Mini Review

Myeloid-derived suppressor cells in autoimmune diseases

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Myeloid-derived suppressor cells (MDSCs) are of myeloid origin and are able to suppress T cell immune responses. Although MDSCs play important roles in tumor progression by suppressing T cell immune responses and inducing immune tolerance, the roles of MDSCs in autoimmune diseases such as rheumatoid arthritis remain controversial. It is difficult to explain why autoimmune diseases occur despite the recruitment and accumulation of MDSCs, which should suppress the immune response. Here, we review the current knowledge regarding the roles played by MDSCs in animal models of autoimmune disease and in human autoimmune disease. We propose that, at least in some cases, MDSCs prevent further progression of autoimmune disorders and suggest novel therapeutic strategies for autoimmune diseases based on the use of endogenous MDSCs.

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Introduction

Myeloid-derived suppressor cells (MDSCs) suppress T cell-mediated anti-tumor immune responses[1], and much research has focused on their role in tumor malignancy and progression. Certain autoimmune diseases are associated with accumulation of MDSCs, although their precise roles remain elusive. Here, we review the current knowledge regarding the role of MDSCs in both animal models of autoimmune disease and in human autoimmune diseases, and suggest that in some cases autoimmune-associated accumulation of MDSCs prevents further disease progression. We also review the mechanisms underlying the accumulation and suppressive function of MDSCs, and discuss the potential use of, and possible problems associated with, novel MDSC-based therapies for autoimmune diseases.

Table 1 Characteristics of MDSCs in autoimmune disease models

Human diseases	Mouse models	Phenotype	Mechanism of suppression	Antigen specificity	Apparent role *in vivo*	Refs
Multiple scrlosis	EAE EAE EAE EAE	$CD11b^+Ly6C^{high}$ $Ly6G^-$ $CD11b^+Ly6C^+CCR2^+$ $CD11b^+Gr\text{-}1^{low}$ $CD11b^+Ly6C^-Ly6G^+$	Nitric oxide Not determined Th17 differentiation PD-L1	Nonspecific Not determined Nonspecific Specific and nonspecific	Not determined Pathologic Pathologic Protective	5 13 17 7
Inflammatory bowel disease	Villin-HA	$CD11b^+Gr\text{-}1^+CD31^+$	Nitric oxide	Specific	Protective	6
Type 1 diabetes	INS-HA/$RAG^{-/-}$	$Gr\text{-}1^+$ $CD115^+$	Not determined	Specific	Protective	10
Rheumatoid arthritis	PGIA CIA	$CD11b^+Gr\text{-}1^+$ $CD11b^+Ly6C^{low}Ly6G^+$	Suppression of DC maturation Arginase and iNOS	Specific Nonspecific	Not determined Protective	18 8
Systemic lupus erythematosus	NZB × NZW	$CD11b^+Gr\text{-}1^{high}$	control of B cell pathogenesis	Nonspecific	Protective	19
Alopecia areata	Alopecia areata-eczema	$CD11b^+Gr\text{-}1^+$	CD3-zeta down-regulation	Nonspecific	Protective	9
Inflammatory eye disease	EAU	$CD11b^+Gr\text{-}1^+Ly6G^-$	Not determined	Nonspecific	Not determined	11

EAE: experimental autoimmune encephalomyelitis, PD-L1: programmed death ligand 1, HA: hemagglutinin, PGIA: proteoglycan-induced arthritis, DC: dendritic cell, CIA: collagen-induced arthritis, iNOS: inducible nitric oxide synthase, EAU: experimental autoimmune uveoretinitis.

Defining MDSCs

In mice, MDSCs are characterized by the co-expression of the myeloid differentiation antigens, Gr-1 and CD11b, and are divided into two major subsets, $Ly6G^+Ly6C^{low}CD11b^+$ granulocytic MDSCs and $Ly6G^-Ly6C^{high}CD11b^+$ monocytic MDSCs, according to their cell surface expression of Ly6G and Ly6C (both recognized by the Gr-1 antibody)[2]. The human counterpart of murine MDSCs is commonly defined as $CD11b^+CD33^+$ $HLA\text{-}DR^-$. Since the cell surface markers used to characterize MDSCs are also expressed by normal myeloid cells, functional analysis of MDSCs is necessary to distinguish them from other myeloid cells. The ability of MDSCs to suppress T cell function is a unique and important characteristic; however, more cell-specific markers will be needed to be identified if these cells are to be thoroughly investigated.

Mechanisms of MDSC-mediated T cell suppression

The mechanisms by which MDSCs suppress T cell immune responses have been extensively studied by researchers in the field of tumor biology. A previous study found that these immunosuppressive properties were mainly related to two enzymes that are involved in the metabolism of L-arginine: arginase 1 and inducible nitric oxide synthase (iNOS)[3]. Both enzymes remove L-arginine from the local environment, thereby depriving T cells of this vital nutrient. Arginase 1 is involved in the generation of reactive oxygen species and iNOS is involved in the generation of nitric oxide (NO), both of which impair T cell functions. MDSCs also inhibit lymphocyte trafficking and viability, produce IL-10, and induce regulatory T cells, which are themselves suppressive[4]. Studies of experimental autoimmune encephalomyelitis (EAE)[5] and inflammatory bowel disease (IBD)[6] models suggest that MDSCs function by generating the production of NO. Another study of EAE suggests that MDSC-mediated immunosuppression requires programmed death ligand 1 (PD-L1)[7]. Both arginase 1 and iNOS are associated with MDSC-mediated suppression in the collagen-induced arthritis (CIA) model[8], and down regulation of T cell receptor ζ-chain (again mediated by MDSCs) contributes to autoreactive T cell silencing in mouse models of alopecia areata[9]. Taken together, these findings suggest that MDSCs exert their suppressive functions via multiple mechanisms. MDSCs suppress antigen-specific T cell responses in some models of autoimmune disease[6, 7, 10]; however, in other models, MDSCs are thought to suppress T cells in response to antigen-nonspecific stimulation (Table 1)[5, 8, 9, 11]. Antigen-specificity of immune suppression by MDSCs is considered to be influenced by the specific microenvironment, i.e., inflammatory microenvironments, and by the levels of activation of the target lymphocytes[12]. Thus, if MDSCs are developed for use in the clinic, care about antigen-specificity must be taken to ensure that their immunosuppressive function does not induce systemic immune suppression, thereby increasing the risk of infection.

Factors that trigger MDSC expansion

Granulocyte-macrophage colony-stimulating factor (GM-CSF) triggers the mobilization of $CD11b^+CD62L^+Ly6C^{high}$ monocytes from the bone marrow in the EAE model[13]; however, these cells are pathogenic because they are the precursors of dendritic cells and macrophages that cause

inflammation within the central nervous system. Tumor models have identified several factors that stimulate MDSCs. For example, GM-CSF is both necessary and sufficient to drive the development of MDSCs in a mouse model of pancreatic ductal adenocarcinoma[14], and tumor necrosis factor (TNF)-α drives the accumulation of MDSCs in subcutaneous tumor models[15]. TNF-α also increases the accumulation and the suppressive activity of MDSCs in a chronic inflammatory mouse model[16]. Given that both GM-CSF and TNF-α have important roles in the development of autoimmune diseases such as rheumatoid arthritis (RA), it is easy to speculate that these cytokines also play roles in the MDSC accumulation observed in autoimmune diseases, although further studies are needed to clarify this.

MDSCs in animal models of autoimmune disease

The roles of MDSCs have been investigated in various models of autoimmune disease (Table), including EAE[5, 7, 13, 17], IBD[6], type 1 diabetes mellitus[10], autoimmune inflammatory arthritis[8, 18], systemic lupus erythematosus(SLE)[19], alopecia areata[9], and experimental autoimmune uveoretinitis (EAU)[11]. Below, we discuss the roles of MDSCs in the EAE and autoimmune inflammatory arthritis mouse models.

The roles of MDSCs in autoimmunity have mainly been studied in EAE, which is an important animal model of multiple sclerosis (MS)[20]. Because pathogenic T cells play a crucial role in EAE, it is easy to speculate that MDSCs play a protective role. Indeed, granulocytic MDSCs do play protective roles in EAE[7]; however, monocytic MDSCs do not. Flow cytometry analysis reveals increased frequency of granulocytic MDSCs in the spinal cord infiltrates isolated from mice during the peak of EAE. The transfer of granulocytic MDSCs into EAE mice results in reduced demyelination and delayed disease onset, which are thought to be mediated through inhibition of pathogenic effector T cells. Immunohistochemistry analysis shows increased accumulation of granulocytic MDSCs at the inflammatory lesion in the meningeal area of spinal cord of granulocytic MDSCs — treated mice. By contrast, $Ly6G^{-}Ly6C^{high}CD11b^{+}$ monocytic cells appear to play pathogenic roles in EAE mice[5, 13, 17]. These findings suggest that the roles played by MDSCs are phenotype (i.e., granulocytic or monocytic) -dependent.

A previous study found that MDSCs in the synovial fluid of animals with proteoglycan-induced arthritis (PGIA), a model of RA, suppressed T cell proliferation *in vitro*[18]. We previously reported that MDSCs modulate CIA (a widely used animal model of RA) by inhibiting $CD4^{+}$ T cell-mediated proinflammatory immune response[8]. We found that the number of MDSCs increased at the peak of the disease, and after that there was a spontaneous improvement in the disease activity. We confirm increased frequency of $Gr\text{-}1^{+}$ cells in the synovium infiltrates isolated from mice during the peak of CIA by immunohistochemistry (unpublished data). Adoptive transfer of MDSCs obtained from the spleens of inflamed mice into CIA mice reduces the severity of arthritis *in vivo*, whereas depletion of MDSCs at recovery stage abrogates the spontaneous improvement in CIA. These findings indicate that MDSCs play a protective role in CIA by inducing a spontaneous improvement in the disease; thus, MDSCs might also play a protective role in patients with RA.

Human diseases

Few studies have examined the roles of MDSCs in human autoimmune disease. The number of $HLA\text{-}DR^{-/low}CD14^{-}CD33^{+}CD15^{+}$ granulocytic MDSCs in the peripheral blood of MS patients is increased, and the cells suppress the activation and expansion of autologous T cells[7]. There is a similar increase in the number of $CD14^{+}HLA\text{-}DR^{-/low}$ monocytic MDSCs in the peripheral blood of IBD patients, and these cells inhibit both the proliferation of autologous peripheral blood mononuclear cells and IFN-γ release[6]. The number of circulating $CD14^{+}HLA\text{-}DR^{-}CD33^{+}CD11b^{+}$ cells is increased in RA patients, and this increase is inversely correlated with the number of Th17 cells[21]; however, no direct roles for these cells are identified due to a lack of functional analysis. Overall, we know little about the roles of MDSCs in human autoimmune diseases, and further studies are needed to identify whether these cells have therapeutic potential.

MDSCs as a new form of cell-based therapy

Because MDSCs have the potential to suppress T cell-mediated immune responses, it is expected that they will be developed as a new form of cell-based therapy for T cell-driven autoimmune diseases. One possibility is the transfer of autologous MDSCs after activation *ex vivo*. Both IL-6 and TNF-α induce the *in vitro* generation of suppressive MDSCs from bone marrow precursor cells[22]. Thus, MDSCs could be cultured and expanded *ex vivo* in the

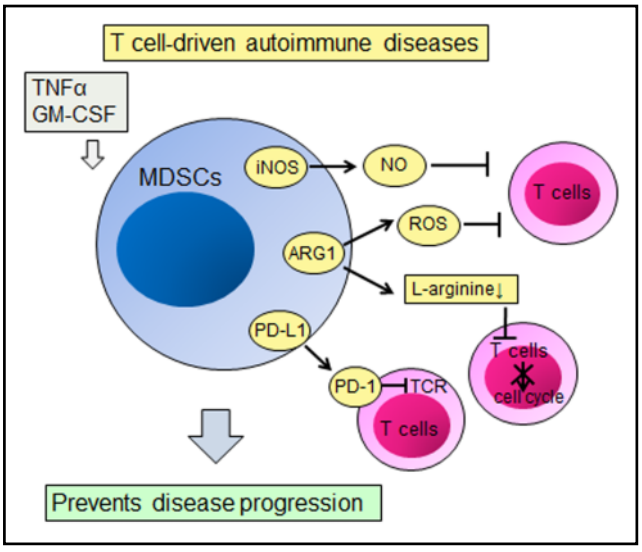

Fig.1 The roles of MDSCs in autoimmune diseases

In autoimmune disorders, MDSCs stimulated by cytokines (such as TNF-α and GM-CSF) prevent further disease progression by inhibiting the proliferation and activation of pathogenic T cells. iNOS: inducible nitric oxide synthase, NO: nitric oxide, ARG1: arginase 1, ROS: reactive oxygen species, PD-L1: programmed death ligand 1, PD-1: programmed death 1, TCR: T cell receptor.

presence of these cytokines and then transferred to the patient. Another possibility is to enhance the suppressive function of the endogenous MDSCs that accumulate naturally in patients with autoimmune diseases. This could be achieved via the administration of suitable drugs, although further studies are needed to explore the possibilities. Several questions still need to be answered. For example, how can MDSCs be reliably distinguished from neutrophils or monocytes? Can MDSCs be cultured *ex vivo*? Will MDSC-mediated immunosuppression increase the risk of infection? Despite these questions, therapeutic strategies based on endogenous MDSCs in patients with autoimmune diseases are appealing.

Conclusions

Several autoimmune disorders are characterized by the accumulation of MDSCs, which inhibit T cell recruitment and activation. We suggest that MDSCs accumulating in response to abnormal autoimmune or inflammatory environments may prevent further disease progression (Fig.1). Although many problems remain, therapies based on endogenous MDSCs could be a novel option for patients with autoimmune disease.

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Conflicts of interest

None declared.

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