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MINIREVIEWS

Role of myeloid-derived suppressor cells in autoimmune disease

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Abstract

Myeloid-derived suppressor cells (MDSCs) represent an important class of immunoregulatory cells that can be activated to suppress T cell functions. These MDSCs can inhibit T cell functions through cell surface interactions and the release of soluble mediators. MDSCs accumulate in the inflamed tissues and lymphoid organs of patients with autoimmune diseases. Much of our knowledge of MDSC function has come from studies involving cancer models, however many recent studies have helped to characterize MDSC involvement in autoimmune diseases. MDSCs are a heterogeneous group of immature myeloid cells with a number of different functions for the suppression of T cell responses. However, we have yet to fully understand their contributions to the development and regulation of autoimmune diseases. A number of studies have described beneficial functions of MDSCs during autoimmune diseases, and thus there appears to be a potential role for MDSCs in the treatment of these diseases. Nevertheless, many questions remain as to the activation, differentiation, and inhibitory functions of MDSCs. This review aims to summarize our current knowledge of MDSC subsets and suppressive functions in tissue-specific autoimmune disorders. We also describe the potential of MDSC-based cell therapy for the treatment of autoimmune diseases and note some of hurdles facing the implementation of this therapy.

Key words: Myeloid-derived suppressor cells; Autoimmune disease; Autoimmunity; T cells; Chronic inflammation; Immune regulation

Core tip: Myeloid-derived suppressor cells (MDSCs) are a heterogeneous group of cells with immunosuppressive abilities. MDSCs inhibit T cell function and regulate immune responses in cancer and autoimmune diseases. Therapeutic administration of MDSCs in the mouse models of multiple sclerosis, rheumatoid arthritis, and diabetes has shown promising results. Thus, MDSCs have potential in cell-based treatments of autoimmune disorders. However, the role of MDSCs in autoimmunity is complex and not fully understood. Further studies are needed before new therapies can be implemented.

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INTRODUCTION

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous group of immature myeloid cells that have the ability to suppress T cell functions[1]. MDSCs are derived from the bone marrow and arise from a delay in maturation during pathologic conditions, such as cancer, chronic inflammation, infection, and traumatic stress[2]. Most studies focus on the pathogenic nature of MDSCs in cancer, where suppression of T cell-mediated immune

responses prevents immune surveillance and clearance of developing tumors[3-5]. Recently, MDSCs have been reported to regulate autoimmunity and control the generation and perpetuation of autoimmune diseases[6]. In this review, we will summarize the current knowledge of MDSC subsets and suppressive functions in tissue-specific autoimmune disorders. We also describe the potential of MDSC-based cell therapy for the treatment of these autoimmune diseases, while noting some of the obstacles that may hinder the implementation of this therapy.

MDSC INVOLVEMENT IN AUTOIMMUNE DISEASES

Our knowledge of the origination and functions of MDSCs has come mainly from studies in tumor models and from cancer patients[1,5,7]. The role of MDSCs in autoimmune diseases is only starting to be elucidated. We now know that MDSCs are involved in a number of different autoimmune disorders, including multiple sclerosis (MS), type 1 diabetes, rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and autoimmune hepatitis. In steady state conditions, MDSCs reside primarily in the bone marrow. Under pathological conditions, MDSC populations expand and can be detected in the spleen, lymph nodes, cancerous tumors, and bloodstream. An early study using a mouse model of autoimmune uveoretinitis showed that the accumulation of nitric oxide-producing monocytes in the choroid and retina of the eye correlated with the severity of disease[8]. A later study showed similar results and confirmed the identity of these cells to be MDSCs[9]. Studies using the mouse model of MS, experimental autoimmune encephalomyelitis (EAE), showed that MDSCs were present in the demyelinated areas of the spinal cord tissue of mice. Another EAE model showed that MDSC accumulation in the spleen correlated with disease progression[10]. Here, they showed that the start of MDSC accumulation occurred during the asymptomatic phase and increased throughout the onset phase. At the peak of the disease, MDSC accumulation reached its highest level, and then began to decrease during the recovery phase and returned to steady state levels by disease resolution. Similar results were found using collagen-induced arthritis (CIA), a mouse model of RA, where MDSC accumulation in the spleen correlated with the course of disease[11]. In humans, MDSCs were found to be enriched in the bloodstream of patients with active MS, but were only slightly elevated in the blood of patients in recovery[12].

MDSCs require certain signals for their expansion and activation. The factors responsible for driving the expansion of MDSCs include cyclooxygenase-2, prostaglandins, interleukin 6 (IL-6), macrophage colony-stimulating factor (M-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF)[9,13-18]. Most of these factors trigger signaling pathways that stimulate the proliferation of myeloid cells in the bone marrow and inhibit their differentiation into mature cells[3]. MDSCs can be activated to suppress T cell functions *via* interferon gamma (IFNγ) and transforming growth factor beta (TGF-β)[13]. Blocking IFNγ production by activated T cells abolishes MDSC-mediated T cell suppression[1,11,19]. Cancer models have identified IL-6, IL-1β, prostaglandin E_2, and the calcium binding proteins S100A8 and S100A9, as factors important for the accumulation of MDSCs at sites of inflammation[17,20,21]. Tumor necrosis factor (TNF) signaling drives MDSC accumulation in the periphery by promoting MDSC survival and inhibiting apoptosis[22]. Treatment with a TNF-α antagonist showed decreased MDSC accumulation in the spleen in response to chronic inflammation[23].

MDSC SUBSETS IN AUTOIMMUNITY

Early classification of MDSCs was based on cell surface expression of CD11b and Gr-1. The $CD11b^+Gr\text{-}1^+$ subgroup is now divided into two separate groups, exhibiting either a monocytic morphology or a granulocytic morphology[24]. Granulocytic MDSCs (G-MDSCs) display a $CD11b^+Ly6C^{low}Ly6G^+$ phenotype, whereas monocytic MDSCs (M-MDSCs) are $CD11b^+Ly6C^+Ly6G^-$[18,24-26]. The two groups also differ in functionality[18,25,27]. MDSCs suppress T cell functions *via* a number of different mechanisms involving the production of soluble mediators or through cell-cell contact[28-31]. G-MDSCs frequently inhibit T cell function through arginase-1 enzyme activity. M-MDSCs more commonly inhibit T cell functions *via* nitric oxide production. IFNγ-mediated activation of MDSCs results in the upregulation of arginase-1 and nitric oxide production. In the CIA model, MDSCs were found to inhibit both T cell proliferation and $CD4^+$ T cell differentiation into Th17 cells[11]. Here, the researchers used the total $CD11b^+Gr\text{-}1^+$ population from the spleen and found both arginase-1 and nitric oxide to be mechanisms of inhibition. The Gr-1 antibody recognizes both Ly6G and Ly6C surface antigens, therefore the population of cells used for their studies contained both G-MDSCs and M-MDSCs. In a mouse model of diabetes, $CD11b^+Gr\text{-}1^+$ cells were found to inhibit $CD8^+$ and $CD4^+$ T cell responses *via* nitric oxide- and IL-10-dependent mechanisms[32]. In the EAE model, G-MDSCs from myelin oligodendrocyte glycoprotein-immunized mice were found to express high levels of programmed cell death 1 ligand 1 (PD-L1), a costimulatory molecule that negatively regulates T cell proliferation. G-MDSCs were found to inhibit autoantigen-priming of Th1 and Th17 cells in a PD-L1-dependent manner[12]. Interestingly, one report showed that $CD11b^+Gr\text{-}1^+$ cells isolated from mice with EAE inhibited T cell proliferation in co-culture but promoted Th17 cell differentiation under Th17-polarizing conditions[33].

M-MDSCs also display immunosuppressive effects during autoimmune diseases. Recent data showed that M-MDSCs induced during the priming phase of EAE were potent suppressors of activated T cells and mediated T cell inhibition through the production of nitric

oxide[18]. Nitric oxide production by MDSCs results in the nitrosylation of cysteine residues, leading to a significant decrease in mRNA stability, and thereby preventing the production of cytokines required for T cell proliferation[28]. Another study demonstrated that activation of M-MDSC suppressive function occurred at the peak of EAE disease[34]. This study determined that the suppression of T cell responses was due to M-MDSC-mediated nitric oxide production. Furthermore, transfer of activated M-MDSCs led to apoptosis of T cells in the central nervous system and decreased EAE severity. In autoimmune arthritis, clinical trials against C-C chemokine receptor 2 (CCR2), the major chemokine receptor mediating monocyte recruitment, were surprisingly unsuccessful as monocytes/macrophages were thought to be pathogenic in RA[35-37]. Interestingly, CCR2-deficient mice are now known to develop exacerbated CIA[38,39]. The underlying mechanisms contributing to the aggravated disease are not clear. However, our data showed that M-MDSCs were absent from the periphery of collagen-immunized CCR2-deficient mice, as CCR2 is required for the emigration of M-MDSCs from the bone marrow[38,40]. Further, M-MDSCs isolated from the bone marrow of CCR2-deficient mice with CIA inhibited $CD4^+$ T cell proliferation and mitigated CIA severity, suggesting M-MDSCs are required for the regulation of autoimmune arthritis[41].

Human MDSCs are identified as $CD14^+CD16^+$ and $CD14^+CD16^-$ cells. These $CD14^+$ cells were found to be abundant in the blood and synovial fluid of RA patients[42,43]. Recently, MDSCs were shown to mediate enhancement of regulatory T cell (Treg) suppressive functions[43]. Here, Tregs were isolated from healthy subjects and their suppressive activity and cytokine expression were analyzed after co-culture with $CD14^+$ cells. Results showed an increase in the expression of IFNγ, TNF-α, IL-17, and IL-10 by Tregs, a sustained Treg phenotype, and an enhanced capacity to suppress T cell-mediated proinflammatory cytokine production and T cell proliferation.

Taken together, these studies demonstrate that MDSCs can use various functions to suppress T cell responses and suggest that MDSC differentiation and function may be influenced by the distinct environment associated with each type of disease. Although both G-MDSCs and M-MDSCs can suppress T cell functions, further research is needed to confirm whether the two subsets have different outcomes in different diseases (Table 1).

MDSC-MEDIATED SUPPRESSION OF ANTIGEN-SPECIFIC IMMUNE RESPONSES

Loss of immunological tolerance is the basis for the development of autoimmune diseases. Recognition of self-antigens leads to autoimmune-driven tissue inflammation. However, regulation of the responses to self-antigens must be highly specific in order for the host immune recognition of pathogens to remain intact. MDSCs may play a crucial role in maintaining this balance as they are capable of suppressing antigen-specific immune responses. It is believed that MDSCs internalize antigens and present them to T cells, bringing the two cells into close contact. Peroxynitrite, a derivative of nitric oxide, causes nitration of tyrosine residues on the T cell receptor (TCR), thereby preventing binding between the major histocompatibility complex (MHC) and peptide[44]. Increased levels of nitrotyrosine have been documented for patients suffering from MS, RA, autoimmune myocarditis, and diabetes[45-48]. In a cancer model, increased production of peroxynitrite and hydrogen peroxide resulted from the interaction between immature myeloid cells and antigen-specific $CD8^+$ T cells in the presence of the specific antigen, but not in the presence of the control antigen[29]. In some cancer models, arginase-1 production is the mechanism of MDSC-mediated suppression[31,49]. The arginase-1 enzyme hydrolyzes arginine, depleting the pool of arginine available to the cell[50-52]. A deficiency in arginine prevents the formation of CD3 molecules[53]. The absence of CD3 prevents signaling through the TCR upon recognition of a specific antigen-MHC complex.

In one study of autoimmune diabetes, MDSCs induced the antigen-specific expansion of Tregs, which resulted in the suppression of T cell proliferation and prevented the onset of disease[54]. The authors described that MDSC-mediated expansion of Tregs was dependent on antigen presentation by MHC class Ⅱ molecules. For these experiments, hemagglutinin (HA)-specific $CD4^+$ T cells were adoptively transferred to mice, followed by the administration of MDSCs and HA antigen. The results showed a significant reduction in disease upon administration of MDSCs and HA, but no decrease in disease when MDSCs were administered with the ovalbumin peptide, confirming that the MDSC-mediated suppression was antigen-specific.

MDSCs also mediate suppression of non-specific T cell responses, *i.e.,* mitogen-activated T cell responses, suggesting MDSCs may be involved in the late phase of tissue inflammation during autoimmune diseases. Others have hypothesized that MDSCs function in both antigen-specific and non-specific manners depending on the signals they are exposed to in a particular microenvironment[55]. Indeed, comparison of MDSCs isolated from the spleen to those isolated from a tumor showed that splenic MDSCs were able to inhibit antigen-specific T cell responses *via* the production of reactive oxygen species, whereas MDSCs isolated from the tumor inhibited T cells nonspecifically and more potently than those from the spleen[56]. T cells isolated from the peripheral lymphoid organs of human cancer patients, or from a mouse tumor model, are still responsive to non-cancer related stimuli, including viruses, IL-2, and anti-CD3/CD28 antibodies[1,57]. This suggests that the expansion of MDSCs does not induce systemic immune suppression. Taken together, these data suggest that MDSCs from the site of inflammation may be more potent and far-reaching

Table 1 Myeloid-derived suppressor cells in autoimmune disease models

Human disease	Mouse model	Phenotype	T cell suppression	Suppressive mechanism	Suppressive role *in vivo*
Multiple sclerosis	EAE	$CD11b^+Ly6C^{high}$ (M-MDSCs)	$CD4^+$ T cells	NO-apoptosis	Not determined[18]
	EAE	$CD11b^+Ly6G^-$ (M-MDSCs)	$CD4^+$, $CD8^+$, Ag-specific $CD4^+$ T cells	NOS	No effect by naïve MDSCs[77]
	EAE	$CD11b^+Ly6C^{high}$ (M-MDSCs)	Not determined	Not determined	Increase severity[73]
	EAE	$Arg\text{-}1^+CD11b^+Gr\text{-}1^{low}$ (M-MDSCs)	$CD3^+$ T cells	Apoptosis	Not determined[10]
	EAE	$CD11b^+Ly6C^+$ (M-MDSCs)	$CD4^+$ T cells	NO	Reduce severity by late phase MDSCs[34]
	EAE	$CD11b^{high}Ly6G^+Ly6C^-$ (G-MDSCs)	Th1 and Th17 cells	PD-L1	Reduce severity[12]
	EAE	$CD11b^+Gr\text{-}1^+$	Promote Th17 cells	IL-1β	Increase severity[33]
	EAE	$CD11b^+Gr\text{-}1^+$	Ag-specific Th17 cells	iNOS, arginase-1 and IL-10	Ablated iNKT-induced disease mitigation[78]
Rheumatoid arthritis	CIA	$CD11b^+Ly6C^+Ly6G^-$ (M-MDSC)	$CD4^+$ T cells	NO	Reduce severity[41]
	CIA	$CD11b^+Gr\text{-}1^+$	Th17 cells	Arginase and iNOS	Reduce severity[11]
	Proteoglycan-induced arthritis	$CD11b^+Gr\text{-}1^+$	Ag-specific T cells	NO and ROS	Not determined[79]
Systemic lupus erythematosus	$MRL\text{-}fas^{lpr}$	$CD11b^+Gr\text{-}1^{low}$ (M-MDSCs)	$CD4^+$ T cells	Arginase-1	Not determined[80]
Inflammatory bowel disease	HA-transgenic mice	$CD11b^+Gr\text{-}1^+$	Ag-specific $CD8^+$ T cells	NO-apoptosis	Reduce severity[14]
	DDS-induced colitis	$CD11b^+Gr\text{-}1^+$	Not determined	Not determined	Reduce severity[75]
	IL-10-/-	$CD11b^+Gr\text{-}1^+$	MLN T cells	Not determined	Not determined[81]
	TNBS-induced colitis	$CD11b^+Gr\text{-}1^+$	Splenocytes	Not determined	Reduce severity[74]
T1D	INS-HA/RAG-/-h-CD20/NOD	$Gr\text{-}1^+CD115^+$ (M-MDSCs)	Induce Tregs and inhibit Teff cells	TGF-β and IL-10	Reduce severity[54]
		$CD11b^+Gr\text{-}1^+$	$CD4^+$ and $CD8^+$ T cells induce Tregs	NO and IL-10	Not determined[32]
Autoimmune hepatitis	Tgfb-/-	$CD11b^+Ly6C^{high}$ $Ly6G^-$ (M-MDSCs)	$CD4^+$ T cells	NO	Not determined[82]
Inflammatory eye disease	EAU	$CD11b^+Gr\text{-}1^+$ $Ly6G^-$ (M-MDSCs)	$CD4^+$ T cells	TNFR-dependent, Arginase	Not Determined[9]
	EAU	REP-induced $CD11b^+Gr\text{-}1^+$	$CD4^+$ T cells	Not determined	Reduce severity[76]
Alopecia areata	Alopecia areata-eczema	$CD11b^+Gr\text{-}1^+$	$CD4^+$ and $CD8^+$ T cells	CD3-zeta down-regulation	Local MDSC administration reduces severity[83]

TID: Type 1 diabetes; EAE: Experimental autoimmune encephalomyelitis; CIA: Collagen-induced arthritis; MLR: Murphy roths large; HA: Hemagglutinin; DDS: Dextran sulphate sodium; INS: Insulin; RAG: Recombination-activating gene; NOD: Non-obese diabetic; EAU: Experimental autoimmune uveitis; M-MDSCs: Monocytic myeloid-derived suppressor cells; G-MDSCs: Granulocytic myeloid-derived suppressor cells; MLN: Mesenteric lymph node; NO: Nitric oxide; NOS: Nitric oxide synthase; PD-L1: Programmed cell death 1 ligand 1; iNOS: Inducible nitric oxide synthase; ROS: Reactive oxygen species; IL-10: Interleukin 10; TGF-β: Transforming growth factor beta; IL-1β: Interleukin 1 beta; TNFR: Tumor necrosis factor receptor.

in their suppressive effects than those MDSCs in the peripheral organs. The MDSCs in circulation may function to prevent the spread of inflammation to other areas of the body, without compromising immune recognition of pathogens.

THERAPEUTIC POTENTIAL OF MDSC-BASED TREATMENTS

Therapeutic approaches involving MDSCs require their purification and/or proliferation *in vitro*. MDSCs migrate to peripheral lymphoid organs where they differentiate into granulocytes, monocytes/macrophages, and dendritic cells (DCs). GM-CSF has been shown to drive MDSC accumulation at sites of inflammation[58,59] and has been used to generate MDSCs from bone marrow cells *in vitro*[60]. However, the concentration of GM-CSF in the media must be tightly regulated as different concentrations of GM-CSF may lead to the generation of neutrophils or DCs[60,61]. Vascular endothelial growth factor (VEGF) is important in the differentiation of hematopoietic progenitor cells[62], and studies have shown that blocking VEGF binding leads to increased differentiation of MDSCs into DCs[63]. Similar results were shown for stem cell factor, where blocking its function led to reduced MDSC expansion[64]. Factors such as granulocyte colony-stimulating factor (G-CSF) and M-CSF are also known to induce MDSC expansion. G-CSF induces the proliferation of G-MDSCs *via* the Janus kinase/signal transducers and activators of transcription pathway (Jak/STAT)[65]. In the presence of IL-6, M-CSF was shown to inhibit DC generation from hematopoietic stem cells (HSCs), thereby redirecting HSC differentiation towards MDSCs[66].

The calcium binding proteins, S100A8 and S100A9, are upregulated in some autoimmune conditions, including RA, MS, and IBD[66-68]. These proteins are secreted by MDSCs[69] and may work in an autocrine fashion to promote the accumulation of MDSCs while simultaneously preventing their differentiation into DCs[70]. MDSC generation, expansion, and gain of specific suppressive abilities occur primarily under inflammatory conditions such as infection, cancer, trauma, and autoimmune diseases. It is important to note that MDSCs are not terminally differentiated, and thus may mature into antigen-presenting cells, such as macrophages or DCs, highlighting a potential complication for therapeutic attempts. Therefore, in order to develop effective MDSC-based therapies, we must first understand how different cell types respond to different inflammatory mediators and determine how these inflammatory mediators affect the potency and/or suppressive mechanisms of MDSCs.

A number of studies have provided insight into the use of MDSCs for treatment of autoimmune diseases. In a murine model of diabetes, MDSCs were generated *in vitro* by culturing hepatic stellate cells with DCs[71]. This method of MDSC generation was previously shown to produce highly suppressive cells in an IFNγ-dependent manner[72]. In the diabetes study, these *in vitro*-generated MDSCs were mixed with pancreatic islet cells and transplanted into diabetic mice. The MDSCs induced Treg expansion in the allograft site, resulting in the inhibition of $CD8^+$ T cell responses[71]. In a mouse model of IBD, MDSCs were found to be upregulated in the spleen and intestine of IBD mice[14]. Further data showed that these MDSCs effectively prevented T cell proliferation and induced T cell apoptosis after transfer of $CD8^+$ T cells[14]. One report showed that the *in vivo* transfer of G-MDSCs in the EAE model resulted in the delayed onset of disease and a significant reduction in demyelination[12], however other studies were not as successful[33,73]. Adoptive transfer of MDSCs also led to reduced disease severity in models of RA[11,41], IBD[74,75], and inflammatory eye disease[76].

CONCLUSION

MDSCs represent an important class of immunoregulatory cells. MDSCs display particular heterogeneity and plasticity, and for these reasons they have become an attractive candidate for the treatment of autoimmune diseases. On the other hand, MDSCs are very difficult to work with because of their diverse nature. MDSCs have multiple phenotypes which inhibit T cell responses by multiple mechanisms, and their environment dictates the development of suppressive properties and activation pathways. Additionally, the maturation/differentiation of these cells may depend on the particular inflammatory signals received from their microenvironment. Though MDSCs hold promise in the treatment of autoimmune diseases, their full utilization is stalled by our limited understanding of their phenotype, differentiation, cellular functions, and influence on the microenvironment.

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