^{high} Ly6C ^{low} Ly6G ^{high} CD49d ⁻	MHC class II ^{low} CD33 ⁺ CD11b ⁺ CD14 ⁻ CD15 ⁺
Monocytic	MHC class II ^{low} CD11b ⁺ GR1 ^{int} Ly6C ^{high} Ly6G ⁻ CD49d ⁺	MHC class II ^{low} CD33 ⁺ CD11b ⁺ CD14 ⁺ CD66b ⁺

demonstrating high levels of expression compared to negligible levels observed in granulocytic MDSC subsets [6]. In addition monocytic and granulocytic MDSC subsets utilize somewhat different suppressive mechanisms for immune modulation [4,5].

MDSC from mice have also been demonstrated to express CD16, CD31, CD40, CD80, CD115, CD124, and F4/80 but to have low levels of CD120b. Several of these phenotypic markers have been suggested to play a role in MDSC mediated suppression of the T cell response. In particular, studies have suggested that interactions between CD40 and CD80 on MDSC and cognate receptors on T cells are required for suppression of T cell activity [7,8].

MDSC function

MDSC suppress proliferation and cytokine secretion in both T and NK lymphocytes, as well as induce apoptosis in T cell subsets [9^{••},10]. Given the heterogeneity of the MDSC population, and the profound differences between T and NK lymphocytes, it is not surprising that multiple mechanisms have been implicated in MDSC mediated immune suppression. Suppressive functions are mediated through combinations of several major molecular pathways, including inducible nitric oxide (NO) synthetase (iNOS) [11^{••}], arginase-1 (Arg-1) [11^{••}], hemoxygenase 1 (HO-1) [12], NADPH oxidase (NOX2) [11^{••}], and TGFβ [13]. Production of NO by iNOS has been shown to block T cell adhesion, differentiation, cytokine production, and proliferation [14]. In addition to direct signaling effects through NO, iNOS can also decrease available levels of its substrate L-arginine, a process that can be further accelerated by the metabolic activities of Arg-1. Together, these enzymes can greatly reduce available L-arginine, in turn decreasing T cell proliferative capacity [15,16]. This metabolic targeting is not unique to L-arginine, as a recent study demonstrated additional metabolic targets for MDSC mediated suppression, specifically cystine and cysteine [17].

Following depletion of arginine, iNOS preferentially produces superoxide. This complements the NOX2-induced production of reactive oxygen species (ROS). ROS are a major component of T cell mediated suppression, as abrogation of ROS using an upstream inhibitor abolished MDSC mediated suppression [18]. The combination of ROS and NO produces peroxynitrite that in turn suppresses T cell responses [19].

While iNOS and Arg-1 are well characterized in MDSC mediated immune suppression, alternative mechanisms have been reported. HO-1 played a vital role in MDSC mediated suppression of alloreactive T cell responses in conjunction with IL-10 [12]. TGFβ presentation by MDSC suppressed NK responses [13]. Further, chronic inflammation-induced Gr-1⁺Mac-1⁺ cells downregulated T cell receptor zeta chain expression resulting in impaired T cell function [20]. MDSC can also directly impact the prevalence of regulatory T cells through IFNγ dependent production of IL-10 or iNOS [21,22^{••}]. Thus, MDSCs can participate in both acute control of T cell responses and the induction of regulatory T cells capable of potentiating long-term suppression. These findings have been reported only in a small number of studies, so confirmatory work will be necessary to determine the relative contribution of these mechanisms to MDSC mediated immune suppression, particularly in transplantation.

While MDSC are usually thought to act directly on T cell functions, MDSC can also modulate innate immunity, particularly by regulating antigen presentation through suppression of MHC class II expression, modulation of macrophage cytokine production [23,24], and blockade of DC differentiation and maturation [12,25,26]. Thus, MDSC suppression can influence both adaptive and innate immunity.

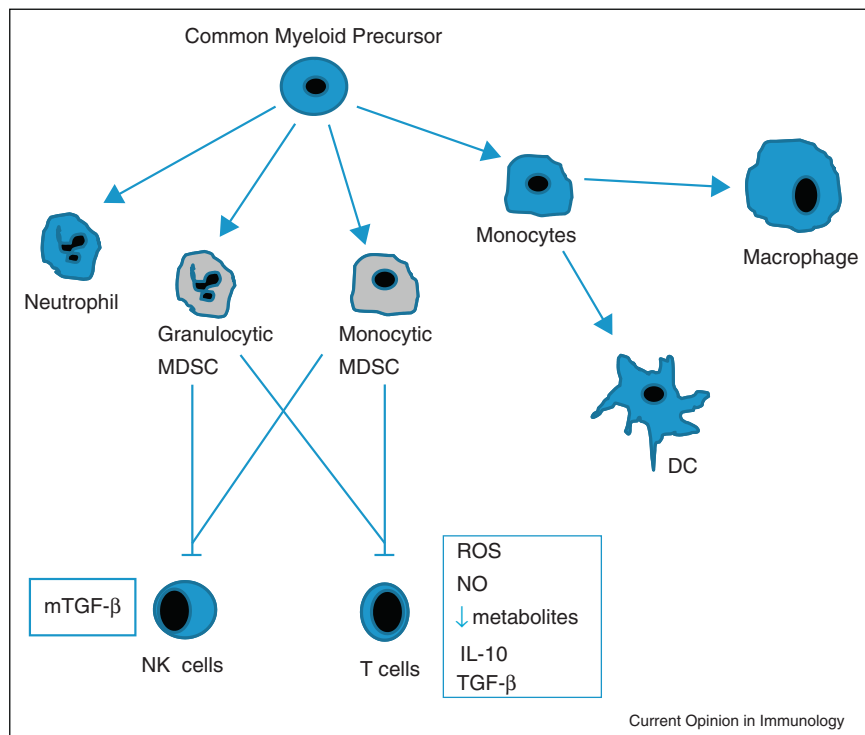
Developmental origin

Hematopoietic stem cells in the bone marrow give rise to common lymphoid and myeloid precursors. In healthy individuals, myeloid precursor cells (MPC) migrate into peripheral lymphatic organs where they differentiate into mature macrophages, DCs or neutrophils (Figure 1). In the context of diverse pathologic conditions, inflammation can inhibit this differentiation of MPC and thereby abrogate the development of functionally competent antigen-presenting cells. Instead myeloid precursors may differentiate into MDSC that produce various immune suppressive factors. Numerous stimulants have been shown to promote MDSC accumulation or activation in cancer; some of these factors are summarized in Box 1.

Association of MDSCs with multiple pathological conditions

Suppressive myeloid cells were first described more than 20 years ago in tumor-bearing mice and patients with

Figure 1



MDSC lineage and suppressive functions. Both currently recognized subsets of MDSC are shown with their common precursor and other cells of myeloid lineage. Boxes adjacent to lymphoid target cells contain MDSC mechanisms known to suppress those cells.

cancer. Up to a tenfold increase in MDSC numbers was detected in the blood of patients with different types of cancer. Similarly, in several mouse tumor models, as many as 20–40% of nucleated splenocytes are MDSCs (in contrast to the 2–4% seen in normal mice). Accordingly, most of the current information on the role of MDSCs in immune responses has come from studies in the field of cancer research. Accumulation of these cells has been recognized as one of the major mechanisms of tumor escape, by virtue of their ability to suppress T cell immune responses by a variety of mechanisms [1,2,4]. MDSCs can also promote tumors by enhancing angiogenesis and tissue remodeling via expression of MMP9 and VEGF [27].

Box 1 Some factors implicated in the expansion and activation of MDSC in cancer.

• Growth factors	VEGF, GM-CSF, G-CSF, M-CSF, SCF
• Prostaglandins	PGE ₂
• Cytokines	IFN γ , IL-1b, IL-6, IL-10, IL-12, IL-13
• Chemokines	CCL2, CXCL5, CXCL12
• Calcium binding proteins	S100A8, S100A9
• Complement	C5a

Accumulating evidence has shown that MDSCs also regulate immune responses during bacterial and parasitic infections, acute and chronic inflammation, sepsis, traumatic stress and autoimmunity. For example, a systemic expansion of both the granulocytic and monocytic subsets of MDSCs has been observed in mice primed with *Mycobacterium tuberculosis* in the form of complete Freund's adjuvant or in mice with acute *Trypanosomacruzi* infection. A similar expansion of MDSCs was reported during acute toxoplasmosis, polymicrobial sepsis, and various chronic infections [11••]. MDSC expansion is also associated with autoimmunity and inflammation. An increase in the number of MDSCs was found in murine autoimmune encephalomyelitis, autoimmune uveoretinitis, and in inflammatory bowel diseases. Interestingly, a transient increase in MDSC numbers was also observed in normal mice following immunization with protein or peptide antigens given together with CFA or staphylococcal enterotoxins [11••]. These observations suggest that the development of MDSCs is common to all inflammatory conditions.

Indirectly relevant to organ transplantation, increased numbers of MDSCs were also found in a model of traumatic stress [28]. CD11b⁺Gr-1⁺ cells accumulate in the spleen within 6 h of trauma for at least 72 h.

Trauma-induced CD11b⁺Gr-1⁺ cells significantly inhibited CD3/CD28-mediated T cell proliferation, TCR zeta chain expression, and IL-2 production. The suppressive effects of CD11b⁺Gr-1⁺ cells were overcome by arginase inhibition.

Role of MDSCs in organ transplantation

Evidence for a role of MDSCs in transplantation is emerging from various animal models. An expansion of MDSCs was first described in a rat model of kidney allograft tolerance induced by anti-CD28 antibodies [9^{••}]. In this model, the cells expressed iNOS and accumulated in the blood and in the tolerized kidney allograft. Inhibition of iNOS broke the established tolerance and led to graft rejection. Adoptive transfer of MDSCs failed to induce kidney allograft tolerance in recently transplanted recipients suggesting that MDSCs alone were not sufficient to induce transplant tolerance in this model. Blood MDSCs from treated recipients inhibited the proliferation of effector T cells *in vitro*, whereas regulatory T cells were resistant to MDSC-induced apoptosis.

Transgenic mice expressing the immunoglobulin-like transcript 2 (ILT2) inhibitory receptor exhibit a two-fold increase in the number of CD11b⁺Gr-1⁺ cells in peripheral blood as compared to wild-type mice [29]. Interestingly, allograft skin transplantation increased the suppressive capacity of MDSCs in ILT2 mice. This effect was associated with a unique MDSC transcriptional profile including upregulation of Arg-1, but not iNOS. Adoptive transfer of CD11b⁺Gr-1⁺ from ILT2 mice significantly delayed the rejection of major MHC class II mismatched skin allografts.

Recently, a critical role for CD11b⁺CD115⁺Gr-1⁺ monocytic suppressive cells was identified in a cardiac transplant model, using CD40 ligand blockade and donor-specific splenocyte transfusion to induce tolerance in the recipient [22^{••}]. These cells were identified using selective depleting agents against monocytes, macrophages, and neutrophils. Mechanisms of action by which these cells exert their immune regulatory function included antigen-nonspecific T cell suppression and development of Tregs.

On the other hand, an increased frequency of MDSCs may favor the development of tumors in transplant patients [30[•]]. MDSCs may contribute to patients' overall immune suppression [31], suggesting that their characterization and enumeration post-transplantation may be important in informing the dosing and eventually the minimization or withdrawal of immunosuppressive drugs.

MDSC-based therapeutic strategies for transplantation

Several therapeutic strategies were developed to target and inhibit MDSCs in cancer [11^{••},32]. In contrast to this

approach, however, the expansion and activation of MDSCs are likely to have a favorable effect on the outcome of organ transplants by weakening immune responses to the graft [33–35]. Administration of selected stimulants such as cytokines or growth factors to transplant recipients may expand MDSC populations *in vivo* [36]. Endotoxin tolerance following repeated injections with lipopolysaccharides from *Escherichia coli* (LPS) is associated with increased MDSCs that inhibit alloimmune responses [12]. MDSCs were recently shown to express the death receptor Fas [37], suggesting that therapeutic inhibition of T cell activation may indirectly promote MDSCs survival.

Alternatively, MDSCs could be developed *in vitro* and adoptively transferred to transplant recipients. This approach was efficient at preventing type 1 diabetes in NOD mice [38]. Protocols to differentiate MDSCs from murine bone marrow progenitor cells [39[•]] or stem cells [40[•]] have been recently described, and need to be carefully evaluated [41].

Conclusion

There is paucity of data about the role MDSCs in transplantation. A better understanding of the degree and mechanisms of immune suppression by these cells after organ transplantation will have important clinical implications and may allow therapeutic manipulation of the myeloid cell differentiation pathway. A better definition of markers and additional murine reagents (antibodies, genetic modifications) is critically needed to answer important scientific questions such as antigen-specificity, cell trafficking, cellular cross-talk and stability of these cells.

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