Mini Review

Myeloid-derived suppressor cells in autoimmune diseases

Wataru Fujii1, *, Eishi Ashihara2) and Yutaka Kawahito1)

1) Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan
2) Department of Clinical and Translational Physiology, Kyoto Pharmaceutical University, Kyoto, Japan

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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*Correspondence should be addressed to:
Wataru Fujii, Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kamigyo-ku, Kyoto 602-8566, Japan. Phone: +81-75-251-5505, Fax: +81-75-252-3721, E-mail: snufkin@koto.kpu-m.ac.jp

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Introduction

Myeloid-derived suppressor cells (MDSCs) suppress T cell-mediated anti-tumor immune responses1), 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.
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−CD11b− granulocytic MDSCs and Ly6G Ly6C−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-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 suppressive4. 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) model8, and down regulation of T cell receptor ζ-chain (again mediated by MDSCs) contributes to autoreactive T cell silencing in mouse models of alopecia areata9. 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 disease6,7,8,9,10; however, in other models, MDSCs are thought to suppress T cells in response to antigen-nonspecific stimulation (Table 1)6,8,9,11. 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 lymphocytes12. 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+ monocytes from the bone marrow in the EAE model13; however, these cells are pathogenic because they are the precursors of dendritic cells and macrophages that cause
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MDSCs in animal models of autoimmune disease

The roles of MDSCs have been investigated in various models of autoimmune disease (Table), including EAE, IBD, type 1 diabetes mellitus, autoimmune inflammatory arthritis, systemic lupus erythematosus (SLE), alopecia areata, and experimental autoimmune uveoretinitis (EAU). 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). 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; 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$^{−}$CD11b$^{+}$ monocytic cells appear to play pathogenic roles in EAE mice. 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. We previously reported that MDSCs modulate CIA (a widely used animal model of RA) by inhibiting CD4$^{+}$ T cell-mediated proinflammatory immune response. 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-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-DR$^{−}$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. There is a similar increase in the number of CD14$^{+}$HLA-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. The number of circulating CD14$^{+}$HLA-DR$^{−}$CD33$^{−}$CD11b$^{−}$ cells is increased in RA patients, and this increase is inversely correlated with the number of Th17 cells; 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. Thus, MDSCs could be cultured and expanded ex vivo in the
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Quantiﬁcation of MDSCs

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.

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Conflicts of interest

None declared.

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