The role and research progress of MDSC in immune aging-related diseases

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Author contributions
Fang XX and Li HZ wrote the manuscript. Piao XM helped revise the manuscript. Wang YM and Bian YH designed and supervised this study. The final manuscript had been approved by all the authors.
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Abbreviations
MDSC, myeloid-derived suppressor cell; NSCLC, non-small cell lung cancer; Tregs, regulatory T cells; IPF, idiopathic pulmonary fibrosis.

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Abstract
Myeloid-derived suppressor cells (MDSCs) are a group of heterogeneous immature cells with a strong immunosuppressive function in myeloid cells, which are impeded in the differentiation of myeloid cells under the pathological conditions of hypoxia, inflammation, infection, and cancer. As individuals age, there is a significant increase in myeloid-derived suppressor cells (MDSCs), which subsequently enhance the immunosuppressive functions of Tregs (regulatory T cells) and Bregs (regulatory B cells). Therefore, MDSC may be related to immune system remodeling, thereby preventing excessive lesions caused by aging. This indicates that MDSC could serve as a potent inducer of immune senescence. Immune senescence, characterized by immune dysfunction with aging, is closely linked to the onset of diseases like infections, pulmonary fibrosis, and tumors. To achieve the purpose of anti-aging by intervening in immune aging and slow down the occurrence and development of related diseases. Therefore, understanding the biological characteristics of MDSC and its role in immune aging is crucial for immunotherapy targeting MDSC. This article reviews the different roles of MDSC in immune aging and its relationship with pulmonary fibrosis, tumor and other related diseases to provide theoretical basis for more comprehensive targeted MDSC immunotherapy.

Keywords: MDSC; immunosenescence; tumor progression; pulmonary fibrosis; immunosenescence therapy
Background

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous group of immature myeloid cells with potent immunosuppressive functions. These cells are characterized by their ability to inhibit T cell responses and promote immune tolerance in various pathological conditions, such as cancer, inflammation, and infection. MDSCs are classified into two main subtypes based on their morphology and surface markers: polymorphonuclear MDSC (PMN-MDSC) and monocytic MDSC (M-MDSC) [1]. MDSC exerts immunosuppressive effects through various mechanisms, such as inhibiting the proliferation and function of T lymphocytes, inducing the proliferation of regulatory T cells (Tregs), and inhibiting the function of macrophages and natural killer cells through secretion of cytokines or direct contact. The concept of “immunoenescence” was proposed by Professor Wal-ford, a pathologist at the University of California in 1962, and is defined as the age-related structural and functional changes of the body’s immune system with the growth of age [2]. Research has revealed that aging can lead to a decline in immune function, which is mainly attributed to the decrease in the number of immune cells and the decline in function. In particular, aging triggers an increase in MDSC cells, which play a key role in the immune response, and their ability to suppress T cell activity weakens the immune effect. Understanding the complex relationship between aging and MDSC will help us to further explore the mechanism of immune aging and provide key clues for the formulation of anti-aging immune strategies. Further exploration of how to regulate the number and function of MDSC may help delay immune aging, enhance the immune function of the elderly, improve their disease resistance and quality of life, so as to combat the decline of tissue and organ function caused by age and the occurrence of diseases such as cancer and pulmonary fibrosis [3, 4]. Studies have shown that age-related MDSC activation has a significant effect on immune system remodeling, especially on immune senescence and senescent cell accumulation, and plays an important role in the occurrence of diseases such as infection, pulmonary fibrosis and tumor. At present, the research of age-related immunosenescence has become a new hotspot in the world. The discovery of key targets of immune aging mechanism is of great significance to reveal the molecular basis of abnormal immune regulation in aging process and scientifically formulate immune intervention strategies for disease treatment. Therefore, by synthesizing literatures related to immune aging and MDSC, this paper focuses on the relationship between MDSC’s intervention in related diseases by influencing immune aging, hoping to provide a new direction for related immunotherapy research (Figure 1).

Overview of MDSC

In the mid-20th century, it was found that tumor progression is accompanied by abnormal differentiation of bone marrow cells that inhibit the number of lymphocytes and the induction and activity of cytotoxic T lymphocytes, which were originally named natural suppressor cells. In the early 2000s, these cells were renamed immature myeloid cells and myelosuppressor cells. In 2007, Gabrilovich et al. first proposed the concept of MDSC to reflect the abnormal myeloid status of such cells in tumors [5].

MDSC is a heterogeneous cell population composed of myeloid progenitor cells and immature myeloid cells, which are expressed in pathological conditions such as tumors, bacterial and parasitic infections, chronic inflammation, sepsis and autoimmune diseases. According to the phenotype and morphological characteristics of MDSC, it is mainly divided into PMN-MDSC and M-MDSC. In mice, the surface of MDSC is labeled CD11b+Gr1−. Based on the Ly6G and Ly6C molecules expressed by the antigenic epitopes of Gr1, MDSC can be divided into CD11b+Ly6ChighLy6G− MDSC and CD11b+Ly6ChiLy6G− MDSC, namely PMN-MDSC and M-MDSC. The surface labeling of human MDSC is different from that of mice, where M-MDSC is CD14+CD15+HLA-DR− and PMN-MDSC is CD11b−CD14+CD15+/−/CD66b+. In addition to PMN-MDSC and M-MDSC, early MDSC (e-MDSC) is only found in the population and contains many immature progenitor cells with the surface label LN− (CD3, CD14, CD15, CD19, CD56) HLA-DR−CD38−. In addition, fibrocyte MDSC (F-MDSC) is a newly discovered subtype of MDSC in humans, which has the characteristics of MDSC, dendritic cells and fibrocyte related markers, but relatively few studies have been conducted on this type of cells [6]. The establishment of subtypes of MDSC has laid a foundation for the study of their functions (Table 1).

Immunosuppressive mechanism of MDSC

Studies have shown that MDSC can play an immunomodulatory role in infectious diseases through a variety of mechanisms, such as inducing high expression of arginase1, consuming amino acids necessary for cellular immune response, blocking the synthesis of TCR-CD3 and blocking cell signal transduction, thus inhibiting cellular immune response. Produce induced nitric oxide synthase, by promoting nitric oxide and reactive oxygen species and direct inhibition of cell function; Inhibiting T helper 2 (Th2) response, reducing interleukin-4 IL-4 secretion, inhibiting Th2 proliferation and inhibiting humoral immunity; Secreting IL-10 and transforming growth factor-beta (TGF-β) to inhibit the function of immune effector cells; Up-regulate the expression of PD-L1, and inhibit cell-mediated reaction activity by interacting with PD-L1 receptors on T cells; Down-regulating L-selectin promoted the decrease of T cells migrating to lymph nodes. It can also promote the production of Treg, thus inducing T cell differentiation imbalance.

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In recent years, the research of MDSC in tumor-related diseases has been gradually deepened [7]. In the tumor microenvironment, MDSC exerts a negative immune regulatory mechanism, and activated MDSC inhibits T cell-mediated immune response through high expression of arginase 1 and inducible nitric oxide synthase [8]. In patients with colorectal cancer, breast cancer, non-small cell lung cancer and thyroid tumors, MDSC is associated with metastasis and prognosis of solid tumors, and its number is positively correlated with cancer stage and tumor load [9-15]. Most tumor cells undergo glycolysis of glucose even under aerobic conditions. In anoxic environment more suitable for tumor cell growth, the Warburg effect of aerobic glycolysis prompts tumor cells to produce high concentration of lactic acid (the end product of glycolysis), which gradually leads to immunosuppressive state of tumor infiltrating neutrophils [16]. Thus, the high expression of granulocyte colony-stimulating factor (GCSF) in the tumor microenvironment is promoted, which further induces the differentiation and recruitment of MDSC and promotes tumor progression (Figure 2) [17-19].

**MDSC interferes with the relationship of diseases by influencing immune aging**

MDSC is a potent inducer of immunosuppression in the adaptive immune system, and its expansion with Treg is significant with aging, which may trigger and maintain the chronic state of immune aging. MDSC-induced immunosuppression is a key remodeling mechanism of immune aging and is essential for tissue survival in chronic inflammation. MDSC may affect immune cells in a direct way, but some of the responses detected in vivo experiments can also be mediated through their interactions with other immunosuppressive cells (such as Tregs and MREGs).

**MDSC and pulmonary fibrosis**

Pulmonary fibrosis is a chronic and progressive interstitial disease characterized by decreased lung function and respiratory failure caused by excessive accumulation of extracellular matrix, while idiopathic pulmonary fibrosis occupies a special position due to its short survival period, high mortality and poor prognosis [20]. Idiopathic pulmonary fibers have hidden onset and complex pathogenesis, involving immune inflammation, oxidative stress, gene damage, etc. Among them, immune inflammation is a key link in the occurrence and development of pulmonary fibrosis. Schafer et al.’s study in 2017 showed that idiopathic pulmonary fibrosis (IPF) is related to the acceleration of senescence cells and senescence accumulation. Removal of senescent cells can inhibit the development of fibrosis in animal models of IPF [21].

MDSC can be subdivided into PMN-MDSC and single-cell (M)-MDSC [22]. More PMN-MDSC was found in the lungs of IPF mice, possibly through increased CXCR2 expression [23]. PMN-MDSC in peripheral blood of patients with interstitial lung disease also increased, while the amount of M-MDSC remained unchanged [24]. An increased number of CD33+CD11b+ cells was found in the pulmonary peripheral blood of patients with IPF (suggestive of MDSC, especially M-MDSC) [25]. Increased number of MDSC is thought to be associated with poor lung function and increased number of Tregs in patients with IPF. In mouse renal and liver fibrosis models, MDSC deletion was found to enhance fibrosis markers, while adoptively transferred MDSC improved mouse renal fibrosis models [26, 27]. However, increased PMN-MDSC is thought to be associated with reduced parenchymal fibrosis and attenuation of BPF in mice [28]. Other studies have also shown that there is a circulating MTSC-like fibrocyte population in cancer [29]. In addition, in a mouse renal fibrosis model, CD11b+CD115+Gr1− MDSC produced cells contribute to renal deposition of type I collagen [30]. As mentioned above, PMN-MDSC plays a key role in promoting Bregs, which may further reinforce the potential protective effect of MDSC in idiopathic pulmonary fibrosis (IPF) [31]. Mesenchymal stem cells (MSCs) from bone marrow have been shown to drive phenotypic transformation of GR1−CD11b+ cells (primarily PMN-MDSC) to GR1+CD11b+, which indicates M-MDSC differentiation. This discovery revealed the important role of MSCs in inhibiting the progression of bleomycin-induced pulmonary fibrosis (BPF) in mice [32].

**MDSC and tumor**

In general, the risk of developing tumors increases with aging. De Santis et al. found that the elderly population had a higher risk of tumor occurrence [33]. Palmer et al. analyzed the age distribution of different tumors and concluded that immune aging was closely related to tumor progression [34]. Pélissier et al. analyzed female mammary epithelial cells and found that immune aging would promote the accumulation of larunar cells and progenitor cells, thus increasing the risk of cancer [35].

The abundance of MDSC in colorectal cancer patients is not merely associated with tumor stage and histological grade; it is also tightly linked to the upregulated expression of genes related to cell proliferation, anti-apoptosis, and migration. All these factors may facilitate the progression of colorectal cancer [36, 37]. When considering cancer vaccines, patients aged up to 71 years who received mucin-1 peptide vaccines exhibited strong immunogenicity, especially among those with a higher baseline MDSC frequency. Generally, responding patients demonstrated a higher level of T cell activation in vitro compared to non-responding patients. Notably, upon eliminating MDSC from the blood of non-responders, the Interferon-gamma (IFN-γ) production by T cells could be restored to levels comparable to those of responders [38].

Most lung cancer cases, approximately 80–85%, are attributed to non-small cell lung cancer (NSCLC). In comparison to early-stage patients, a higher abundance of MDSC is observed in more severe stages, including brain metastases [39]. Clinical observations indicate that a reduction in MDSC levels is closely linked to improved survival rates. For instance, individuals aged 56–70 years who had a higher baseline MDSC frequency exhibited significant survival improvements after undergoing immune checkpoint blocking immunotherapy, further validating the association between MDSC reduction and clinical benefit [40]. Comparable findings have been reported in studies involving patients aged 56–85 years who underwent chemotherapy combined with immunotherapy [41]. Among patients aged 65–80 years, stereotactic body radiotherapy was associated with a gradual increase in NK and CD4+ cells, while CD8+ T cells did not exhibit significant changes. Additionally, there was a slight decrease in both PMN-MDSC and M-MDSC levels from the initiation of treatment to six months [42]. These diverse but common cases of solid tumors highlight the importance of MDSC in age-related diseases and their widespread and heterogeneous impact (Table 2) [36-42].

**Discussion**

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<table>
<thead>
<tr>
<th>Subtype</th>
<th>Phenotype</th>
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<tbody>
<tr>
<td>Mice</td>
<td>CD11b+Ly6G+Ly6C+</td>
</tr>
<tr>
<td>Human</td>
<td>CD15+/CD11b+/CD33+/HLA-DR−Lin−</td>
</tr>
<tr>
<td>Human</td>
<td>CD14+/CD11b+/CD33+/HLA-DR−Lin−</td>
</tr>
</tbody>
</table>

Table 1 Main subtypes and functional proteins of MDSCs
Figure 2 MDSC-mediated mechanisms of immunosuppression. TGF-β, transforming growth factor-β; ROS, reactive oxygen species; Arg1, arginase 1; INOS, inducible nitric oxide synthase; IL, interleukin; CCL2, chemokine (C–C motif) ligand 2; AMP, adenosine monophosphate; NK, natural killer.

Table 2 Presence and impact of MDSCs in aged individuals

<table>
<thead>
<tr>
<th>Reference</th>
<th>Condition</th>
<th>Species</th>
<th>Age</th>
<th>MDSC</th>
<th>MDSC effect(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[36, 37]</td>
<td>Colorectal cancer</td>
<td>Human</td>
<td>&lt; 71</td>
<td>CD3+ CD19− 56 HLA-DR CD11b+ CD33+ CD33+ HLA-DR−/low CD14+ CD15+ (PMN-MDSC) and CD33+ HLA-DR−/low CD14− (M-MDSC)</td>
<td>Increased MDSC correlated with reduced apoptosis &amp; cell proliferation</td>
</tr>
<tr>
<td>[38]</td>
<td>Colorectal cancer</td>
<td>Human</td>
<td>Up to 71</td>
<td>CD11b+ CD33+ HLA-DR−/low</td>
<td>In vitro MDSC depletion restored T cell activation to mucin-1 vaccine</td>
</tr>
<tr>
<td>[40]</td>
<td>Lung cancer</td>
<td>Human</td>
<td>56–70</td>
<td>Lin− HLA-DR−/low CD33+ CD13+ CD11b+ CD15+ C D14+ (PMN-MDSC)</td>
<td>Decreased MDSC associated with successful checkpoint blockade immunotherapy</td>
</tr>
<tr>
<td>[41]</td>
<td>Lung cancer</td>
<td>Human</td>
<td>56–85</td>
<td>CD14+ HLA-DR−/low (M-MDSC)</td>
<td>Decreased MDSC associated with improved response to chemotherapeutic blockade immunotherapy</td>
</tr>
<tr>
<td>[42]</td>
<td>Lung cancer</td>
<td>Human</td>
<td>65–80</td>
<td>CD33+ CD11b+ CD14− (PMN-MDSC) and CD33+ CD11b+ CD14− HLA-DR−/low (M-MDSC)</td>
<td>Decreased MDSC associated with stereotactic radiation therapy</td>
</tr>
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MDSCs, granulocytic myeloid-derived suppressor cells.

As a key immunosuppressive cell, MDSC not only regulates the immunosuppressive network, but also plays an important role in immune aging. However, the specific role of immune aging in aging remains unclear. Although the literature largely supports immune system decline with age, it is challenging to fully assess its benefits and harms. Given that mild inflammation is difficult to eliminate, immune aging appears to be an important remodeling mechanism for maintaining tissue homeostasis.

IPF is a devastating interstitial lung disease, and although it has been extensively studied, its characteristics and causes are still poorly understood. The complexity of the disease and its chronic, progressive, and destructive nature make both research and treatment extremely challenging. At present, the effect of drug treatment is still unsatisfactory, and lung transplantation has become the only truly effective treatment. Despite advances in our understanding of IPF in recent years, there are still many contradictions and unknowns regarding the role of regulatory immune cells, especially MDSC. The fact that many of the regulatory immune cells involved play both harmful and beneficial roles in IPF confuses us about their specific role in the disease process. The role of MDSC in IPF is very little known, and its phenotype and function need to be further studied. To design new effective drug treatments as well as to improve lung transplant success and prevent associated graft-versus-host disease, we need to further understand the potential role of regulatory immune cells in mouse models of IPF, with a particular focus on the function of these cells in human IPF. Therefore, more preclinical and human studies are urgently needed to better understand and define the role of
immunomodulatory cells in the pathogenesis of IPF, thus providing an important basis for the development of new treatments.

In a variety of inflammatory settings, especially tumor-related inflammation, MDSC plays an important role as a powerful immunosuppressive cell and works collaboratively with other immunosuppressive cells such as Treg, Bregs, and Mregs to suppress immune function [43]. And, with age, the number of MDSC also increases, supporting the idea that they play a key role in coordinating immune aging. Cancer treatment research has revealed that many chemotherapy and immunotherapy approaches can inhibit the function of MDSC [44, 45]. For example, different compounds, such as all-trans retinoic acid (ATRA) and beta-glucan, can induce MDSC to mature into innate immune cells [46, 47]. In addition, inhibitors of signaling pathways, such as STAT3 and COX-2/PGE2 inhibitors, can be used in cancer studies to reduce MDSC activation [48]. However, there are still many deficiencies in the current research. Although the phenotypes of MDSC and other immune cells have been identified in tumor studies, the phenotypes of immune cells in non-immune tissues have not been characterized in immunooaging. Of concern is whether the presence of accumulation of MDSC and other immunosuppressive cells in aging tissues is associated with increased levels of chronic low-grade inflammatory markers. These are all issues that need further attention in future research.

Therefore, by delving deeper into the research findings, we can elucidate the intricate interactions between MDSC, immune senescence, and various diseases, such as infection, pulmonary fibrosis, and cancer. Furthermore, highlighting the potential implications of targeting MDSC in mitigating age-related immune dysfunction and disease development can provide valuable insights for future research and therapeutic strategies.

References


