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The potential therapeutic role of myeloid-derived suppressor cells in autoimmune arthritis

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ABSTRACT

Objective: The aim of this review is to evaluate the roles of myeloid-derived suppressor cells (MDSC) in autoimmune arthritis.
Methods: The terms "myeloid-derived suppressor cells," "regulatory T cell," "Th17 cell" and "autoimmune arthritis" were used for literature search from the PubMed. The publications about the characteristics of MDSC, the immunosuppression of MDSC, the role of MDSC in the regulation of Tregs and Th17 cells, and the potential clinical applications of MDSC against rheumatoid arthritis (RA) were identified, retrieved and reviewed.
Results: MDSC are defined as a heterogeneous population of pathologically activated immature and mature myeloid cells consisting of granulocytic and monocytic subsets. Published data showed that the role of MDSC in Tregs and Th17 cells expansion were inconsistent. Given their role in suppressing T-cell responses, MDSC have been tested for their capability of preventing RA.
Conclusions: Although MDSC hold promise in the treatment of RA, their exact role in the expansion of Tregs and Th17 cells is unclear during RA. The definite effect of MDSC in RA therapy needs to be studied further.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease, which is characterized by the sequestration of various leukocyte subpopulations within both the synovial space and the developing pannus, resulting in the inflammation of multiple joints, following by destruction of the joint cartilage and erosion of bone [1]. It is generally accepted that $CD4^+$ T cells play a critical role in the initiation and perpetuation of this chronic inflammation. Th17 cells, characterized by the production of IL-17 and other pro-inflammatory cytokines, play a central role in RA pathogenesis and has aroused wide interest as treated target [2,3]. Th17 cells significantly increased in peripheral blood, inflamed synovial tissue, and synovial fluid from RA patients [3,4]. Regulatory T cells (Tregs) play a critical role in the maintenance of peripheral tolerance and the prevention of autoimmunity when the immune response is launched in patients with RA [5,6]. The loss of Th17/Tregs balance has been reported to be involved in the regulation of RA pathogenesis. MDSC are a heterogeneous group of myeloid cells that play an important role in the regulation of immune responses in inflammation, which are associated with autoimmunity. Although MDSC have been linked to T-cell tolerance, their role in autoimmune RA remains elusive. The potential association of MDSC with the disease pathogenesis of RA and their value in the treatment of RA will be discussed in this review.

MDSC are a heterogeneous family of myeloid cells

MDSC are a heterogeneous population of cells that consists of myeloid progenitor cells and immature dendritic cells (DCs), immature granulocytes and immature macrophages [7]. In healthy individuals, MDSC generated in the bone marrow quickly differentiate into mature granulocytes, macrophages or DCs. However, chronic inflammation associated with the pathological state blocks their normal differentiation leading to the expansion of MDSC [7]. In addition, MDSC also express histamine and histamine receptor 1 (HR1) which enhance the survival and expansion of MDSC [8]. In mice, MDSC are identified as cells that express CD11b and Gr-1. Gr-1 molecule includes the macrophage and neutrophil markers

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Ly6C and Ly6G, respectively. $CD11b^{+}Ly\text{-}6G^{-}Ly\text{-}6C^{high}$ cells have monocytic-like morphology and have been termed monocytic-MDSC (M-MDSC). $CD11b^{+}Ly\text{-}6G^{+}Ly\text{-}6C^{low}$ cells have granulocyte-like morphology and have been termed granulocytic MDSC (G-MDSC) [9]. In human, MDSC are defined as cells that express CD33 but lack expression of markers of mature myeloid and lymphoid cells [10]. MDSC accumulated and activated in secondary lymphoid tissues and peripheral areas of inflammation increase the production of reactive oxygen species (ROS), arginase 1 (Arg-1) and nitric oxide (NO) to suppress the immune responses of $CD4^{+}$ T cells, $CD8^{+}$ T cells and NK cells. Notably, the heterogeneity of MDSC indicates that there may be no unique phenotypic marker that precisely represents MDSC, and the suppressive activity is the ultimate defining characteristic.

Mechanisms of MDSC-mediated immune suppression

MDSC have been recognized in the last years as tolerogenic cells, since they are able to induce tolerance to a variety of immune response mediated by effector T cells, NK cells, and naïve T cells (Fig. 1). Both G-MDSC and M-MDSC could inhibit effector T cells by different ways [7]. G-MDSC predominantly plays the role of immune suppression by the production of ROS, whereas the secretion of Arg-1 and generation of NO are mainly used by M-MDSC [11]. Peroxynitrite which formed by the cooperative activity of ROS with NO is another factor that inhibits effector T cells [12]. Peroxynitrite leads to the nitration of tyrosines in the T-cell receptor (TCR)–CD8 complex. This reaction damages the conformational flexibility of TCR–CD8 complex, affects its interaction with peptide-loaded MHC-I and leads to the unresponsiveness of $CD8^{+}$ T cells to antigen-specific stimulation [13]. Moreover, peroxynitrite can damage the MHC-II expression and mediate T-cell apoptosis [7,14]. MDSC also directly down-regulate L-selectin (CD62L) on the surface of naïve T cells through the expression of ADAM17 (a disintegrin and metalloproteinase domain 17) which is an enzyme that cleaves the ectodomain of L-selectin. As a result, the ability of T cells to migrate from home to sites where they could be activated decrease, and the number of $CD4^{+}$ and $CD8^{+}$ T cells are reduced [15]. The suppressive activity of Arg-1 is based on its role in the hepatic urea cycle, metabolizing L-arginine to L-ornithine. Expression of Arg-1 has been reported to decrease CD3ξ-chain biosynthesis and down-regulate TCR on cell surface [16]. As a result, T cells are arrested in the G_0–G_1 phase of the cell cycle which is associated with a deficiency of protein kinase complexes that play an important role in G_1 phase progression [17]. In vitro, this phenomenon can be completely reversed by the replenishment of L-arginine [16]. In vivo, the depletion of G-MDSC can re-establish CD3ξ-chain biosynthesis and T-cell proliferation [17]. The shortage of L-arginine also inhibits T-cell proliferation by preventing up-regulation of the expression of the cell cycle regulators cyclin D3 and cyclin-dependent kinase 4 (CDK4) [18]. NO suppresses T-cell function involving the induction of T-cell apoptosis [19], the inhibition of MHC-II expression [20], and the inhibition of JAK5 and STAT3 in T cells [21]. MDSC also suppress T-cell response through cyclooxygenase 2 (Cox-2)-prostaglandin E_2 (PGE_2) axis [22]. Tumor-expanded MDSC induce anergy in NK cells via membrane-bound TGF-β or NKp30 receptor [23–25]. In addition to the suppressive effects on adaptive immune responses, MDSC also regulate innate immune responses. MDSC also suppress cytotoxicity of NK cell via inhibiting the production of NKG2D and interferon-γ (IFN-γ) in models of glioma [26]. Recent study showed that IL-13 mediated its effect through the IL-4R-STAT6 pathway and induced TGF-β-producing $CD11b^{+}Gr\text{-}1^{+}$ MDSC [27]. The production of TGF-β, IL-13, and IL-4 impairs the function of NK cell [28].

Regulation of Th17 cells by MDSC

Th17 cells are thought to play a detrimental role in the pathogenesis of collagen-induced arthritis (CIA) mice and patients with RA. The frequency of Th17 cells increased significantly in peripheral blood mononuclear cells (PBMC) of RA patients [4]. Blocking the function of Th17 cells could prevent the development of RA. In a recent study, Th17 cells have been used as a drug target for the treatment of RA [29]. Report on the interaction between Th17 cells

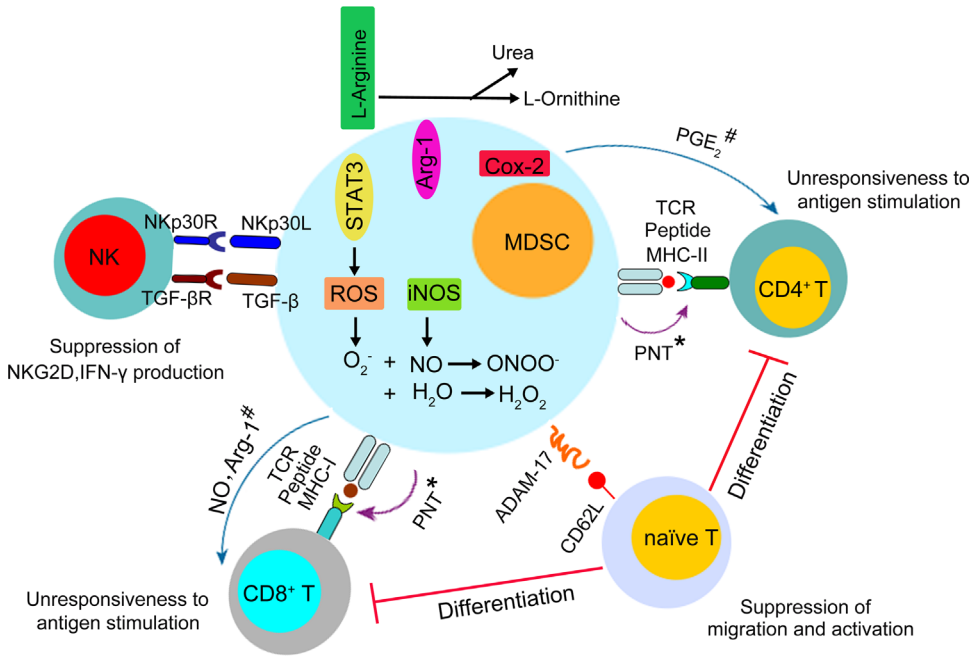

Fig. 1. Complex immunosuppression of MDSC in pathologic conditions associated with inflammation. See description in the text. *represents Ag-specific suppression, #represents non-specific suppression.