The Role of Myeloid-Derived Suppressor Cells in Rheumatoid Arthritis: An Update

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Abstract

Rheumatoid arthritis (RA) is an autoimmune disease that generally affects the joints. In the late stages of the disease, it can be associated with several complications. Although the exact etiology of RA is unknown, various studies have been performed to understand better the immunological mechanisms involved in the pathogenesis of RA. At the onset of the disease, various immune cells migrate to the joints and increase the recruitment of immune cells to the joints by several immunological mediators such as cytokines and chemokines. The function of specific immune cells in RA is well-established. The shift of immune responses to Th1 or Th17 is one of the most essential factors in the development of RA. Myeloid-derived suppressor cells (MDSCs), as a heterogeneous population of myeloid cells, play a regulatory role in the immune system that inhibits T cell activity through several mechanisms. Various studies have been performed on the function of these cells in RA, which in some cases have yielded conflicting results. Therefore, the purpose of this review article is to comprehensively understand the pro-inflammatory and anti-inflammatory functions of MDSCs in the pathogenesis of RA.

Keywords: MDSC; Rheumatoid Arthritis; Inflammation; Autoimmunity

Introduction

RA, as a common autoimmune disease, has a worldwide prevalence of 0.5 to 1 percent. Due to a loss of tolerance to self-proteins, RA often presents with symmetrical polyarthritis in hand or foot's synovial joints. The development of RA requires a high-risk genetic background in association with epigenetic markers and environmental factors. Environmental factors, including smoking, hormones, obesity, dietary factors, lifestyle, and infections, have been associated with an increased RA risk. Also, advances in medical genetic have led to genes being discovered that can increase RA susceptibility. The strong association between RA and human leukocyte antigen DRB1 (HLA-DRB1 * 04) has been reported in 80% of patients. These risk factors may trigger post-translational modifications by activating the enzyme peptidyl arginine deiminase 4, which changes protein structure by citrullinating residues of C-terminal arginine. Loss of tolerance to these neopeptides triggers an immune response that generates specific autoantibodies, such as Anti-CCP (Anti-cyclic citrullinated peptide). In the serum and synovial fluid of people with RA, an autoantibody (in most cases IgM) is found, known as rheumatoid factor (RF). RF reactions with the FC portion of IgG immunoglobulin, leading to the formation of an immune complex. Deposition of these immune complexes causes symptoms of the disease. Approximately 80% of RA patients have been reported to have at least one of the two autoantibodies, Anti-CCP and RF (1).

The pattern of RA joints changes starts with inflammation of the soft tissue and continues with cartilage destruction. The final stage is characterized by marginal bone erosion, which is seen along with a decrease in bone density around the joints. Joint involvement starts after joint-resident cells such as fibroblast-like synoviocytes (FLS) interact with joint infiltrated cells (B and T lymphocytes, macrophages, and dendritic cells). The interaction between dendritic cells and lymphocytes occurs as an autoimmune reaction to self-proteins containing citrulline in the lymph node. Numerous studies have shown that in RA, activated pro-inflammatory helper T cells (Th1) increase, whereas anti-inflammatory helper T cells (Th2) are seldom identified. Subsequently, Th1 cells increase the penetration of macrophages and neutrophils into the joint by secreting inflammatory cytokines and chemokines. One of the essential factors in the development of RA is the imbalance between Th1 and Th2 cells, leading to an increase in IFN-γ (interferon-gamma) produced by Th1 and decreased IL-4 produced by Th2, which is associated with augmented inflammation. In the peripheral blood of patients with RA, the percentage of Th1 cells, the Th1/Th2 ratio, and the shift of responses to Th1 increase significantly. Currently, Th17 is recognized as an essential cell group in the development of RA. These cells are known to secrete IL-17, which may induce pro-inflammatory mediators, which plays a critical role in the progression of inflammation. The increased population of Th17 lymphocytes also plays a vital role in generating and sustaining the inflammatory process in RA (Fig.1).

Treg cells (T regulatory cells, $CD4^{+}CD25^{+}$) inhibit immune responses as well as autoimmune lymphocytes. These cells function through various mechanisms, including cell-cell interactions and the secretion of inhibitory cytokines such as IL-10 and TGFβ (Transforming growth factor β). Studies also found that the population of regulatory cells declines in autoimmune conditions such as RA.

The human body has many pathways that recognize and remove self-reactive B cells in two different stages. In the first step, self-reactive B cell deletion occurs in the bone marrow, called the central checkpoint. During this stage, B cells that can recognize self-antigens are deleted to avoid autoimmune diseases. Outside the bone marrow, peripheral checkpoints exist where B cells tolerate to self-antigens, so no immune response is formed. The peripheral checkpoint is monitored by regulatory T cells. In RA patients, peripheral and central checkpoints are disrupted, leading to self-reacting B cells development. Studies show that the number of self-reactive B cells in these patients is 3.4 times higher than in healthy individuals.

Various medications are used to treat RA, primarily non-biological disease-modifying anti-rheumatic drugs (DMARDs), including hydroxychloroquine, methotrexate, leflunomide sulfasalazine. In advanced stages of the disease, biological agents such as TNF (Tumor necrosis factor) inhibitors or lymphocytes inhibitors can be used. TNF inhibitors are pharmaceutical medications that are used to treat inflammatory diseases like RA. This class of drugs inhibits the inflammatory effects of TNF, hence used to help reduce inflammation. Another therapeutic strategy for RA is lymphocyte suppression. Leflunomide is a T-lymphocytes inhibitor used alone or in combination with other drugs. Inhibition of T-lymphocytes can be useful in the suppression of inflammatory immune responses in RA. Using such medications may have adverse side effects. It was also found that these agents' use is not effective in approximately 30% of patients or may increase infections' susceptibility.

Taking advantage of cell therapy promise has raised high hopes for treating RA (3 ,2). Myeloid-derived suppressor cells (MDSCs) as a heterogeneous population of myeloid cells derived from immature myeloid precursors and proliferate under pathological conditions. MDSCs play a regulatory role in the immune system and inhibit T cells' function through many mechanisms. Evidence suggests that MDSCs have the potential to suppress antigen-dependent and antigen-independent T cell activation (4). MDSCs employ a variety of means to inhibit the immune response against tumors. Many research studies have demonstrated these cells' role in cancer's pathogenesis (6 ,5). Since MDSCs have the property of regulating the immune response, consideration has been given to those cells' role and function in autoimmune diseases and their therapeutic application in their treatment. In this aspect, there is a need for a more complete and comprehensive understanding of the MDSCs' role in autoimmune disease. In this review, we discuss the phenotype and function of MDSCs in autoimmune diseases and then examine these cells' role in RA.

Differentiation and morphological characteristics of MDSCs

Hematopoietic stem cells (HSCs) are differentiated into different types of cells in the blood. In the myeloid lineage, granulocyte-monocyte progenitor cells (GMP) differentiate into innate immune system cells, including granulocytes and monocytes. Colony-stimulating factor (CSFs) play an important role in differentiating GMP to monocyte progenitor (MP) or granulocyte progenitor (GP) by altering protein gene expression. Granulocyte progenitors are associated with increased regulation of CCAAT enhancer-binding proteins (C/EBP) α and β, granulocyte-macrophage colony-stimulating factor receptor (GM-CSFR), growth-factor independent-1 protein (Gfi-1), and granulocyte colony-stimulating factor Receptor (G-CSFR). In contrast, monocyte progenitors are

associated with an increased regulation of PU.1 (SPI1), interferon-regulatory factor 8 (IRF8), early growth response proteins 1 and 2 (Egr), GM-CSFR, and macrophage colony-stimulating factor receptor (M-CSFR) (7-9). In acute inflammation, monocyte and granulocyte progenitor proliferate and differentiate into granulocytes and active pro-inflammatory monocytes, respectively. Pro-inflammatory monocytes have the potential to differentiate into macrophages and dendritic cells after migration to various tissues (10). Disruption of myeloid ancestors' differentiation into adult immune cells in chronic inflammatory conditions, including chronic infections, cancer, and autoimmune diseases, leads to immature myeloid cell development called MDSCs (11-13). Monocyte progenitor differentiates into monocytes and M-MDSCs (monocytic myeloid-derived suppressor cells), and granulocyte differentiation into granulocytes and PMN-MDSCs (polymorphonuclear myeloid-derived suppressor cells) (Fig.2). Continuous stimulation of the myeloid cell compartment with signals from tumors or chronic inflammatory sites results in the differentiation of MDSCs with low phagocytic capacity and high levels production of myeloperoxidase (MPO), nitrogen oxide (NO), reactive oxygen species (ROS), and anti-inflammatory cytokines. Consequently, these cells cannot effectively perform myeloid cells' normal functions and can suppress the immune cells (15 ,14). Several transcription and regulatory factors are involved in the differentiation pathway of MDSCs cells (Table 1). MDSCs require specific signals for activation and expansion, including interleukin 6 (IL-6), GM-CSF, and M-CSF (16). Most of these factors stimulate the signaling pathways that promote myeloid cells' proliferation and inhibit their differentiation into adult cells in the bone marrow (17). M-MDSCs and PMN-MDSCs are two categories of MDSCs based on specific markers expression, which are morphologically similar but genetically distinct to monocytes and neutrophils, respectively (Table 2). Many studies have been performed on MDSCs in animal and human models. MDSCs show high elastic properties and respond quickly to changing conditions such as infection, cancer, and inflammation. Many studies in animal and human models have shown that MDSCs have potent immunosuppressive properties. Much of the knowledge gained about these cells come from using animal models. MDSCs function has many similarities in animal and human models; for example, MDSCs in the mouse and human system were found to express CD39/CD73, which have a similar function (16-18).

The mechanism for immune response inhibition by the MDSCs

MDSCs play a role in regulating antitumor immune responses. These cells cause developing tumors by stimulating tumor cell invasion, angiogenesis, and premetastatic niche development (20 ,19). MDSCs modulate immune cell function such as lymphocytes T and B, macrophages, NK cells, NKT cells, and Treg cells (22 ,21). NK cells originate from hematopoietic progenitor cells in the bone marrow that have the $CD56^+$ /$CD16^+$ phenotype. Studies indicate that the NK cell population increases in the joint and peripheral blood of RA patients. The destructive effects of NK cells are induced by cytokines and granules containing perforin and granzyme(23). NKT cells originate from the bone marrow and express TCR (T cell receptor) on their surface in addition to NK cell markers. IL-4 produced by NKT cells can differentiate Th cells into Th2, which is effective in reducing inflammation. The decreased population of NKT cells in RA patients can be one reason for the increase in inflammation (24). In the following, we will explore the mechanism of MDSCs' action in the immune system.

The inhibition of T-cell activity by MDSCs is mainly regulated by three metabolic processes, including (1) arginase-1 (Arg1) and arginine intake, (2) the production of inducible nitric oxide synthase (iNOS) and nitric oxide (NO), (3) the production of reactive oxygen species (ROS) including superoxide anion (O_2^-), peroxynitrite ($ONOO^-$) and hydrogen peroxide (H_2O_2). PMN-MDSCs and M-MDSCs inhibit T cell proliferation using various mechanisms. PMN-MDSCs express high ROS (Reactive oxygen species) and low NO, while M-MDSCs increase NO and reduce ROS, and both express Arg1. Since ROS is only stable and shortly activated, strong cellular interaction with T lymphocytes is needed for PMN-MDSCs to exercise their role(25). M-MDSCs produces abundant amounts of Arg1, NO, and immunosuppressive cytokines. Since these molecules have a prolonged half-life than ROS, there is no need for cellular contact between M-MDSCs and T cells. Furthermore, M-MDSCs inhibit nonspecific T cell responses effectively ,26) (27. In the following sections, various mechanisms used by MDSCs in inhibiting the immune response are described (Fig.3).

1. MDSCs consume vital T cell nutrients in the microenvironment.

One mechanism is through the reduction of required amino acids and the production of immunosuppressive metabolites. Metabolic conversion of L-arginine (L-Arg) via iNOS or Arg1 is the first and foremost mechanism of immunosuppression by MDSCs. The Arg-1 inhibitory activity is related to the hepatic urea cycle, which metabolizes L-arginine to L-ornithine. Arg1 reduces the nutrient T lymphocyte (by consuming L-arginine) in the microenvironment and produces ornithine and polyamines, inducing tumor cell proliferation (29 ,28). iNOS causes T cell death by producing NO and tyrosine nitration (reaction of a nitro group to an organic chemical compound) and S-cysteine nitrosation (converting organic compounds into nitroso derivatives) of various proteins. Low levels of L-arginine in the microenvironment reduce the zeta chain expression of the TCR-CD3 on T cells. It also stops cell cycling in the G0/G1 phase by preventing the re-expression of cyclin-dependent kinase 4 (CDK4) and cycle regulators cyclin D3 in T cells (31 ,30).

The dendritic cells (DC) and macrophages (MQ) take up cystine through the Xc- transporter (encoded by the *SLC7A11* gene) and transform it into cysteine. The ASC transporter (encoded by the *SLC7A10* gene) releases cysteine from these cells in the microenvironment, and then T lymphocytes import it via the ASC transporter. T lymphocytes are unable to produce cysteine due to lack of cystathionine gamma-lyase; on the other hand, due to lack of Xc-transporters, they cannot absorb cystine into themselves. Hence, T lymphocytes rely on other cells to provide the required cysteine, such as DC and MQ. Moreover, MDSCs import cystine through Xc- transporters and convert it to cysteine but cannot export it due to the lack of an ASC vector. Therefore, the extracellular reservoir of cysteine required for T cells is limited, and thus the function of T lymphocytes is disrupted (32).

MDSCs can also suppress immune cell activity via L-tryptophan degradation. MDSCs produce large amounts of IDO1 (Indoleamine 2,3-Dioxygenase 1), which converts tryptophan to kynurenine, which caused increased Treg cell proliferation. Also, kynurenine decreased NK cell proliferation and activity, zeta chain expression of the TCR-CD3, and DC immunogenicity. On the other hand, it deprives T cells of essential nutrients (Fig.3 A).

2. MDSCs release a wide range of immunosuppressive molecules.

These mediators include reactive nitrogen species (RNS) and reactive oxygen species (ROS). O_2^- , H_2O_2, NO, and $ONOO^-$ are produced by MDSCs through the activity of NADPH oxidase, Arg-1, and iNOS. These molecules have different types of immunosuppressive effects on T cells, so that H_2O_2 disrupts the expression of the zeta chain TCR-CD3 and inhibits T cell proliferation, and induces apoptosis. NO inhibits IL-2 signaling, T cell proliferation, and migration. $ONOO^-$ increases apoptosis of T cell with nitration or nitrosylation (Covalent bond between a nitrosyl moiety of nitric oxide with an organic molecule) of multiple target molecules TCR-CD3, CD8, and CCL2, which ultimately inhibits T cell activation (34 ,33). Both ROS and iNOS pathways decrease L-arginine in the microenvironment related to the reduced T lymphocyte function ,30) (35 (Fig.3 B).

3. Expression of immune system inhibitor receptors. MDSCs may also suppress T cell function through direct involvement of T cell inhibitory receptors and apoptosis-inducing receptors. MDSCs express high levels of inhibitory receptor ligands such as PD-L1 (Programmed Death Protein 1), Fas Ligand, and Galectin-9. The interaction of these ligands with their expressed receptors on the T cell surface, PD-1, Fas/CD95, and Tim-3 (T cell immunoglobulin domain and mucin domain 3), leads to T cell apoptosis. In response to various microenvironmental signals, such as IFN-γ, hypoxia, VEGF, and MCSF, MDSCs up-regulate PD-L1 expression (36) (Fig. 3 C).

4. MDSCs accumulation by S100A8/A9. MDSCs facilitate accumulation through an autocrine S100A8/A9 (S100 calcium-binding protein A8/A9) feedback loop. MDSCs synthesize and secrete calcium-binding proteins, S100A8, and S100A9, which bind to the receptor's N-glycan motif for advanced glycation end products (RAGE) on the surface of MDSCs. S100A8/A9 interaction with these receptors increases the accumulation and migration of MDSCs, prevents myeloid progenitor cell differentiation, and attracts MDSCs to the tumor microenvironment. Besides, in cancer models, IL-6, IL-1β, and PGE2 (Prostaglandin E2) have also been identified as essential factors for infiltration MDSCs at the inflammation site (37-39) (Fig.3 D).

5. Production of extracellular adenosine. Ectonucleotidases CD39 and CD73 are found on many cancer cells, and some immune cells such as MDSCs. The function of these markers is to hydrolyze ATP or AMP to adenosine. In the tumor microenvironment, ATP and adenosine have pro-inflammatory and immunosuppressive roles, respectively. Extracellular adenosine is an immunosuppressive agent that signals through the A2a and A2b receptors on various immune cells' surface. Maintaining a balance between these two ectonucleotidases is the key to regulating immune responses in the tumor microenvironment. Adenosine inhibits the function of DC through inhibition of maturation, IL-12 secretion, and promoting the production of the immunosuppressive molecules. It also inhibits the activity of effective T cells, NKT cells, and NK cells. On the other hand, it causes an increase in M2 Macrophages and Treg cell activation (40-42)(Fig.3 E).

6. Production of PGE2 and inhibitory cytokines. MDSCs also produce a high level of immunosuppressive cytokines such as TGFβ and IL-10, which differentiate Treg cells. They have a direct inhibitory effect on the effector T cells (43). Together, these cytokines inhibit the

activation, differentiation, proliferation, and the production of cytokines by effector T cells. TGFβ induces FoxP3 (Forkhead box protein P3) expression in $CD4^+/CD25^-$ T cells to promote a repressive phenotype, while IL-10 converts active T cells to Tr1 cells producing IL-10, TGFβ. TGFβ also reduces the expression of NKG2D (natural-killer group 2 member D, also known as KLRK1 and CD314) and NKp30 (or CD337, as a stimulatory receptor) on NK cells and $CD8^+$ T cells, leading to reduced proliferation and cytotoxicity. It also increases macrophages' polarization toward an M2 phenotype and inhibits DC maturation, migration, expression of costimulatory molecules, and IL-12 production. Macrophages are generally classified into two groups: M1 macrophages are macrophages activated by IFN-γ along with lipopolysaccharide (LPS) or TNF, while M2 refers to macrophages activated by IL-4. M1 macrophages have a pro-inflammatory function, but M2 macrophages have anti-inflammatory activity.

Studies have shown that MDSCs suppress the immune system via secrete exosomes containing various molecules, such as S100A8 / 9, ARG1, and oncogenic miR-126a (44-49). MDSCs can suppress T cell function via IFN-γ and TGFβ. Blocking IFN-γ production by active T cells reverses the MDSCs-mediated T cell suppression. TNF signaling increases MDSCs survival and inhibits apoptosis, leading to MDSCs accumulation at the inflammation site (50-52). MDSCs also produce PGE2 through increased expression of COX2 and PGES1 enzymes. PGE2 made by MDSCs, in autocrine state and through its receptor on the surface of MDSCs, up-regulates Arg1 expression and increases their suppressive activity. Also, PGE2 has been shown to differentiate MDSCs from hematopoietic stem cells, thereby promoting the development of MDSCs. PGE2 also inhibits CTL (Cytotoxic T lymphocytes) and NK cells cytolysis activity and IFN-γ production. PGE also inhibits the early stages of dendritic cell differentiation, IL-2 production, and T cell response (Fig.3 F).

7. MDSCs modulate T cell homing to the lymph nodes. MDSCs restrict naive T cells' movement to lymph nodes by increasing ADAM17 (a metalloproteinase and disintegrin) expression, which leads to the down-regulation of CD62L on naive T cells. MDSCs can also impair the effector T cell recruitment by down-regulating CD162 and CD44 adhesion molecules. CD62L plays an essential role in T cells trafficking from blood to the lymph nodes, where they can be activated. In the presence of MDSCs, CD62L cleaves on naive T cells with ADAM17, thus preventing them from migrating. In contrast, MDSCs facilitate Treg $CCR5^+$ cell recruitment by producing CCL3, CCL4, and CCL5 (53-55).

The role of MDSCs in autoimmune diseases

The tolerance process to self-antigens is a well-regulated mechanism that involves both innate and acquired immunity and leads to the elimination or inhibition of autoreactive cells. In autoimmune diseases, this process is disrupted, and the self-reacting lymphocytes are not eliminated from the microenvironment, which can trigger autoimmune diseases. Genetic and environmental factors have a significant role in disrupting the tolerance process in autoimmune diseases, resulting in self-reacting B and T cell development (56).

In autoimmune diseases and some infectious diseases, the host immune response cannot remove the immune system's interior or external stimuli. This constant immune response leads to chronic inflammatory conditions. Chronic inflammation can cause pathological differentiation of myeloid

cells. The development of MDSCs has been reported following chronic inflammatory conditions and in autoimmune diseases (13). Innate immune system activation, cytokines and growth factor production are the main regulators of M-MDSCs proliferation in infections (58 ,57).

Furthermore, MDSCs are responsible for immune system regulation in inflammatory disorders. In pathological conditions, the infiltration of M-MDSCs is triggered to limit the effector T cell functions and utilize Treg to alleviate the inflammation and maintain immune homeostasis. In tumors, increased MDSCs activity can have adverse effects that ultimately reduce the effective immune response to tumors. On the other hand, MDSCs activity through the increase of regulatory cells and the inhibition of effector cells can play an important role in controlling autoimmune diseases because of the modulated immune responses. Despite their detrimental role in tumors, beneficial properties of MDSCs have been assessed in several models of autoimmune disorders (59). In this regard, new studies indicate that the infiltration of MDSCs in the secondary lymphoid organs of autoimmune disorders patients (60 ,13). Therefore, the insight of using MDSCs to treat autoimmune diseases has been considered. Under stable status, MDSCs reside predominantly in the bone marrow. In pathological situations, the MDSCs population expands and is detectable in the lymph nodes, spleen, blood, and microenvironment around cancerous tumors. In an experimental study of autoimmune uveoretinitis, the nitric oxide-producing monocytes were accumulated in the choroid and retina, associated with disease severity (61). Subsequent investigations revealed similar results and identified these cells as MDSCs (62). Experimental studies show that MDSCs existed in the spinal cord's affected areas in the MS mouse model. Another study using experimental autoimmune encephalomyelitis (EAE) indicated that splenic MDSCs accumulation was related to disease progression (63). It was demonstrated that MDSC expansion is a progressive process, beginning before the symptom onset and continuing during symptomatic stages. The highest level of MDSCs occurs in the active phase of the disease, which declines in the remission phase and tends to be at a stable level in the elimination stage. Consistent with previous studies, in collagen-induced arthritis (CIA) mice, MDSCs accumulation in the spleen was associated with different disease stages (64). In humans, increased MDSCs in active MS were followed by a slight increase in the remission phase (65).

Regarding the pathogenic potential of monocytes/macrophages in autoimmune arthritis, clinical studies against the CC chemokine receptor 2 (CCR2) were unsuccessful (66-68). On the other hand, the development of CIA in mice with a CCR2 deficiency is more severe (70 ,69). The underlying mechanisms in the development of exacerbated disease are not known. However, findings indicated that M-MDSCs are absent in collagen-induced CCR2-deficient mice because CCR2 is required to migrate M-MDSCs from bone marrow (71). Besides, M-MDSCs derived from the bone marrow of collagen-induced $CCR2^{-}$ deficient, inhibit $TCD4^{+}$ cell proliferation and reduce the severity of CIA, proposing that M-MDSCs are necessary to regulate autoimmune arthritis (72). It has also been shown that in CIA mice, MDSCs inhibit T cell proliferation and differentiate to Th17 cells (64). Researchers used the $CD11b^{+}$ $Gr\text{-}1^{+}$ spleen population and considered Arg1 and nitric oxide as inhibition mechanisms. The Gr-1 antibody recognizes both Ly6G and Ly6C surface antigens, so it can be said that the cell populations used for these studies include PMN-MDSC and M-MDSC.

The inflammatory impacts of MDSCs are mostly mediated by promoting Th17 cell differentiation and TCD8$^+$ cell activation, which is comprehended in animal models (73 ,53). Human MDSCs are determined as CD14$^+$ CD16$^+$ and CD14$^+$ CD16$^-$ cells. Synovial fluid and serum from RA patients are rich in CD14$^+$ cells (75 ,74). MDSCs have recently been shown to mediate improved suppressive functions of Treg cells (74). In the study mentioned, Treg cells were isolated from healthy individuals, and the suppressive property and cytokine expression were examined after co-culture with CD14$^+$ cells. The results showed an increase in Tregs population and expression of TNF-α, IFN-γ, IL-10, and IL-17. They have also improved the ability to suppress T cell proliferation and pro-inflammatory cytokine production. Despite raised cytokine production, cells retained the CD25$^+$ FoxP3$^+$ CD39$^+$ Treg phenotype and inhibited proliferation and inflammatory cytokines production by effector T cells.

Looking closer at studies of MDSCs and autoimmune diseases, it can be concluded that the role of these cells in hindering or progressing the disease depends on several factors. One of the most important is the local microenvironment, regulating immune cells' function, and MDSCs are no exception.

Distribution of M-MDSCs and PMN-MDSCs in RA

M-MDSCs have a more inhibitory effect in tumor mouse models than PMN-MDSCs, but the frequency of PMN-MDSCs in circulation is higher than M-MDSCs (76). Both PMN-MDSCs and M-MDSCs play a pivotal role in RA, and the frequency of PMN-MDSCs in blood, lymph nodes, spleen, and paws is higher than M-MDSCs. These cells use relatively distinct pathways to suppress the immune response, but PMN-MDSCs are generally more repressive than M-MDSCs (77-79). Adaptive transfer of PMN-MDSCs alleviates joint damage in CIA mice. PMN-MDSCs also inhibits T cell proliferation and Th17 cell differentiation more strongly than M-MDSCs, and induce Treg cell differentiation through pathways such as IL-10, TGFβ1, CCR5, and CXCR2 ,79) (80.

The role of MDSCs in inhibiting or inducing Th17 and Treg responses

Two perspectives exist regarding the role of MDSCs in RA. Some studies have shown that in patients with RA, MDSCs inhibit Treg cell response and induce Th17 cell differentiation associated with the disease's worsening. On the other hand, some evidence indicates the opposite effects of MDSCs on Th17/ Treg cell balance, decreasing Th17 cell differentiation and increasing Treg cell population, which is correlated with a relative improvement in the disease. This incompatibility can be due to the flexibility of differentiation between Th17 and Treg cells. Certain variables that may assess the anti-inflammatory or pro-inflammatory role of MDSCs in RA may also be the interaction of different immune cells with MDSCs and cytokine composition in the microenvironment, as well as the disease stage. We will discuss the inflammatory and anti-inflammatory function of MDSCs in RA in greater detail below.

Cytokine profile in synovial fluid plays a vital role in RA's pathogenesis since they promote the differentiation of TCD4$^+$ cells into pro-inflammatory and anti-inflammatory Tcell populations, including Th1, Th2, Th17, and Treg cells (13). Elevated levels of Th17 inflammatory cells, as well as defects of Treg anti-inflammatory cells, have been identified in human and experimental

arthritis; however, the mechanisms regulating Th17/Treg cell imbalances resulting in RA remain unclear (85-81). MDSCs increased in peripheral blood and synovial fluid in patients with RA ,86) (87 and spleen, paws, bone marrow, and lymph node drainage (DLN) in mouse models of RA ,77) (88 ,78. The surface markers used in some studies to identify MDSCs are listed in Table 3.

There is scarce data on peripheral distribution MDSCs in various autoimmune disorders. Multiple cytokines are involved in the pathogenesis of MDSCs accumulation in RA, including IL-6, IL-17, and TNF-α. Increased serum levels of TNF-α have been associated with RA and CIA formation. (84). In experimental autoimmune models, the upregulation of TNF-α and GM-CSF increased the proliferation of MDSCs. (90 ,89). However, other contradictory studies regarding MDSCs indicate that their function is reversible according to the surrounding microenvironment. Some animal data reported reduced severity of autoimmune disorders by MDSCs (92 ,91) while others showed worse prognosis (94 ,93). The small-scale environment around the cell is called the microenvironment, which contains physical and chemical signals (includes electrolytes, pH, temperature, oxygen, immune mediators like cytokines, metabolites) that can directly or indirectly affect cellular behavior (95, 96). The microenvironment contents determine the cell's behavior, so that naive T cells present in the microenvironment containing the IL-4 can lead to the differentiation of Th2 cells. In contrast, the presence of IFN-γ in the microenvironment can induce Th1 differentiation(97). The function of MDSCs in cancer has been extensively studied, and there is evidence of MDSCs immunomodulatory function that can lead to cancer progression(98, 99). Therefore, using the MDSCs immunomodulatory potential to reduce inflammation in autoimmune diseases was an excellent suggestion. There have been many studies on the use of MDSCs in autoimmune diseases, some of which indicate these cells' effectiveness in curing the disease. Still, others have reported conflicting results that indicate increased inflammation after using MDSCs. It can be said that MDSCs microenvironment can play an important role in the inflammatory or anti-inflammatory function of these cells, so that in the tumor microenvironment, the predominant function of these cells is immunomodulatory. In contrast, in the autoimmune microenvironment, they can perform inflammatory functions in some cases. MDSCs microenvironment determines the role and function of these cells in their autoimmune patients. Many studies are needed to better understand the behavior of MDSCs in different microenvironments, and it is not yet possible to say what factors affect the behavior of MDSCs in the autoimmune microenvironment. It is possible that the conflicting results obtained from the studies are due to the influence of different factors on MDSCs such as types of MDSCs (PMN-MDSCs or M-MDSCs), the source of MDSCs, the dose of MDSCs, and the stage of diseases, which requires further investigation in the future. Hence, the microenvironment is an essential factor to be considered in all studies to provide accurate outcomes. MDSCs are vital in controlling autoimmune processes, but their role in RA is controversial. MDSCs mediate the function of T lymphocytes and could be useful in the treatment of RA. The exact function of MDSCs on RA is still unknown, with some reports suggesting that adaptive transmission of MDSCs may have a therapeutic effect on the animal model of RA ,64) (100-103 ,88, but some other articles have reported an exacerbation of inflammatory arthritis after transmission of MDSCs to mice (104 ,78 ,77). In the following, we review studies that have examined the anti-inflammatory and pro-inflammatory role of MDSCs in RA.

The anti-inflammatory role of MDSCs in RA

Egelston et al. (2012) investigated that synovial fluid of proteoglycan-induced arthritis (PGIA) mice contained about 90% of the PMN-MDSCs. This study showed that MDSCs suppress DC maturation and T cell proliferation through ROS and iNOS. Synovial fluid cells significantly inhibit the proliferation of DC-activated autologous T cells but do not affect the proliferation of anti-CD3- or CD28-stimulated T cells, so these cells could have the ability to restrict the expansion of autoreactive T cells (105).

A study conducted in 2013 showed that plasma levels of MDSCs and Arg-1 in patients with RA were more significant than in the healthy group. The frequency of Th17 cells in patients with RA was significantly higher than healthy control and negatively correlated with the frequency of MDSCs and plasma Arg-1. A negative correlation has also been observed between MDSCs and plasma TNF-α. The negative correlation between the rise of circulating MDSCs and Th17 cells in patients with RA provides new insights into the mechanisms involved in RA. These findings suggest that cross-inhibition may exist between MDSCs and Th17 cells and that dynamic interaction might be meaningful in RA development (106).

In research performed by Fujii et al. (2013), MDSCs were found to play a significant role in regulating the inflammatory immune response in a CIA mouse model. In this study, MDSCs accumulation was shown in the spleen of CIA mice with high arthritic severity. Experimental studies have indicated that MDSCs inhibit TCD4 cell proliferation and differentiation into Th17 cells and inhibit cytokine production by TCD4 cells such as IFN-γ, IL-2, TNF-α, and IL-6, also increases IL-10 production. MDSCs adoptive transmission to CIA mice reduces disease severity, which is associated with a decrease in the number of TCD4 and Th17 cells in the lymph nodes. It can be argued that MDSCs in the CIA inhibit disease progression by inhibiting the pro-inflammatory immune response of TCD4 cells (52).

Júlia Kurkó et al. (2012) found that the predominant population of MDSCs is PMN-MDSC, which is detectable in the synovial fluid of patients with RA. These cells are usually inflammatory neutrophils. Their presence in synovial fluid is likely beneficial since they can restrict T cells' infiltration to RA patients' joints. The proliferation of autologous T cells induced by specific and unspecific antigens was significantly inhibited by RA synovial fluid cells. However, the simultaneous comparison has shown that RA synovial fluid cells have a more intense suppressive impact on autologous T cells' alloantigen-induced proliferation than nonspecific antigen-stimulated (autologous T-stimulated by anti-CD3/CD28) (86).

Another study found that MDSCs (CD11b+ Gr-1+) population increased with the disease's progression in CIA mice's spleen. PMN-MDSCs have demonstrated a more robust capacity to suppress polyclonal T cell proliferation compared to M-MDSCs. The adaptive transmission of PMN-MDSCs reduces joint inflammation, along with decreased cytokine secretion and Th1/Th17 cell differentiation in lymph nodes. However, the adaptive transmission of M-MDSCs does not affect inflammation, and although it inhibits T cell proliferation, it does not inhibit Th1 differentiation. It also causes a limited differentiation to Th17. These findings reveal a change from highly repressive PMN-MDSCs to weakly suppressive M-MDSCs during experimental arthritis progression, indicates that M-MDSCs are unable to suppress autoimmune arthritis (80).

Another study investigated the M-MDSC percentage in CIA mice. In mice with CCR2-deficiency, MDSCs were absent in the periphery, which was associated with the disease's worsening, and the administration of M-MDSC prevented disease progression. Isolated M-MDSCs from immunized mice inhibit autologous TCD4 cell proliferation via NO and IFN-γ production, but independent of IL-17. Besides, M-MDSCs from CIA mice also inhibit autologous B cell proliferation and antibody production. M-MDSCs suppress B cells by cell-cell contact and NO and PGE2 production. M-MDSCs may play a role in disease improvement by inhibiting the B and T cells (107).

A study by Perfilyeva et al. found that MDSCs increased in the spleen of adjuvant-induced arthritis mice. MDSCs contributed a lot in generating an immunosuppressive microenvironment that is a typical characteristic of chronic inflammation. MDSCs suppressed the proliferation of T lymphocytes by secreting ROS (108).

Another study examined the therapeutic effect of MDSCs in the animal model of rheumatoid arthritis (CIA). In vitro examination has shown that MDSCs suppress IL-17 production and increase FOXP3 expression in mice's TCD4 cells. In vivo injection of MDSCs significantly improves inflammatory arthritis. In MDSCs-treated mice, Th17 and Th1 cells decreased while Treg cells increased in the spleen, possibly via IL-10. MDSCs inhibited T cell proliferation, and the addition of anti-IL-10 antibodies completely blocked the anti-proliferative effects of MDSCs on T cells and inhibited Treg cell proliferation. However, MDSCs injections were unsuccessful in suppressing inflammatory arthritis in the IL-10 gene knocked out mice. MDSCs can regulate the Th17/Treg cells axis and suppress the CIA via IL-10 production. The mentioned study also showed that the M-MDSCs were stronger than PMN-MDSCs in improving joint inflammation and inhibiting Th17 differentiation and Treg proliferation, possibly through IL-10 (100).

The pro-inflammatory role of MDSCs in RA

Evidence suggests that MDSCs play a significant role in promoting inflammation and exacerbating the inflammatory conditions that occur in RA. Undesired inflammatory properties of MDSCs have been observed in RA experimental models.

One study found that the number of MDSCs increased in arthritic mice's lymph tissues and inflammatory paws (C57BL/6). This study showed that there was a positive relationship between Th17 and MDSCs with the intensity of RA. Higher levels of inflammatory cytokines such as IL-1β and TNF-α are found in mice with high MDSCs populations. PMN-MDSCs obtained from the spleen of mice cannot suppress T lymphocyte proliferation and IFN-γ secretion. In contrast, M-MDSCs were able to inhibit T lymphocyte proliferation and IFN-γ production using the iNOS pathway and increase IL-1β-dependent Th17 differentiation. Also, the synergistic transmission of splenic MDSCs of CIA mice worsened the severity of RA in arthritic mice, while eliminating them reduced the severity of the disease and decreased Th17 proliferation and IL-17A secretion. The results showed that patients with more severe symptoms have higher MDSCs load than healthy controls or patients with milder symptoms. The MDSCs frequency in RA patients' synovial fluid is correlated to IL-17A levels and ability of Th17 differentiation, suggesting that MDSCs are the main component of the inflammatory process in autoimmune arthritis (77).

Another study showed that MDSCs and Th17 cells proliferated significantly in CIA mice. Throughout CIA development, the MDSCs, PMN- and M-MDSC subsets have different ratios. The proportion of these cells increases in the later stages of disease (disease progression phase). The depletion of MDSCs reduced T cell proliferation and decreased production of IL-17A and IL-1β. MDSC's adaptive transfusion restored the severity of arthritis and Th17 cell differentiation. MDSCs isolated from CIA mice produced a higher level of IL-1β and differentiated Th17 cells. The distribution of circulating M-MDSCs and RA patients' joint fluid was positively correlated with increased Th17 cells and DAS28 (Disease Activity Score-28). DAS28 is a measure of disease activity in patients with RA in which the DAS stands for "disease activity score" and the 28 refers to the number of joints being examined. DAS28 is a general assessment criterion for evaluating disease progression or improvement. An increase in the frequency of MDSCs in the blood of patients with high 28-joint disease activity score has been observed compared with healthy control and low 28-joint disease activity score (77, 81). These findings support the theory that MDSCs may play an important role in the prognosis of CIA and RA by inducing Th17 development in an IL-1β-dependent manner (104).
Chen et al. showed that circulating MDSCs were significantly in RA patients compared to healthy groups. The research also found that MDSCs were prevalent in patients with RA with high disease severity, and their frequency was positively correlated with disease activity. Also, MDSCs can dramatically increase autologous B cell proliferation in vitro. Besides, MDSCs can significantly increase the proliferation of autologous B cells in vitro, suggesting that MDSCs may be involved in RA's pathogenesis by regulating B cell function (87).

A comprehensive study conducted in 2018 examined the population of MDSCs in patients with rheumatic disorders, including rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and systemic lupus erythematosus with arthritis. The population of MDSCs was raised significantly in RA patients compared to the healthy control group. This increase was also seen in other diseases associated with arthritis. The MDSCs and M-MDSCs ratios are often related to indicators of joint inflammation and disease activity. The prevalence of MDSCs and their subtypes were associated with disease activity and arthritis in patients with various rheumatic diseases (109).

Another study examined the distribution of MDSCs in patients with RA, primary or secondary Sjögren syndrome, to understand the role of MDSCs in the pathogenesis of autoimmune diseases. The proportion of MDSCs in rheumatoid arthritis and secondary Sjögren's syndrome was significantly higher than the healthy group. Also, the highest absolute number of M-MDSCs is manifested in the RA group. This research found that the most noticeable increase in MDSCs and M-MDSCs was seen in the RA and secondary Sjögren's syndrome groups, leading us to believe that the rise in MDSCs is related to the rheumatic processes (110).

The application of MDSCs in the treatment of RA

As stated before, the role of MDSCs in regulating or causing inflammation is controversial and requires further research. In this section, we investigate the adoptive transfer of MDSCs to RA mouse models and discuss these studies' results. The results of some studies showed that arthritis improved after the transfer of the MDSCs population by reducing the response of antigen-specific T lymphocytes and suppressing the accumulation and response of Th17 and Th1 cells, inflammatory cytokines, and antibody reduction (102 ,101 ,88 ,64). Nonetheless, several other

studies indicate an increase in the number, differentiation, and response of Th17 cells with exacerbated RA effects (104 ,78 ,77). Evaluating the time points used in the above studies to transfer MDSCs, it can be concluded that adaptive injections of MDSCs before the establishment of CIA can have anti-inflammatory effects and be associated with a relative improvement of the disease. However, the injection of MDSCs after CIA establishment is often associated with disease progression and inflammatory effects. This finding suggests that the suppressive functions of transmitted MDSCs may be more effective in non-inflammatory or less inflammatory microenvironments.

On the other hand, the inflammatory environments may differentiate MDSCs into their subsets, often M-MDSCs. In one study, splenic M-MDSCs were used for adaptive transmission before the onset of arthritis, which was associated with increased Th17 cell differentiation, and the results showed the inflammatory properties of M-MDSCs cells (77). The study of Wang et al. also showed that the adoptive transfer of PMN-MDSCs was more effective in managing the disease than M-MDSCs by inhibiting Th17 cells and inflammatory cytokines secretion (80). These data support the above hypothesis that M-MDSCs tend to cause inflammation during autoimmune arthritis. Moreover, the ratio of M-MDSCs, unlike PMN-MDSCs, has been reported to increase steadily among the entire MDSCs population in arthritis peak (88). As a result, it is possible that the microenvironment after the onset of arthritis is more conducive to the growth of M-MDSCs with inflammatory functions than PMN-MDSCs, and causes exacerbated symptoms. Since the in vivo functional mechanism of MDSCs is determined by various factors such as disease stage and dominant cytokine concentration, this treatment requires many in vitro and in vivo studies that can create conditions in which injection of MDSCs is related to the immune system inhibition.

Given that the use of MDSCs immunomodulatory potential can be influenced by various factors such as the types of MDSCs (PMN-MDSCs or M-MDSCs), the source of MDSCs, the dose of MDSCs, and the stage of diseases, exosome-based therapy can be a new treatment strategy for RA. Exosomes are small lipid vesicles with a bilayer membrane (30–100 nm) found in body fluids such as blood and saliva. Exosomes have different contents based on cellular origin, but it can be said that most exosomes contain proteins, growth factors, DNA, micro RNA, and mRNA (111, 112). Studies have shown that MDSCs suppress the immune system via secrete exosomes containing various molecules, such as oncogenic miR-126a, S100A8 / 9, and ARG1 (44-49). Exosomes can reach the recipient cell and alter the behavior and activity of the target cell. Zoller et al. (2018) reported that MDSCs derived exosomes significantly induced the Treg cell expansion and inhibit T cell responses in the model of autoimmune alopecia areata(113). In a study conducted by Dongwei Zhu et al., It was reported that the use of MDSC-derived exosomes reduced inflammation, joint destruction, and the population of Th1 and Th17 lymphocytes in CIA mice (114). A 2020 study reported that the use of MDSCs-derived exosomes could improve murine CIA. Treatment of mice with exosomes obtained from PMN-MDSCs reduces inflammation and inflammatory cell infiltration, decreases plasma cell and Th population in lymph nodes, increases IL-10 producing B cells, and decreases serum IgG(115). The use of MDSCs-derived exosomes in various autoimmune diseases such as RA possibility could provide a clear pathway to exploit the immunomodulatory function of MDSC cells.

Conclusion

Many factors induce the differentiation, migration, expansion, and activation of MDSCs. As MDSCs research progresses, more questions arise about the biological roles of MDSCs. MDSCs immunomodulatory potential can be influenced by various factors such as the types of MDSCs (PMN-MDSCs or M-MDSCs), the source of MDSCs, the dose of MDSCs, and the stage of diseases. MDSCs isolated from inflammatory sites inhibit T cells' response depending on multiple mechanisms such as NO and Arg-1. The induction and suppression of MDSCs were different between in vivo and in vitro studies, and the difference between the activity of endogenous and exogenous MDSCs is unknown. Endogenous MDSCs may be inflammatory and ineffective in the remission of autoimmune diseases. Therefore, a definitive conclusion regarding the function of MDSCs in autoimmune diseases is a challenge. Further investigations are needed to understand the functional mechanism of MDSCs in different microenvironments comprehensively.

Declaration of interests

None.

Funding

None.

Table1: Regulatory factors controlling the expansion and suppressive function of MDSCs

Factors	MDSCs Expansion	MDSCs suppressive function	Ref
Transcription factor	IRF4, IRF8, ERK, MAPK, C/EBP	HIF1α, STAT3, STAT5, NrF2, Chop, NF-KB, NOTCH	,116) (117
Regulatory protein	Estrogen, HMGB1	S100A8/9, PGE2, C5a, HMGB1, HDAC11	,118 ,11) (119
cytokines	G-CSF, M-CSF, GM-CSF, VEGF, IL-6, Adenosine	IL1-β, IL-6, IL-17, TNF-α, Sema4D	119-) (121

IRF (interferon-regulatory factor), ERK (extracellular signal-regulated kinase), MAPK (mitogen-activated protein kinase), C/EBP (CCAAT enhancer-binding protein), HMGB1 (High mobility group box protein 1), G-CSF (Granulocyte colony-stimulating factor), M-CSF (Macrophage colony-stimulating factor), GM-CSF (Granulocyte-macrophage colony-stimulating factor), VEGF (Vascular endothelial growth factor), HIF1 (Hypoxia-inducible factor 1), STAT (Signal transducer and activator of transcription), NrF2 (Nuclear factor erythroid 2-related factor 2), Chop (C/EBP Homologous Protein), NF-KB (Nuclear Factor Kappa B), PGE (Prostaglandin E), HDAC11 (Histone deacetylase 11), IL (Interleukin), TNF (Tumor necrosis factor), Sema4D (Semaphorin-4D).

Table2: The phenotypes of mouse and human M-MDSC and PMN-MDSC

Subsets	Different markers on MDSCs	Common markers on MDSCs	Ref
Mouse PMN-MDCSs	Ly6C $^{low/-}$ Ly6G+, F4/80^{-}, CD115^{low}, CCR2^{-}, CD124^{+-}, iNOS^{-}	CD11b^{+}, Gr-1$^{+,}$ ROS^{+}, Arg1^{+}	,122) (123
Mouse M-MDSCs	Ly6C^{high}, Ly6G^{low}, F4/80^{+}, CD115^{+},CCR2^{+}, CD124^{+}, iNOS^{+}		
Human PMN-MDCSs	CD15^{+}, CD14^{-}, CD66b^{+}	Lin^{-}, CD11b^{+}, CD33^{+}, CD124^{+}, HLA-DR^{-}, Arg1^{+}, ROS^{+}	,46) (116
Human M-MDSCs	CD15^{-}, CD14^{+}, CD66b^{-}		
PMN-MDSCs (Polymorphonucler myeloid-derived suppressor cells), M-MDSCs (Monocytes myeloid-derived suppressor cells), CD (Clusters of Differentiation), HLA (Human Leukocyte Antigen), Ly6G (Lymphocyte antigen 6 complex locus G6D), Ly6C (lymphocyte Ag 6C), CCR2 (C-C chemokine receptor type 2), Gr1 (Granulocyte differentiation antigen 1), iNOS (inducible nitric oxide synthase), ROS (Reactive oxygen species), Arg1 (arginase-1), Lin (lineage-negative).			

Table3: The surface markers to identify MDSCs in RA

Disease	Site	M-MDSC	PMN-MDSC	Ref
RA patients	SF	-	CD11b+ CD33+ CD15+ CD14- HLA-DR ^{low}	(86)
RA patients	SF and PB	CD14+ HLA-DR ^{low}	-	(104)
RA patients	PB	CD14- HLA-DR- CD33+ CD11b+		(106)
RA patients	PB	HLA-DR$^{low/neg}$ CD33+ CD11b+ CD14+	-	(110)
RA patients	PB	CD11b+CD33+HLA-DRlow/- CD14+	CD11b+CD33+HLA-DRlow/- CD15+	(109)
CIA (DBA/1J mice)	SP	CD11b+ Gr-1^{mod} F4/80+ Ly6C+ CD11C^{low} MHCII (I-Ab)^{low}	CD11b+ Ly6G+ CD11C^{low} MHCII (I-Ab)^{low}	(104)
CIA (DBA/1 mice)	SP	CD11b+ Gr-1+ Ly6G- Ly6C^{high}	CD11b+ Gr-1+ Ly6G+ Ly6C^{low}	(52)
CIA (C57BL/6 mice)	SP and Paws	CD11b+ CD115+ CD62L+ CCR2+ F4/80^{low} Ly6C^{high} Ly6G^{low}	CD11b+ Ly6C^{low} Ly6G+	(77)
CIA (DBA/1J mice)	SP	CD11b+ Ly6C+ Ly6G-	CD11b+ Ly6C+ Ly6G+	(80)
CIA (DBA/1J mice)	BM	CD11b+ Gr-1^{mod} Ly6G- F4/80^{low} Ly6C^{high} CD11C- CD115+ CCR2+	CD11b+ Gr-1^{high} Ly6G+ F4/80- Ly6C+ CD11C- CD115^{low} CCR2-	(107)
CIA (DBA/1J mice)	SP	CD11b+ Ly6G- Ly6C^{high} CD11c-	CD11b+ Ly6G+ Ly6C^{low} CD11c-	(100)
Adjuvant Arthritis (CD1 mice)	SP	Gr-1^{dim} Ly6G-	Gr-1^{high} Ly6G^{high} CD49+	(108)
PGIA (BALB/C mice)	SP and SF	Ly6G^{low} Ly6C^{high}	Ly6G^{high} Ly6C^{low}	(105)
CIA (Collagen-induced arthritis), PGIA (Proteoglycan-induced arthritis), SF (Synovial Fluid), BM (Bone Marrow), PB (Peripheral Blood), SP (Spleen), CD (Clusters of Differentiation), HLA (Human Leukocyte Antigen), MHC (Major Histocompatibility Complex), Ly6G (Lymphocyte antigen 6 complex locus G6D), Ly6C (lymphocyte Ag 6C), CCR2 (C-C chemokine receptor type 2), Gr1 (Granulocyte differentiation antigen 1).				

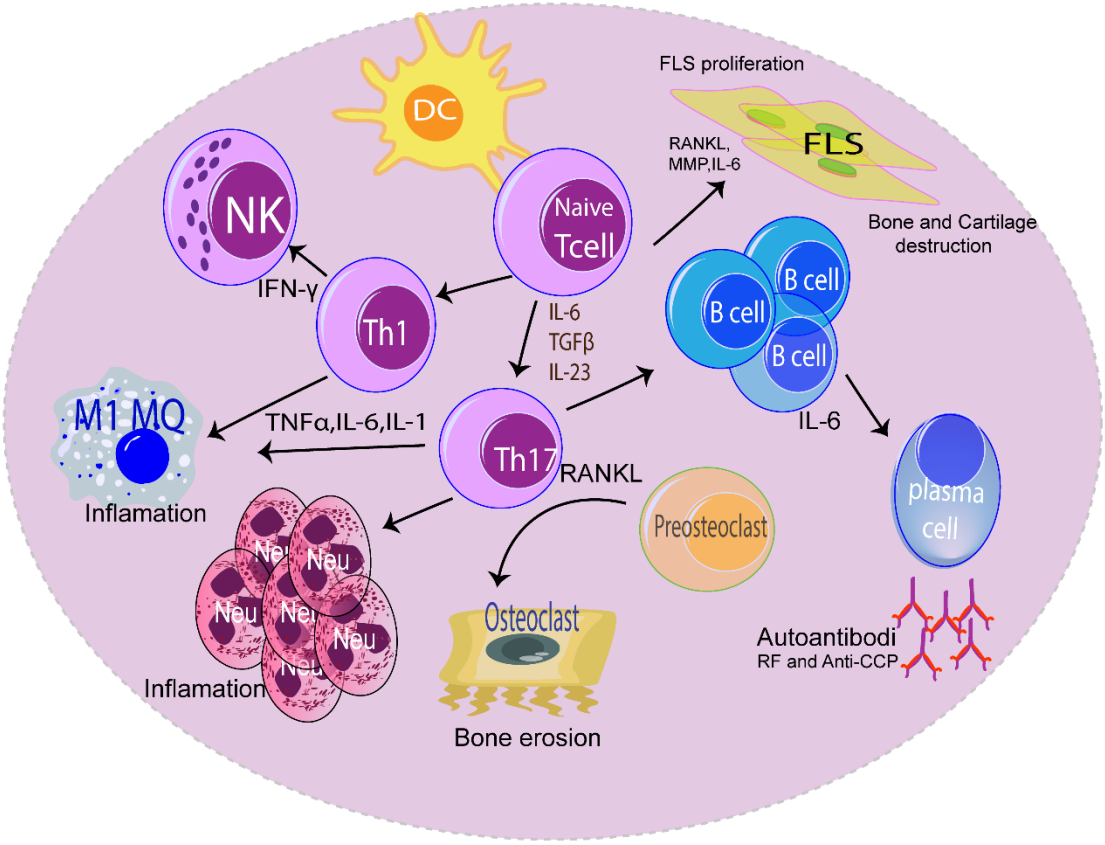

Fig.1: Inflammatory immune responses leading to the development of bone destructive in RA. DC (Dendritic cells), FLS (Fibroblast-like synoviocytes), Th (T helper cells), Neu (Neutrophil), M1MQ (M1 Macrophage), IFN-γ (interferon-gamma), IL (Interleukin), TGFβ (Transforming growth factor β), RANKL (Receptor activator of nuclear factor-kappa-B ligand), MMP (Matrix metalloproteinase), TNF (Tumor necrosis factor).

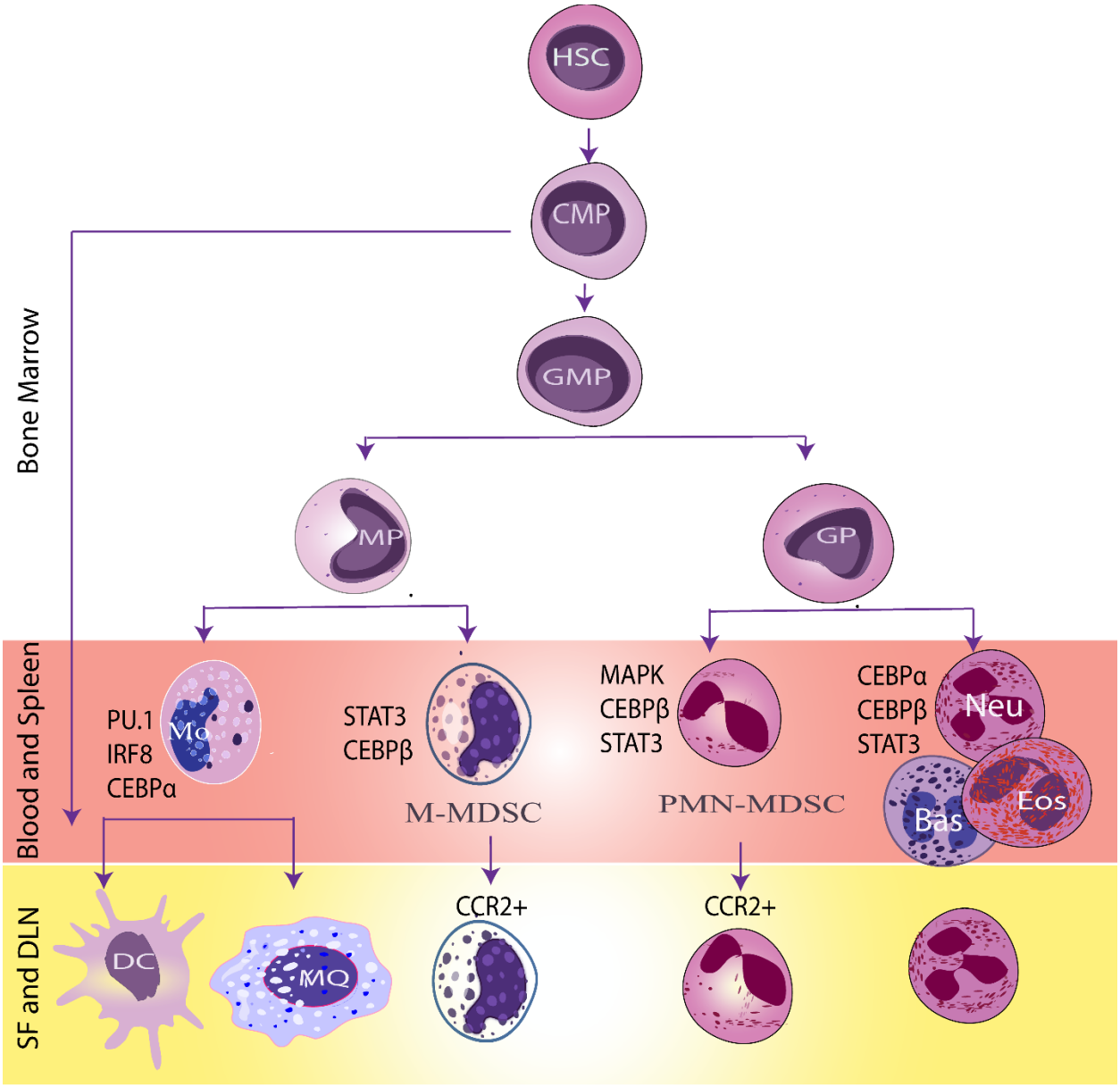

Fig.2: Chronic inflammation affects myelopoiesis. Under physiological conditions, HPC differentiates via CMP into GMP. Monocyte progenitor differentiates into monocytes and M-MDSCs and granulocyte differentiation into granulocytes and PMN-MDSCs. MDSC is expanded following myelopoiesis regulation in bone marrow by hormones, growth and transcription factors. Continuous stimulation of the myeloid cell compartment with signals from tumors or chronic inflammatory sites resulting in differentiation of MDSCs having the low phagocytic capacity and developing high levels of ROS, MPO, NO, and anti-inflammatory cytokines. HPC (Hematopoietic Progenitor Cells), CMP (Common Myeloid Progenitor Cells), GMP (Granulocyte/Macrophage

Progenitor Cells), GP (Granulocyte Progenitor Cells), MP (Macrophage Progenitor Cells), PMN-MDSCs (Polymorphonuclear Myeloid-Derived Suppressor Cells), M-MDSCs (Monocytic Myeloid-Derived Suppressor Cells), Neu (neutrophils), Bas (Basophils), Eos (Eosinophils), DC (Dendritic cells), MQ (Macrophages), SF (synovial fluid), DLN (draining lymph nodes), IRF (Interferon-Regulatory Factor), CEBP (CCAAT enhancer-binding protein), STAT (Signal transducer and activator of transcription), MAPK (mitogen-activated protein kinase), CCR (C-C chemokine receptor).

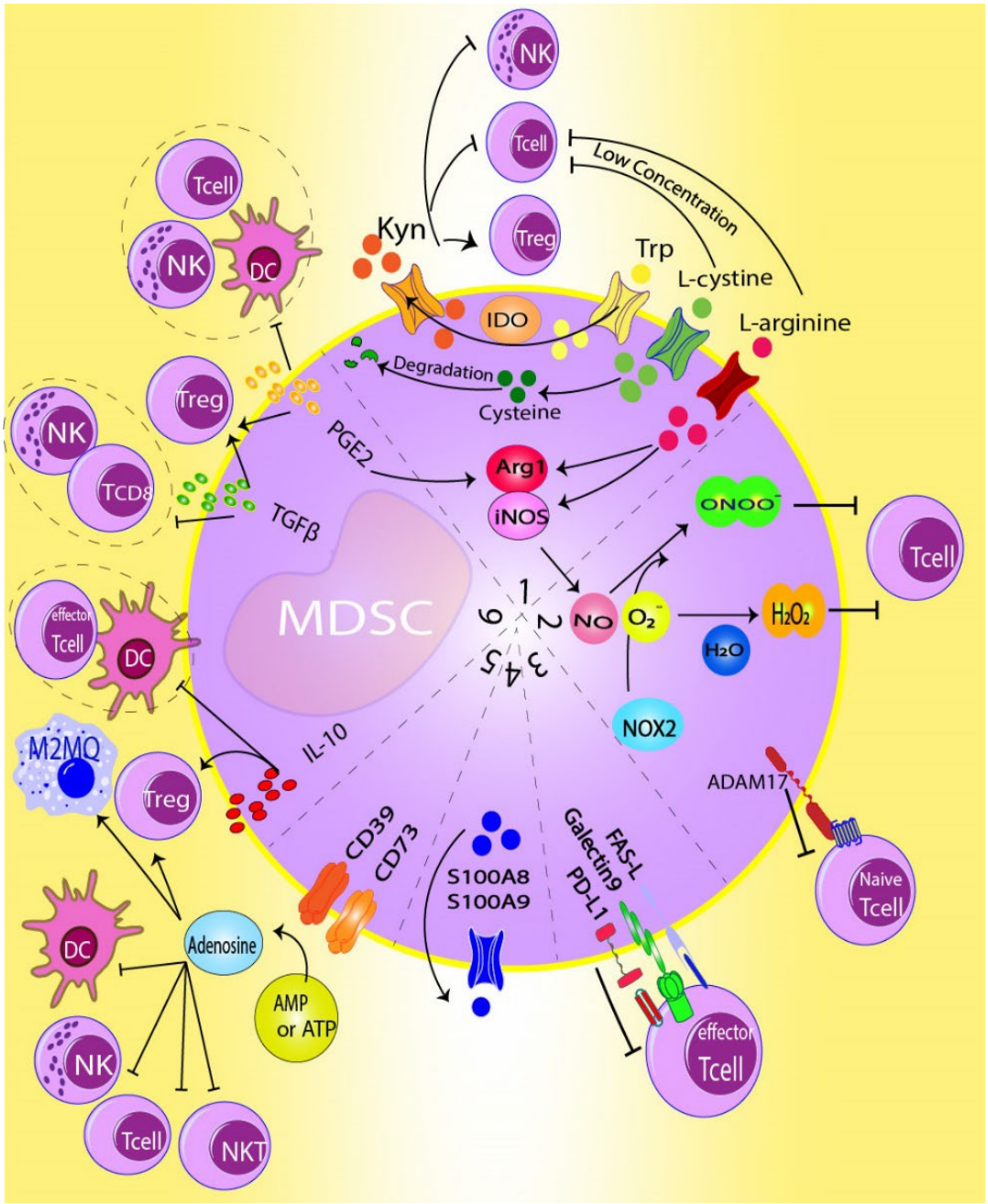

Fig.3: The main mechanisms of immunosuppression mediated by myeloid-derived suppressor cells (MDSCs) target innate and adaptive arms of the immune system. A: Amino acid depletion and production of immunosuppressive metabolites. B: Generation of reactive oxygen species

(ROS) and reactive nitrogen species (RNS); Inhibition of T cell homing to the lymph nodes. C: Direct engagement of T cell inhibitory and apoptotic receptors. D: S100A8/A9-mediated accumulation of MDSCs. E: Production of extracellular adenosine. F: Production of PGE2 and inhibitory cytokines. Arg1 (arginase-1), iNOS (inducible nitric oxide synthase), IDO (Indoleamine 2,3-Dioxygenase 1), Trp (Tryptophan), Kyn (Kynurenine), O2- (superoxide anion), H2O2 (hydrogen peroxide), ONOO- (peroxynitrite), ADAM17 (A disintegrin and metalloprotease 17), FasL (Fas Ligand), S100A8/A9 (S100 calcium-binding protein A8/A9), IL (Interleukin), TGFβ (Transforming growth factor β), PGE2 (Prostaglandin E2), ATP (Adenosine triphosphate), AMP (Adenosine monophosphate).

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