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**Role of myeloid-derived suppressor cells in autoimmune disease**

Crook KR *et al*. Role of MDSCs 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 through the release of soluble mediators. MDSCs accumulate in the inflamed tissues and lymphoid organs of patients with autoimmune disease. Much of our knowledge of MDSC function has come from studies involving cancer models, however many recent studies have helped to characterize the MDSC involvement in autoimmune disease. MDSCs are a heterogeneous group of immature myeloid cells with a number of different functions for the suppression of T cells responses. However, we have yet to fully understand their contributions to the development and regulation of autoimmune disease. A number of studies have described beneficial functions of MDSCs during autoimmune disease and thus there appears to be a potential role for MDSCs in the treatment of this disease. 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 disease and note some of hurdles facing the implementation of this therapy.

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**Keywords:** 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. Administration of MDSCs in the mouse models of multiple sclerosis, rheumatoid arthritis, and diabetes has shown promising results. Thus, MDSCs have therapeutic potential in cell-based treatment of autoimmune disorders. However the full role of MDSCs in autoimmunity is complex and not fully understood. Further studies are needed before new therapy can be implemented.

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**INTRODUCTION**

Myeloid derived suppressor cells (MDSCs) are a heterogeneous group of immature myeloid cells that have a strong ability to suppress T cell functions[1]. MDSCs are derived from the bone marrow and arise from a delay in maturation occurring during pathologic conditions, such as tumor suppression, 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 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 these diseases and note some of hurdles facing the implementation of this therapy.

**MDSCs ARE INVOLVED IN AUTOIMMUNE DISEASE**

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 disease is only beginning to be elucidated. We now know that MDSCs are involved in a number of different autoimmune disorders including multiple sclerosis (MS), type 1 diabetes (T1D), rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and autoimmune hepatitis (AIH). In steady state conditions MDSCs reside primarily in the bone marrow. Under pathological conditions they are expanded and can be detected in the spleen, lymph nodes, cancerous tumors, and the bloodstream. An early study using a mouse model of autoimmune uveoretinitis showed accumulation of nitric oxide-producing monocytes in the choroid and retina of the eye which correlated with disease severity[8]. A later study showed similar results and confirmed the identity of these cells to be MDSCs[9]. Use of the mouse model of MS, called experimental autoimmune encephalomyelitis (EAE) showed MDSCs were present in the demyelinated areas of the spinal cord tissue of mice. Another EAE model showed MDSC accumulation in the spleen correlated with disease progression[10]. Here they showed the start of MDSC accumulation occurred during the asymptomatic phase and increased during the onset phase. At the peak of the disease MDSC accumulation reached its highest level then began to decrease during the recovery phase and had returned to steady state levels by disease resolution. Similar results were found using the collagen-induced arthritis (CIA), a mouse model of RA, where MDSC accumulation in the spleen correlated with the course of disease[11]. In human 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, IL-6, M-CSF, and 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 differentiating into mature cells[3]. MDSCs can be activated to suppress T cell functions *via* IFNγ and TGFβ[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, PGE2, and the calcium binding proteins S100A8 and S100A9 as factors important for the accumulation of MDSCs at sites of inflammation[17,20,21]. TNF signaling drives MDSC accumulation in the periphery by promoting MDSC survival and inhibiting apoptosis[22]. Treatment with a TNFα 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-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+Ly6ClowLy6G+ phenotype, whereas monocytic MDSCs (M-MDSCs) are CD11b+Ly6C+Ly6G-[18,24-26]. The two groups also differ in functionality[18, 25,27]. MDSCs can 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 will result 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 Gr-1+ population from the spleen and found both arginase-1 and nitric oxide to be mechanisms of inhibition. The Gr-1 antibody will recognize both Ly6G and Ly6C surface antigens therefore the population of cells used for their studies would contain both G-MDSCs and M-MDSCs. In a mouse model of diabetes CD11b+Gr-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 (MOG)-immunized mice were found to express high levels of 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-1+ cells isolated from mice with EAE inhibited T cell proliferation in T cell co-culture but promoted Th17 cells under Th17-polarizing conditions[33].

M-MDSCs also display immunosuppressive effects during autoimmune disease. Recent data showed 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 will result 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 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 CNS and decreased EAE severity. In autoimmune arthritis, clinical trials against CCR2, the major chemokine receptor mediating monocyte recruitment, were surprisingly unsuccessful as monocytes/macrophages were thought to be pathogenic in rheumatoid arthritis[35-37]. Interestingly, CCR2-deficient mice are now known to develop exacerbated collagen-induced arthritis (CIA)[38,39]. The underlying mechanisms contributing to the aggravated disease are not clear. However our data show M-MDSCs to be 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 Treg expression of IFNγ, TNFα, IL-17, and IL-10 as well as a sustained Treg phenotype and an enhanced capacity to suppress proinflammatory cytokine production and proliferation by T cells.

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 distinctive 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 endpoint effect 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 disease. Recognition of self-antigens will lead to autoimmune-driven tissue inflammation. However, regulation of the response 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 response. MDSCs are believed to take up antigens and present them to T cells, bringing the two cells into close contact. Peroxynitrite will cause nitration of tyrosine residues on the T cell receptor (TCR) thereby preventing binding between MHC and peptide[44]. An increase in the levels of nitrosylated tyrosine has been documented for patients suffering from MS, RA, autoimmune myocarditis, and diabetes[45-48]. In a cancer model interactions between immature myeloid cells and antigen-specific CD8+ T cells resulted in increased production of peroxynitrite and hydrogen peroxide 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]. Here the authors describe MDSC-mediated expansion of Tregs to be dependent on antigen presentation by MHC class II. For these experiments 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 OVA peptide confirming the MDSC-mediated suppression was antigen-specific.

MDSCs also mediated suppression of non-specific, *i.e.* mitogen-activated T cell responses suggesting MDSCs may be involved in the late phase of tissue inflammation during autoimmune disease. Others have hypothesized that MDSCs will function in both an antigen-specific and non-specific manner depending on the signals they are exposed to in a particular microenvironment[55]. Indeed a comparison of MDSCs isolated from the spleen to those isolated from a tumor showed splenic MDSCs were able to inhibit antigen-specific T cell responses *via* production of reactive oxygen species (ROS) 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 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 would require their purification and/or proliferation *in vitro*. It is known that MDSCs will migrate to peripheral lymphoid organs where they differentiate into granulocytes, monocytes/macrophages, and dendritic cells. 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 dendritic cells[60,61]. VEGF is also known to be important in the differentiation of hematopoietic progenitor cells[62] and studies have shown blocking VEGF binding will lead 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 G-CSF and M-CSF are also known to induce MDSC expansion. G-CSF will induce the proliferation of G-MDSCs *via* JAK/STAT signaling[65]. M-CSF has been shown to inhibit DC generation from hematopoietic stem cells (HSCs) when IL-6 is also present 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 dendritic cells 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 disease. In a murine model of diabetes MDSCs were generated *in vitro* by culturing hepatic stellate cells with dendritic cells[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 prevention 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 these MDSC effectively prevented T cell proliferation and induced T cell apoptosis after transfer of CD8+ T cells[14]. One report has shown 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 disease. On the other hand, the diverse nature of MDSCs makes them a particularly difficult class of cells to work with. MDSCs have multiple phenotypes which inhibit T cell responses by multiple mechanisms and their environment dictates their development of suppressive properties and method of activation. Additionally, the maturation/differentiation of these cells will 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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