Immune Netw. 2021 Jun;21(3):e21
https://doi.org/10.4110/in.2021.21.e21
pISSN 1598-2629·eISSN 2092-6685

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Review Article

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Mechanisms Underlying the Role of Myeloid-Derived Suppressor Cells in Clinical Diseases: Good or Bad

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OPEN ACCESS

Received: Oct 21, 2020
Revised: May 16, 2021
Accepted: May 18, 2021

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ABSTRACT

Myeloid-derived suppressor cells (MDSCs) have strong immunosuppressive activity and are morphologically similar to conventional monocytes and granulocytes. The development and classification of these cells have, however, been controversial. The activation network of MDSCs is relatively complex, and their mechanism of action is poorly understood, creating an avenue for further research. In recent years, MDSCs have been found to play an important role in immune regulation and in effectively inhibiting the activity of effector lymphocytes. Under certain conditions, particularly in the case of tissue damage or inflammation, MDSCs play a leading role in the immune response of the central nervous system. In cancer, however, this can lead to tumor immune evasion and the development of related diseases. Under cancerous conditions, tumors often alter bone marrow formation, thus affecting progenitor cell differentiation, and ultimately, MDSC accumulation. MDSCs are important contributors to tumor progression and play a key role in promoting tumor growth and metastasis, and even reduce the efficacy of immunotherapy. Currently, a number of studies have demonstrated that MDSCs play a key regulatory role in many clinical diseases. In light of these studies, this review discusses the origin of MDSCs, the mechanisms underlying their activation, their role in a variety of clinical diseases, and their function in immune response regulation.

Keywords: Myeloid-derived suppressor cells; Immunosuppression; Tumor disease; Neuroinflammatory

INTRODUCTION

Myeloid derived suppressor cells (MDSCs) are a group of heterogeneous bone marrow cells that play an immunosuppressive role in the body (1). MDSCs are composed of immature myeloid cells (IMCs) and can be divided into 2 cell subtypes: 1) mononuclear MDSCs (M-MDSCs), and 2) polymorphonuclear MDSCs (PMN-MDSCs), also described as granulocytic MDSCs (G-MDSCs) (2). Both types of MDSCs have been shown to have inhibitory effects in mouse tumor models and several human cancers (3). Mouse MDSCs are characterized by co-expression of CD11b and Gr-1, while human MDSCs are most characterized by $CD11b^+$ and $CD33^+$ and low level of HLA-DR, which is the MHC class II molecule (4,5). Moreover, in addition to the 2 major subtypes mentioned above, there is

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Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
Arg-I, arginase-I; BBB, blood-brain barrier; BC, breast cancer; C/EBPβ, CCAAT enhancer-binding protein β; CNS, central nervous system; COX-2, cyclooxygenase 2; CRC, colorectal cancer; CSF, colony-stimulating factor; DC, dendritic cell; EAE, experimental autoimmune encephalomyelitis; EAU, experimental autoimmune uveoretinitis; e-MDSC, early myeloid-derived suppressor cell; GAM, gliomas microglia/macrophage; GBM, glioblastoma; G-MDSC, granulocytic myeloid-derived suppressor cell; HC, healthy control; HIF-1α, hypoxia inducible factor-1α; ICAM, intercellular adhesion molecule; IDO, indoleamine 2,3-dioxygenase; IMC, immature myeloid cell; iNOS, inducible nitric oxide synthase; IRF8, interferon regulatory factor 8; LC, lung cancer; MDSC, myeloid-derived suppressor cell; M-MDSC, mononuclear myeloid-derived suppressor cell; MS, multiple sclerosis; PGE2, prostaglandin E2; PMN, polynucleated; PMN-MDSC, polymorphonuclear myeloid-derived suppressor cell; RPE, retinal pigment epithelium; S1PR1, sphingosine-1-phosphate receptor 1; TAM, tumor-associated macrophage; TAN, tumor associated neutrophils; TME, tumor microenvironment; TNBC, triple-negative breast cancer.

Author Contributions
Conceptualization: Zhang J; Software: Jia Q; Visualization: Ge Y, Cheng D, Xiong H; Writing - original draft: Ge Y; Writing - review & editing: Xiong H, Zhang J.

another subtype lacking macrophage and granulocyte markers, which is called early MDSCs (e-MDSCs) (6,7). The function of MDSCs is defined as its ability to inhibit the response of T cells, NK cells and B cells, so as to change the disease outcome under various pathological conditions (8).The immunosuppression mediated by MDSCs is related to arginase-I (Arg-I), inducible nitric oxide synthase (iNOS), TGF-β, IL-10, cyclooxygenase 2 (COX-2), indoleamine 2,3-dioxygenase (IDO) chelating cysteine, and other factors. Decreased expression of T cells and L-selectin are also involved in MDSC immunosuppression (9-12). MDSCs accumulate in tumor and inflammatory tissues, and block immune cell effector function (13). Although MDSCs are involved in immunosuppression related to many different cells, they play a key role in T cell tolerance (14). However, MDSCs also regulate other cell populations, including B cells, in the inflammatory response. In fact, B cells are essential for an Ab-mediated immune response. MDSCs regulate the immune response of B cells directly by expressing effector molecules and indirectly by controlling other immunomodulatory cells. As the B cell-mediated immune response is the main component of the overall immune response, MDSCs play a prominent role in its regulation (15). Human neutrophils, as effective effector cells, play a well-known role in killing pathogenic microorganisms. In addition to their role in innate immunity, neutrophils also have the ability to inhibit T-cell-mediated immune responses, known as G-MDSCs, affecting clinical outcomes in various diseases, such as cancer. These findings also suggest that MDSC activity does not completely overlap with the antimicrobial activity of human neutrophils and provide an opportunity to elucidate the unique characteristics of their T cell inhibitory activity (16). Leiber et al. (17) reported that the phagocytic activity of G-MDSCs towards *Escherichia coli* cells is similar to that of mature neutrophil, but apoptosis is reduced in case of the former, whereas the proliferation of T cells is strongly inhibited in the presence of G-MDSCs. Emerging research is revealing the role of MDSCs in clinical disease, which is of serious concern; however, it is yet to be extensively studied. This review summarizes the origin of MDSCs, the mechanism underlying their activation, their role in various clinical diseases, and their immune response-regulatory function.

ORIGIN AND CLUSTERING OF MDSCs

MDSCs are composed of myeloid progenitor cells and IMCs, which have the ability to inhibit immune response at different levels (18). The different cells forming heterogeneous MDSC populations originate and develop in the bone marrow. During MDSC formation, hematopoietic stem cells are differentiated into normal myeloid progenitor cells and IMCs, via complex molecular networks (4). In general, bone marrow stromal cells account for ≤20%–30% of the normal bone marrow. They migrate to different peripheral organs and rapidly differentiate into mature granulocytes, macrophages, and dendritic cells (DCs). Under pathological conditions, however, IMCs cannot differentiate into mature cells. Further, MDSCs can proliferate, activate, and accumulate as immature cells due to long-term pathological conditions, such as chronic inflammation or cancer (19). Immunosuppression caused by MDSCs plays an important role in addressing acute inflammation. However, in chronic inflammatory diseases, MDSC activation suppresses both inherent and adaptive immune responses, thereby aggravating disease processes associated with tumors, chronic infections, and many degenerative diseases (20). MDSCs have been reported to play a role in amplifying and suppressing host immune responses during chronic viral infection (21). Currently, MDSCs mainly include PMN-MDSCs and M-MDSCs, which are phenotypically and morphologically similar to neutrophils and monocytes, respectively (22,23). These MDSCs perform their immunosuppressive functions via different mechanisms: PMN-

Table 1. Characteristics of M-MDSCs and PMN-MDSCs

Characteristics	M-MDSCs	PMN-MDSCs	References
Phenotype	$CD11b^+Ly6G^-Ly6C^{high}$	$CD11b^+Ly6G^+Ly6C^{lo}$	(25)
Definition	$CD11b^+CD15^-CD14^+HLA\text{-}DR^{-/low}$	$CD11b^+CD14^-CD15^+/CD66b^+$	(26)
Similarly	Monocytes	Neutrophils	(22)
Main mechanism of action	Ag-specific and nonspecific methods	Ag-specific T cell tolerance	(24)
In tumor tissue	In large proportion, strong inhibition	A relatively low percentage	(27)
Main expressed markers	PD-L1	LOX-1	(28)
Co-expressed markers		CD33	(29)

LOX-1, low-density lipoprotein receptor-1.

MDSCs act mainly through the induction of Ag-specific T cell tolerance, whereas M-MDSC activity is dependent on the blocking of T cell response in Ag-specific and non-specific ways by cytokines (24). Based on the above studies, we summarized the characteristics of the 2 main subtypes of MDSCs, so as to better distinguish them (**Table 1**). In addition, there is no unified standard for human surface molecular markers. MDSCs and many other markers have been reported gradually. The phenotypes of common reported specific markers are as follows: $CD16^{low}$ $CD11b^+$ $CD14^-$ $HLA\text{-}DR^-$ $CD15^+$ $CD33^+$ (30), $CD14^+$ $HLA\text{-}DR^{-/low}$ (31,32), $CD11b^+$ $CD14^-$ $HLA\text{-}DR^-$ $CD33^+$ $CD15^+$ ILT3 high (33), Lin^- $CD14^-$ $CD11b^+$ $CD39^+$ $CD73^+$ (34), Lin^- $CD14^-$ $HLA\text{-}DR^-$ (35), Lin^- $CD33^+$ $CD14^+$ $CD15^-$ $HLA\text{-}DR^-$ (36), $CD33^+$ $CD11b^+$ $CD14^-$ and $CD33^+$ $CD11b^+$ $CD14^+$ $HLA\text{-}DR^{-/low}$ (37). In humans, MDSCs can be isolated from neutrophils and monocytes based on phenotypic markers and density gradients (38). Human PMN-MDSCs have a gene expression profile that distinguishes them from neutrophils in cancer patients and healthy donors (39). In addition to gene and protein expression profiles, MDSCs differ from neutrophils and monocytes in the activity and expression of specific molecules. STAT3 upregulation is a marker of MDSCs because this transcription factor is directly involved in MDSC accumulation in humans and mice (40,41). The phenotypic and functional differences between MDSCs, neutrophils, and monocytes are described in **Table 2**.

MECHANISM UNDERLYING THE ACTIVATION OF MDSCs

The activation of MDSCs is a very complex process, wherein the main signal pathways and transduction are closely related to the STATs. The classical activation of MDSCs occur in response to strong signals, which often appear in the form of pathogen-associated molecular patterns or damage associated molecular patterns. This activation is relatively short-lived. When the stimulation stops, the activation mode stops, showing strong phagocytosis, respiratory burst, and the release of pro-inflammatory cytokines (42-44). Therefore, MDSCs can play an inflammatory role (45). When MDSCs are recruited to inflammatory tissues, they inhibit the acute inflammatory response and trigger the regression of inflammation; however, if the pathogenic agents are not eliminated, long-existing MDSCs can suppress the host's immune defenses, increasing susceptibility to infection and tumorogenesis (46). Currently, the dual signal model is mainly used to describe the process. One group is majorly driven by tumor-derived growth factors, including STAT-3, interferon regulatory factor 8

Table 2. Differences between human neutrophils, monocytes, and MDSCs

Type	Surface phenotype	Density	Immunosuppression	STAT-3	ROS	NO	Arg-1
Neutrophils	$CD11b^+CD14^-CD15^+CD66b^+LOX\text{-}1^-$	High	–	–/+	+	–	+
Monocytes	$CD14^+CD15^-HLA\text{-}DR^+$	Low	–	–/+	–/+	+	–
M-MDSCs	$CD14^+CD15^-HLA\text{-}DR^{-/low}$	Low	++	++	–/+	+++	–
PMN-MDSCs	$CD11b^+CD14^-CD15^+CD66b^+LOX\text{-}1^+$	Low	+	++	+++	+	++

LOX-1, low-density lipoprotein receptor-1.

https://doi.org/10.4110/in.2021.21.e21

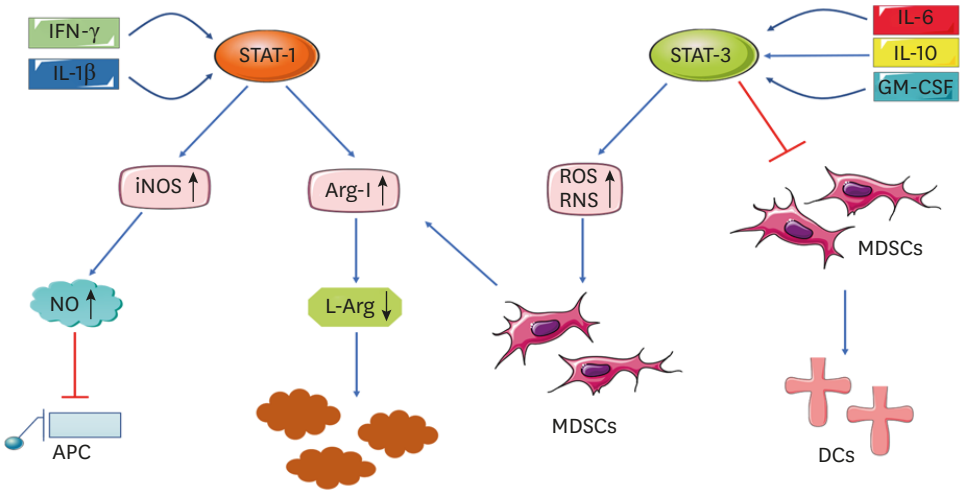

Figure 1. Activation mechanism of MDSCs. Several factors are involved in the activation and immunosuppressive function of MDSCs. STAT, such as STAT-1 and STAT-3, are involved in MDSC regulation. IFN-γ and IL-1 β can trigger STAT-1 signals, leading to high levels of iNOS and Arg-I. IL-6, IL-10, and GM-CSF can activate the STAT-3 signaling pathway, thereby promoting the high expression of ROS in MDSCs, inhibiting the differentiation of MDSCs into DCs, and enhancing the immunosuppressive function of MDSCs. When ROS and RNS increase, MDSCs are activated. MDSCs can induce Arg-I, which leads to non-production and depletion of L-arginine, and finally, T cell inactivation or programmed apoptosis, thus promoting the immunosuppressive function of MDSCs.
RNS, reactive nitrogen species.

(IRF8), CCAAT enhancer-binding protein β (C/EBPβ), notch, adenosine receptor A2B signal transduction, and nucleotide-binding oligomerization domain-like receptor protein 3 (47). Another group of signals are mainly mediated by related factors produced by the tumor matrix, including NF-κB pathway, STAT-1, STAT-6, prostaglandin E2 (PGE2), and COX-2 (48). In fact, STAT-3 regulates the proliferation and activation of MDSCs in different ways. First, the inhibition of STAT-3 signals can significantly inhibit MDSC proliferation. Second, STAT-3 is involved in regulating the immunosuppressive function of MDSCs. *In vitro* and *in vivo* studies have shown that certain factors induce MDSCs to produce IL-6, which leads to STAT-3 phosphorylation and enhances the immunosuppressive function of MDSCs (49). Here, we draw the **Fig. 1** to more vividly depict the activation mechanism.

THE MECHANISMS OF ACTION OF MDSCs IN TUMOR DISEASES

Tumor microenvironment (TME) is a complex network of epithelial cells and stromal cells, in which stromal components support tumor cells at all stages of tumorigenesis. These stromal cell populations include myeloid cells, which are mainly composed of tumor-associated macrophages (TAMs), DCs, MDSCs, and tumor-associated neutrophils (TANs), among which MDSCs play a major role in tumor growth (50). The pathophysiological characteristics of tumors are influenced by the interaction of tumor cells, T cells, and myeloid cells in the TME. The study of the interaction between them by researchers has become critical in the study of tumor immunology (51). During the differentiation and development of MDSCs, their functions are also affected by a series of regulatory factors in the TME, such as metabolic reprogramming, epigenetic modification, and cell signaling pathways, and there is crosstalk among these regulatory factors (52). There is a strong correlation between

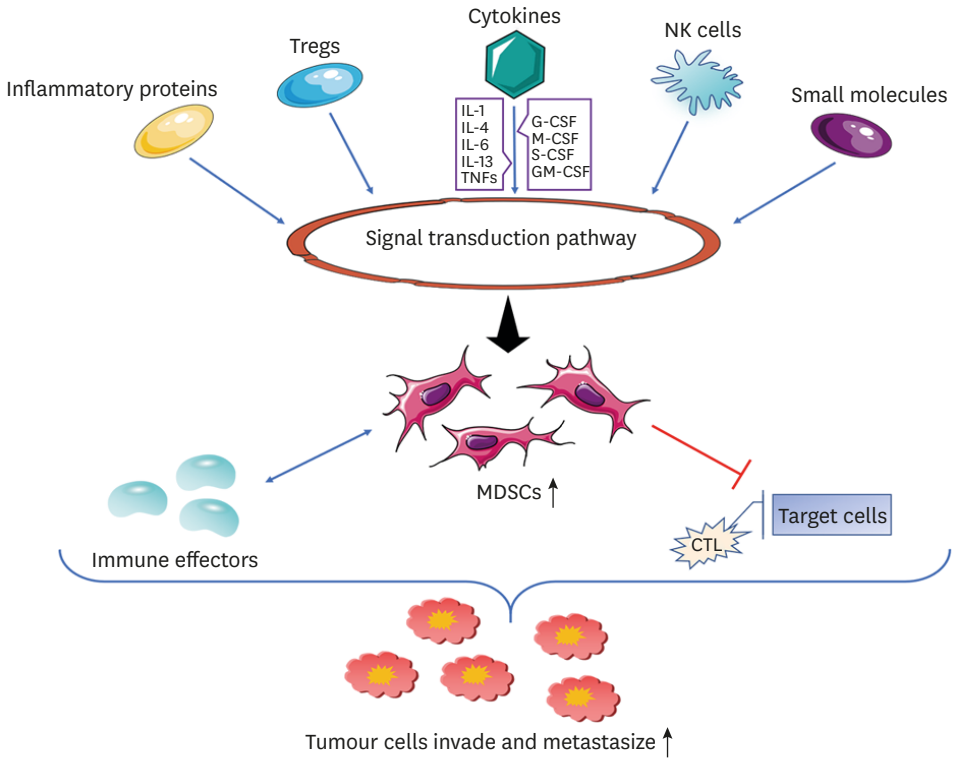

Figure 2. Regulation mechanism of MDSC in TME. In TME, some small molecules, NK cells, cytokines, inflammatory proteins and Tregs promote the immunosuppressive effect of MDSCs through signal transduction pathways. Among them, cytokines mainly include two categories of cytokines required for proliferation (G-CSF, M-CSF, GM-CSF and S-CSF, etc.) and cytokines related to functional maturation (IL-1 family cytokines, IL-4, IL-6, IL-13 and TNFs, etc.), which can induce and activate MDSCs. MDSCs have bidirectional activation effect with the immune effectors with anti-tumor activity. After activation, MDSCs can inhibit the response of CTLs to target cells and reduce the anti-tumor activity of the body, thus providing a tolerant environment for tumor cells and promoting tumor invasion and metastasis.

TME and MDSCs, We used **Fig. 2** to describe the mechanism of action between related cytokines and MDSCs in the background of tumor microenvironment, which ultimately promoted the invasion and metastasis of tumor cells. With developments in oncology, there is enough evidence that MDSCs and neutrophils play a key role in the occurrence and development of tumors (53,54). At present, there is also growing evidence that MDSCs are a key factor in immunosuppression in cancer patients (55). MDSCs were first observed in patients with advanced cancer, and in a variety of tumor entities, a high number of circulating MDSCs is associated with advanced tumor stage, poorer prognosis, and a weaker response to treatment (56). The main inhibitory immune cells in tumor sites are MDSCs, TAMs, and Treg cells. The main roles of these inhibitory immune cells include blocking T cell activity and supporting tumor progression and survival (57). In addition, it has been reported that M-MDSCs have stronger inhibitory effect than PMN-MDSCs, and have become an important mediator of tumor-induced immunosuppression (58). MDSCs play a crucial role in the immunosuppression of tumor hosts. MDSCs express Arg-I and indoleamine 2, 3-dioxygenase. They inhibit T cell function by decreasing L-arginine and L-tryptophan levels, respectively (59). MDSCs can inhibit the activation of T cells in TME, cause immune response inhibition, reduce the anti-tumor activity of the body, and promote tumor invasion and metastasis, thus playing an important role in promoting tumor growth (60). The growing tumor has many mechanisms that can resist the recognition of the immune system, one of

which includes MDSCs, that provide a tolerant environment for tumor cells by inhibiting the immune specificity of T cells. This mechanism leads to a disorder in the immune function of the body, which is conducive to tumor occurrence, development, and escape (61). The immunosuppressive effect of MDSCs is mainly related to some small molecules, NK cells, cytokines, inflammatory proteins, Tregs, and the signal transduction pathway. For example, cytokines are needed for proliferation; colony-stimulating factors (CSFs) such as G-CSF, M-CSF, GM-CSF, S-CSF, and those related to functional maturity (IL-1 family cytokines, IL-4, IL-6, IL-13, TNF, etc.) can induce MDSCs (38,62). Among them, the cytokine IL-6 has been found to be a key regulator of MDSC accumulation and activation, as well as a factor that stimulates the proliferation, survival, invasion, and metastasis of tumor cells (63). The host immune response is the basic mechanism for slowing cancer progression. Studies have revealed the tumor suppressor mediated the IL-6/G-MDSC S/$CD8^+$ T cell immune cascade, which protects the host's adaptive anti-tumor immunity (64). Currently, many reports have revealed the critical role of MDSCs in tumor progression. Zhang et al. (65) found that intestinal microbiome can control the formation of immunosuppressive environment in liver cells by increasing PMN-MDSC, thus promoting the occurrence of liver cancer. Sun et al. (66) demonstrated that MDSCs and Th17 are closely associated with the progression of cell-dependent lymphoma. Tavukçuoğlu et al. (67) reported significantly higher levels of low-density PMN-MDSCs in the spleens of cancer patients compared to peripheral blood, but low levels of e-MDSCs and M-MDSCs. Low-density polynucleated (PMN) cells were enriched in IMCs and showed higher levels of CD10, CD16, and ROS than blood-derived cells. Both low-density and normal-density PMN cells from the human spleen inhibited T cell proliferation and IFN-γ production (67). Recent studies have shown the value of MDSCs in predicting the treatment response for various cancers: M-MDSC levels are inversely correlated with chemotherapy response in breast, cervical, prostate, and colorectal cancers (CRCs), and likewise, in CRC, the PMN-MDSC value is inversely correlated with chemotherapy response (68-70). Recent studies have also shown that MDSCs can be used as prognostic biomarkers and targets for cancer immunotherapy. Preclinical and clinical studies have identified novel approaches to combined immunoregulatory therapy that deplete MDSC populations and inhibit MDSC function, including chemotherapeutic agents combined with immune checkpoint-guided therapy (71). In addition, the motor capacity of MDSCs is affected by cancer cells and tumor cell secretory bodies. Epithelial dedifferentiation may be the mechanism by which cancer cells respond to changes in the movement of MDSCs. These results highlight the biochemical and biological structural conditions that MDSCs support cancer cell migration, thus providing a new avenue for research and treatment to inhibit cancer progression (72). The immunosuppressive nature of the TME is a major factor hindering the success of many cancer therapies. Therefore, the deletion or reprogramming of MDSCs and Tregs to restore tumor immunosuppression is urgently needed clinically (73). Therefore, it is of great significance to study the relevant mechanism of action of MDSCs.

CRC and MDSCs

CRC has a relatively high incidence and is one of the more common malignant tumors in the world (74). CRC occurrence and development involve many pathological factors. Several studies have shown a close relationship between the increased risk of CRC and the immune escape microenvironment formed by chronic inflammation or autoimmune diseases (75). Karakasheva et al. (76) used flow cytometry to quantitatively detect diseased and normal groups, and showed that $CD38^+$ M-MDSCs and $CD38^+$ PMN-MDSCs were significantly increased in CRC patients (accompanied by increased CD38 expression in M-MDSCs and PMN-MDSCs). M-MDSCs mainly produce nitric oxide as the precursor of TAMs, while

https://doi.org/10.4110/in.2021.21.e21

G-MDSCs can produce living oxygen and differentiate into TANs (77). Wang et al. (78) demonstrated that G-MDSCs promote stem cell formation and growth of CRC cells through S100A9 exosomes. Some studies have shown that STAT-3 plays a key role in CRC expression; the interaction between sphingosine-1-phosphate receptor 1 (S1PR1) and STAT-3 can induce MDSCs to form a pre-metastasis niche in CRC cells and promote organ specific metastasis (79,80). Recent studies have further revealed that intestinal flora play a role in CRC. Long et al. (81) analyzed the tumor infiltrated immune cell population of $Apc^{(Min/+)}$ mice treated with *Peptostreptococcus anaerobius* and found that MDSCs, TAMs, and TANs increased significantly. The selective enrichment of these immunosuppressive cells revealed another mechanism of anoxic *Plasmodium*-promoting CRC (81). Pro-inflammatory cytokine expression is widely induced by anaerobic *Plasmodium in vivo*, which may be mediated by NF-κB activation. Increase in MDSCs can promote IL-6 and IL-10 production, thereby directly inhibiting $CD4^+$ and $CD8^+$ T cell activity, whereas TAMs block the anti-tumor immune response of T cells and contribute to angiogenesis and tumor cell metastasis (82). Furthermore, Ibrahim et al. (83) found that IL-6 activates STAT3 to up-regulate the expression of DNMT1 and DNMT3b in colon cancer cells, thus revealing an epigenetic mechanism that mediates the IL-6–STAT3 signaling pathway in colon cancer. In conclusion, MDSCs promote the inhibition of autologous T cell proliferation and CRC cell development *in vitro* and *in vivo* by inducing the increase of the S1PR1-STAT3-IL-6 axis and the S100A9 exosome.

Lung cancer (LC) and MDSCs

LC is the second most common cancer worldwide. Despite advances in cancer treatment, it remains the leading cause of cancer mortality, with a 5-year survival rate of 18%, the lowest of all malignancies (84,85). The occurrence of LC can cause local and systemic immunosuppression, promote tumor occurrence and development, and do great harm to human beings. Immunosuppressive cells, such as MDSCs, TAMs, and Tregs, act as inhibitory time components to weaken the immune response. In these cells, the role of MDSCs in the prognosis, development, and treatment of LC has attracted more and more attention (86-88). As found in other types of tumors, there is increasing evidence that MDSCs play multiple roles in the promotion and progression of LC. This includes inhibition of tumor growth and progression mediated by anti-tumor immunity, and the relationship between MDSCs and poor prognosis and increased resistance to chemotherapy and immunotherapy (89). Li et al. (90) collected the peripheral blood of patients with metastatic brain tumor and LC before metastasis, and quantitatively detected immunosuppressive monocytes, MDSCs, and Tregs via flow cytometry. T cell activity analysis via ELISPOT assay showed that compared with the patients before early metastasis and the healthy control (HC) group, the PD-L1 and MDSC abundance and percentage of Tregs in peripheral blood mononuclear cells of patients having LC with brain metastasis increased (90). Related data showed that upregulation of K-ras gene expression and activation of the JAK-STAT signaling pathway were closely related to disease progression (91). Lee et al. (92) found that using $Trp53^{FloxFlox}$; $Kras^{G12D/+}$; $Rosa26^{LSL\text{-}Luciferase/LSL\text{-}Luciferase}$ (PKL) gene-engineered mice cultured with autologous lung tumors, PD-L1 was highly expressed in both tumor-containing lungs and MDSCs, thus confirming that MDSCs played an important role in promoting LC development. It has been reported that MDSCs in patients with non-small cell LC can inhibit T cell activity, enhance immunosuppression, and accelerate tumor progression through arginase, ROS, and the IL-13/IL-4R axis (31). Li et al. (34) showed that phosphorylation of the mammalian rapamycin target protein induced by TGF-β could activate hypoxia inducible factor-1α (HIF-1α), and then induce MDSCs to express CD39/CD73. CD39 and CD73 can produce adenosine, and then inhibit the antitumor activity of NK cells, effector T cells, and other effector cells according to paracrine signals, so as to

https://doi.org/10.4110/in.2021.21.e21

further promote the escape of tumor cells from cytotoxic T cell responses (34). Based on a large number of studies, we conclude that exposure of MDSCs to hypoxia in TME leads to the increase of arg1 and iNOS mediated by HIF-1 α and the up-regulation of PD-L1, which is the surface inhibitor of MDSCs. MDSCs can also produce cytokines such as IL-10 and TGF-β, which can attract Treg cells to tumor sites, enhance their immunosuppressive function, and inhibit B cells, NK cells, D cells, and the function of C. Adenosine from CD39-high/CD73-high MDSCs is another major NK suppressor. At the same time, due to the effect of hypoxia, the activity of STAT3 in MDSCs was greatly reduced, which led to the rapid differentiation of M-MDSCs into TAMs. PMN MDSCs die rapidly due to endoplasmic reticulum stress, and the factors released by the dead cells can promote the immunosuppressive mechanism. MDSCs can promote tumor angiogenesis and metastasis by producing VEGF, MMPs and exons. Tumor-derived exons can also affect the recruitment and immunosuppression of MDSCs (89). In conclusion, we can understand that the mTOR-HIF-1α-CD39/CD73-adenosine-MDSCs-PDL1 pathway is the main mechanism of MDSCs involved in LC.

Breast cancer (BC) and MDSCs

BC is one of the most common malignant tumors in the world. Although progress has been made in diagnosis and treatment, it remains a major cause of cancer-related deaths (93,94). Tumor and immune analysis revealed the potential mechanism of immune evasion in BC, as well as the unique aspects of the TME. These elements include those related to Ag processing and presentation, as well as immunosuppressive elements (95). MDSCs play a key role in malignant BC differentiation. BC cells can recruit tumor infiltrating leukocytes, such as Tregs, MDSCs, and type II macrophages, to form the TME, which aids tumor development and plays a "downregulatory" role in anti-tumor immunity (96). Invasive MDSCs can induce epithelial mesenchymal transition of tumor cells and increase the metastasis of BC by up-regulating the levels of TGF-β1, VEGF, and IL-10 (97). Hoffmann et al. (98) found that in BC models containing the polyoma virus middle T Ag, overall recruitment of MDSCs to promote tumor immunosuppression increased. Safarzadeh et al. (99) co-cultured purified HLA-DR$^-$CD33$^+$ MDSCs with CD3$^+$ T cells and showed that MDSCs in the BC group inhibit T cell proliferation more effectively than those in the healthy group. MDSCs are more abundant and are effective as T cell inhibitors with double immunosuppressive effect (99). Hsu et al. (100) showed that the secretion of CXCL17 by BC cells increases the accumulation of CD11b$^+$Gr-1$^+$ MDSCs in the lung. Metastatic lung infiltration of CD11b$^+$Gr-1$^+$ MDSCs can play a role in inducing pulmonary angiogenesis, promoting tumor extravasation and survival, BC proliferation, and ultimately promoting lung metastasis (100). Additionally, MDSCs can directly react with BC cells. The STAT3-NF-κB-IDO, STAT3/IRF-8, and PTEN/Akt pathways play a decisive role in MDSC recruitment from tumor cells (101). The direct effect of MDSCs and BC cells is also evident in the activation of IL-6 produced by MDSCs, which simultaneously express IL-6 and soluble IL-6Rα. The trans signal of IL-6 then stimulates STAT-3 phosphorylation in BC cells, which is helpful for BC invasion and metastasis (102). Triple-negative BC (TNBC) accounts for 20% of all BC patients. Compared with estrogen receptor positive BC, which can be effectively controlled by endocrine therapy, TNBC is more invasive and has a worse prognosis (103). Kumar et al. (104) found that MDSCs promote TNBC stem cell function by secreting MMP9 and chitinase 3-like-1 protein, which confirmed the non-immune effect of MDSCs in promoting TNBC progression and metastasis. Further, some studies have shown that glycolysis is closely related to tumor development (105,106). Through the AMP-activated protein kinase-Unc-like kinase 1, autophagy, and C/EBPβ pathways, tumor glycolysis restrictively inhibits the expression of the tumor G-CSF and GM-CSF, thereby inhibiting the development of MDSCs and maintaining

https://doi.org/10.4110/in.2021.21.e21

tumor immunosuppression (107). Therefore, aerobic glycolysis regulates the development of MDSCs through a unique molecular mechanism, thus affecting tumor progression and outcomes. Based on the above studies, MDSCs mainly affect the BC stage through the STAT3-NF-κB-IDO pathway and directly promote the occurrence of BC by increasing IL-6. MDSCs also act on T and NK cells to inhibit immune-induced tolerance of the body and promote BC progression and metastasis. Therefore, in BC, MDSCs do not only weaken anti-tumor immunity and promote BC occurrence and progression, but also reduce the effect of other immunotherapies.

MDSCs IN NEUROINFLAMMATORY

Neuroinflammatory and neurodegenerative diseases are characterized by the interaction of several molecular pathways that can be evaluated through biological fluids, especially cerebrospinal fluid and blood (108). In recent years, the concept of immune system regulation has received extensive attention in the field of neuroimmunology (109). The central nervous system (CNS) is an important system in the human body and has certain immune functions. Immune response in the CNS is relatively complex, and microglia play a leading role. MDSCs can play a corresponding role when the phagocytic activity of M2-polarized microglia decreases (110). Under the condition of focal brain injury, MDSC infiltration can inhibit neuronal inflammation and interact with microglia and other immune cells (111,112). However, MDSCs can increase Tregs, that have immunosuppressive effects and inhibit M1 macrophages, that in turn have tumor inhibitory effects (112). The role of Tregs in the immune system is closely related to the activation of $CD4^+$ T cells and the differentiation of related effector subsets. The initial activation of $CD4^+$ T cells requires intercellular adhesion molecule (ICAM)-1. ICAM-1 and ICAM-2 mediate the migration of Th1 and Th17 cells in the blood-brain barrier (BBB). They travel through the BBB to the CNS to induce related neuroinflammation (113). Th1 is related to the production of IFN-γ and TNF-α, and Th1 type T cells also play a role in tissue damage (114). T cells provide important immune monitoring for the CNS, and CSF is considered to be the main entry pathway of T cells (115). All these activities are specialized in producing different mediators and recruiting different immune cells, thus causing certain inflammatory reactions. For the mechanism of MDSCs in neuroinflammation, we simply drew **Fig. 3** to describe it. Some studies have shown that $Ly6G^+$ cells are recruited into the CNS in experimental autoimmune encephalomyelitis (EAE), interact with B cells to produce the cytokines, GM-CSF and IL-6, and rely on the signal transducer, STAT-3, to obtain the characteristics of PMN-MDSCs in CNS. Conditional ablation of STAT-3 leads to the depletion or dysfunction of $Ly6G^+$ cells, which further leads to selective accumulation of GM-CSF-producing B cells in CNS chambers, thus promoting phenotype activation of microglia and making it difficult to recover from EAE (116). In the context of neuroimmunology, MDSCs are not only a powerful controller of T cell activity, but also an important regulator of immune recovery (117). With the above information, we can conclude that MDSCs play an important role in neuroinflammatory diseases.

Multiple sclerosis (MS) and MDSCs

MS, which involves an imbalance of brain-derived T cells in the CNS, is a difficult disease to cure. MS is the second major cause of paraplegia in young people, second only to various types of CNS injury (118). MDSCs are recognized for their important role in regulating T cell responses (119). MS is an autoimmune demyelinating disease that mainly occurs in young people. In addition, it is a chronic autoimmune disease that cannot be cured (120,121).

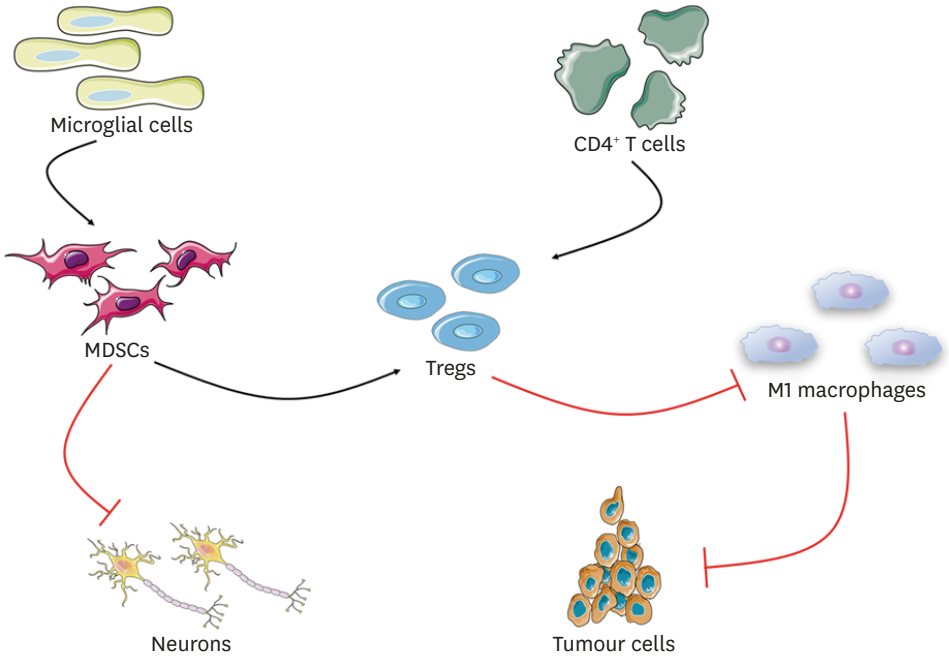

Figure 3. Schematic diagram of the mechanism of MDSCs in neuroinflammatory. In the case of local brain injury, microglia cell activity was reduced, and the infiltration of MDSCs could directly inhibit the inflammatory process of nerve cells. Initial $CD4^+$ T cells via the activation of ICAM-1 and ICAM-2 mediated into Tregs, MDSCs can play a role of immunosuppression by increasing Tregs, Tregs inhibits the M1 macrophages, and macrophages can exert the function of inhibiting tumor cell, eventually forming an inhibition ring, have the effect of immunosuppression, inhibiting the inflammatory process.

Available data show that MDSCs may be a clinical target for the diagnosis and treatment of several neuroimmunologic diseases, including MS (117). The "inside out" model proposed by neuroscientists indicates that MS is a primary degenerative disease with secondary host abnormal inflammatory response (122). However, EAE is the most commonly used animal model for studying the inflammatory components of MS. Several cell types are involved in the regulation of EAE immune response. MDSCs can be an important factor in EAE immune regulation because of their role in inducing T cell apoptosis and inhibiting inflammatory responses (123). MDSCs are cells in the innate immune system that regulate the activity of T cells in EAE (120). In fact, some researchers have observed that the number and maturity of M-MDSCs are negatively correlated with the clinical results of EAE (123,124). In addition, the increase in the number and activity of M-MDSCs paralleled the improvement of clinical course in different MS animal models (125,126). Cantoni et al. (127) demonstrated that bone marrow derived cells play an important regulatory role in MS and EAE models. MDSCs can inhibit T cell activity in EAE, thus playing an immunosuppressive role (127). It has been shown that the number of $CD138^+$ B cells is negatively correlated with PMN-MDSCs in the examination of CSF from MS patients. Cytokines and chemokines in EAE models promote Th1 and Th17 to regulate the migration of leukocytes to the CNS during disease (116). Pathogenic T lymphocyte subsets, such as Th1 and Th17 cells, play an important role in the pathogenesis, development, and subsequent autoimmune cascade of tissue damage in MS. Hence, DCs, MDSCs, $\gamma\,\delta$ T cells, and NK subsets regulate the autoimmune response of the CNS under certain conditions. MDSCs can induce T cell apoptosis by preventing the proliferation of $CD4^+$ T cells and related inflammatory cytokines (128). In MS, T cells abnormally recognize myelin autopeptides and attack the CNS (129). Based on the above information and other studies, we further summarize the mechanism of MDSCs in MS as

https://doi.org/10.4110/in.2021.21.e21

follows: under MS conditions, MDSCs rapidly proliferate and are activated, showing a strong inhibitory and potential pro-inflammatory phenotype, which can produce cytokines, such as IL-6, accelerate the differentiation of Th17, and induce T cell inactivation. To provide protection against MS, MDSCs eventually inhibit the proliferation of $CD4^+$ T cells and the secretion of related inflammatory cytokines by Arg-I-mediated cell contact (122,127-130).

Glioblastoma (GBM) and MDSCs

Glioma is the most common and fatal primary brain malignant tumor. A large amount of evidence supports the important contribution of MDSCs to the tumor immunosuppressive microenvironment, which is the key factor to stimulate the progression of glioma (131). GBM accounts for 56% of all newly diagnosed gliomas and has a high incidence rate and aggressive characteristics (132). One of the mechanisms of GBM induced immunosuppression is the accumulation of Tregs and MDSCs (133). *In vivo*, GBM particularly exhibits a large number of immune cells, such as microglia and tumor infiltrating macrophages, in which MDSCs account for a large proportion, and play a variety of roles in the development of tumors, including promoting tumor cell proliferation, survival, migration, and immunosuppression of the organism (134). Two subgroups of MDSCs have been found in the blood and tumor tissues of glioma (including GBM multiforme) patients (135). It can be concluded that the glioma microenvironment may contribute to the immunosuppressive function of MDSCs and negatively regulate immune system response (136). Hence, it is believed that the interaction between MDSCs and glioma cells can lead to the inhibition of effective antitumor immune response. However, based on *in vitro* studies, researchers have proposed that MDSCs play an important role in promoting the growth, invasion, and angiogenesis of glioma and the systematic expansion of Tregs cells (137). LOX-1+ PMN-MDSCs inhibit T cell proliferation and enhance immunosuppression, which may play a key role in driving the progression of GBM (138). Alban et al. (139) analyzed 259 patients with primary and metastatic brain tumors from benign to malignant by flow cytometry. They found that the MDSCs in the peripheral blood of GBM patients increased significantly, whereas the Tregs of immunosuppression were not found to be significantly increased. The increase in MDSCs in the recurrent GBM indicates a poor prognosis (139). Another study showed that glioma cells expressed many factors (IL-6, IL-10, VEGF, PGE-2, GM-CSF, and TGF-β2) related to MDSC proliferation. On the contrary, blocking the CCL2 signaling pathway of chemokines in glioma cells reduced recruitment of MDSCs, indicating that MDSCs need to play a unique role in the corresponding TME produced by glioma cells in GBM (140). Gielen et al. (141) found that the intracellular S100A8/9 level of M-MDSCs in GBM patients was higher than that in HCs, which was related to the increase in serum arginase activity. PMN-MDSCs highly express arginase in blood and tumor tissue, and PMN-MDSCs from blood strongly inhibit T-cells *in vitro*, suggesting that PMN-MDSCs play a role in GBM by inhibiting T cell function (141). According to relevant research data, glioma-associated microglia/macrophages are negatively correlated with survival time of patients with malignant gliomas microglia/macrophages (GAMs), MDSCs have the highest intratumoral density, and both GAMs and MDSCs have the ability to attract Tregs to tumors. The presence of Tregs may further lead to a lack of effective immune activation in gliomas (142). The above results suggest that MDSCs can promote the growth and deterioration of GBM by inhibiting NK cell-mediated cytotoxicity, thus releasing a variety of cytokines and chemokines and hindering the activation of $CD4^+$ and $CD8^+$ T cells.

Uveitis and MDSCs

Uveitis is a group of diseases characterized by intraocular inflammation, including inflammation of adjacent intraocular structures, such as the retina, vitreous body,

and optic nerve. It can be caused by some autoimmune factors and is a major cause of blindness worldwide (143,144). Systemic diseases are often associated with uveitis (145). The experimental autoimmune uveoretinitis (EAU) model, which is used to study human endophthalmitis, is a common laboratory animal model for studying uveitis (146). Jeong et al. (147) proved that the number of HLA-DR$^-$CD11b$^+$CD33$^+$CD14$^+$ human MDSCs and CD11b$^+$Ly6G$^-$Ly6C$^+$ mouse MDSCs increased significantly before and after the regression period of EAU. CD11b$^+$Ly6C$^+$ monocytes can be isolated from the EAU model; they can block T cell proliferation during culture, and the adoptive transfer of cells can accelerate the remission of EAU in mice (147). Therefore, mononuclear MDSCs are the key regulatory cells that mediate the regression of EAU. Tu et al. (148) found that there may be another mechanism for the control of retinal immune response, that is, the indirect control mechanism of MDSCs through the induction of the retinal pigment epithelium (RPE). However, IL-6 also plays a key role in the differentiation of MDSCs induced by RPE cells (148). The above studies indicate that MDSCs were recruited to the inflammatory site to inhibit the autoimmunity, thus playing a protective role in the development of EAU (149). In general, although there are studies that prove that MDSCs play an important role in the protection against uveitis, the specific mechanism underlying the involvement of MDSCs in uveitis is not clear; this needs to be further explored by researchers.

SUMMARY AND PROSPECT

In conclusion, MDSCs have a unique immunosuppressive function in tumor and nervous system-related diseases as well as other clinical diseases. They also play an important role in autoimmune diseases. Therefore, MDSC research has become an important aspect in the field of tumor immunology. Several studies have shown that MDSCs can be used as a therapeutic target to enhance the efficacy of checkpoint inhibitors by reducing their pre-tumorigenic function and immunosuppressive activity. MDSCs are not only involved in cancer, but also in chronic inflammation, bacterial/viral infections, autoimmune diseases, trauma, and graft-versus-host disease. However, compared with cancer and infectious diseases, MDSC expansion in these other conditions is not significant, which leads to greater heterogeneity in the myeloid population, and the variable frequency of MDSCs among myeloid cells may lead to conflicting results. This heterogeneity is obviously due to the different severity of autoimmune diseases and the particularity of the microenvironment. The related mechanism can be used to study the treatment and prognosis of related diseases and improve its clinical utilization. At present, we can make good use of existing resources and conditions to better understand the biological characteristics of MDSCs and provide a more reliable theoretical basis for targeted therapy. Notably, the absence of MDSCs in homeostasis conditions provides a unique opportunity to target these cells without side effects. Understanding the molecular mechanisms that regulate the accumulation and function of these cells offers the possibility of more precise targeted therapies. The clinical significance of MDSCs in cancer and some infectious diseases is now well established. In future studies, we need to focus on whether targeting MDSCs can provide real clinical benefits. If we can make good use of these research findings, it will be of great benefit to many clinical diseases. We hope that our research can go deep, in order to seek more accurate targeted treatment, find the right target, symptomatic in-depth, so as to benefit more patients.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (No. 81801557, 81671632, 81874169), Shandong Provincial Natural Science Foundation Key Project (No. ZR2020KH033), National Training Program of Innovation and Entrepreneurship for Undergraduates (No. 201910443013), Jining Medical University Training Program of Innovation and Entrepreneurship for Undergraduates (No. cx2019002).

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