

Myeloid-Derived Suppressor Cells in Infection: A General Overview

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Abstract

After initial infection, the immune response that serves to restrict the invading pathogen needs to be tightly calibrated in order to avoid collateral immunopathological damage. This calibration is performed by specialized suppressor mechanisms, which are capable of dampening overwhelming or unremitting inflammation in order to prevent tissue damage. Myeloid-derived suppressor cells (MDSC) are emerging as key players in counter-balancing inflammatory responses and pathogenesis during infection. However, some pathogens are able to exploit the suppressive activities of MDSC to favor pathogen persistence and chronic infections. In this article, we review the current knowledge about the importance of MDSC in the context of bacterial, virus, parasites, and fungal infections.

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Myeloid-Derived Suppressor Cells

Myeloid-derived suppressor cells (MDSC) are a highly heterogeneous cell population with strong immunosuppressive effects on T-cell responses [1]. MDSC arise from common myeloid progenitors and are arrested in an immature phase of differentiation [1]. The frequency of MDSC in steady-state conditions is very low but increases dramatically in pathological conditions such as cancer, autoimmunity, and infection [2]. Although MDSC are phenotypically and functionally very heterogeneous, different MDSC subsets have been identified based on the expression of distinct cell surface markers. Traditionally, MDSC have been classified as monocytic CD11b⁺Ly6C⁺Ly6G^{low} (M-MDSC) or granulocytic CD11b⁺Ly6C^{low}Ly6G⁺ (PMN-MDSC) based on the Ly6C and Ly6G expression levels [2]. Recently, a new subset of MDSC has been identified in mice with chronic *Staphylococcus aureus* infection that was termed Eo-MDSC because they depicted phenotypic features typical of immature eosinophils including CD11b⁺Sytlec-F⁺CCR3^{low}IL-5Rα^{low}SSC-A^{high} [3]. Phenotypic markers for human MDSC subsets in peripheral blood include CD11b⁺CD14⁻CD15⁺ or CD11b⁺CD14⁻CD66b⁺

for PMN-MDSC, CD11b⁺CD14⁺HLA-DR^{-/low}CD15⁻ for M-MDSC, and Lin⁻HLA-DR⁻CD33⁺ for more immature MDSC progenitors [4].

Major drivers for MDSC expansion under pathological conditions are inflammatory factors such as prostaglandin E2 [5], pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-alpha), interleukin 6 (IL-6), and IL-1 β [6] and myeloid-related calgranulin B (S100A9) [7] among others. MDSC exercise their immunosuppressive activities through various mechanisms, including the generation of high levels of inducible nitric oxide (iNOS, mainly M-MDSC) and reactive oxygen species (ROS, mainly PMN-MDSC) that induce the nitration of the T-cell receptor and prevent its interaction with cognate antigen-major histocompatibility complex (MHC) [8], as well as by the production of arginase-1 that in combination with high levels of iNOS restricts the availability of the amino acid L-arginine, which is essential for T-cell proliferation [9]. It has been suggested that the usage of each mechanism may depend on the specific MDSC subset and the site of immunosuppression [10].

Condamine and Gabrilovich [11] proposed a model to explain why the release of inflammatory mediators during acute inflammation does not result in the expansion and accumulation of MDSC. The proposed model involved 2 steps, the first step is mediated by cytokines (e.g., IL-6) and growth factors (e.g., granulocyte-macrophage colony-stimulating factor [GM-CSF], macrophage CSF, granulocyte CSF) produced during chronic inflammation that prevent differentiation of immature myeloid cells and drive expansion of MDSC via signaling through the transcription factors signal transducer and activator of transcription 3 (STAT3) and STAT5 [11]. The second step is mediated by proinflammatory cytokines such as interferon gamma (IFN γ) and IL-1 β as well as by toll-like receptor (TLR) ligands that induce the upregulation of immunosuppressive mechanisms in MDSC (e.g., arginase and nitric oxide [NO]) via STAT1 and NF- κ B transcription factors [11].

While initial studies with MDSC focused on their role in tumor biology, accumulating evidence indicates an important role for MDSC in the control of immune responses to pathogens [12]. MDSC can be of benefit to the host by reducing immune-mediated pathology that can result as collateral damage associated with a robust host immune response to the pathogen. On the other hand, because their remarkable capacity to suppress effector T-cells, MDSC can prevent the immune system from mounting an effective immune response, thus favoring pathogen persistence and chronic infection. In the next sections, we address the role of MDSC in bacterial, viral, parasites, and fungal infections (summarized in Table 1).

MDSC in Bacterial Infections

Based on a clinical study performed in patients with septic shock and sepsis caused by Gram-negative and Gram-positive bacteria, Janols et al. [13] suggested that different bacteria can induce distinct MDSC subsets. Thus, whereas the frequency of M-MDSC determined by the phenotypic markers CD14⁺HLA-DR^{low} was very high in all sepsis patients, increased proportion of PMN-MDSC (CD14^{low}) with strong immunosuppressive effect was observed preferentially in patients infected with Gram-positive bacteria [13]. The authors suggested that release of immature myeloid cells phenotypically and functionally resembling PMN-MDSC from bone marrow is largely induced by Gram-positive but not by Gram-negative sepsis [13]. In this regard, it has been proposed that the observed difference in MDSC subsets in septic patients may be the consequence of fundamental differences in the host responses to Gram-positive and Gram-negative bacterial infections [14]. Thus, Gram-negative pathogens generally induce stronger inflammatory responses than Gram-positive resulting in fast mobilization of bone marrow bactericidal neutrophils rather than immunosuppressive PMN-MDSC [14]. Gram-positive, on the other hand, induce a milder and more prolonged inflammatory reaction that favor the expansion of immunosuppressive PMN-MDSC [14]. The influence of the magnitude of the inflammatory response to infection for the generation and activity of MDSC has been currently demonstrated in an experimental model of lethal pulmonary tularemia [15]. The authors demonstrated that infection caused by highly virulent *Francisella tularensis*, a Gram-negative intracellular pathogen classified as category A bio-threat agent, induced the recruitment of a large amount of MDSC to the lungs and spleens that eventually led to organ damage and host death, whereas the host response to sub-lethal *F. tularensis* infection was associated with the recruitment of mature myeloid cells leading to bacterial clearance and host survival [15].

A functional correlation between MDSCs frequency and infection phase and duration was demonstrated in patients with tuberculosis, a highly contagious infection of the lungs caused by the Gram-positive bacterium *Mycobacterium tuberculosis* and the most common cause of disease-related mortality worldwide [16]. Thus, high frequencies of MDSC with strong immunosuppressive effect on protective T-cell responses were detected in peripheral blood in tuberculosis patients and at the site of infection in tuberculosis pleuritic cases [16]. However, MDSC from long-term tuberculosis patients induced

Table 1. MDSC and their role in different infection settings

Infection category	Organism	Infection type	Effect	References
<i>Bacterial infections</i>				
<i>Francisella tularensis</i>	Mouse	Lung infection (intranasal inoculation)	Detrimental	[15]
<i>Mycobacterium tuberculosis</i>	Human	Lung infection	Detrimental	[16]
<i>Mycobacterium tuberculosis</i>	Mouse	Lung infection (intratracheal inoculation)	Detrimental	[17]
<i>Mycobacterium tuberculosis</i>	Mouse	Lung infection (aerosol inoculation)	Detrimental	[18]
<i>Salmonella typhimurium</i>	Mouse	Intestinal infection (intra-gastric inoculation)	Beneficial at low frequency and detrimental at high frequency	[19]
<i>Staphylococcus aureus</i>	Mouse	Chronic abscess (intravenous inoculation)	Detrimental	[22]
<i>Staphylococcus aureus</i>	Mouse	Prosthetic joint infection/biofilm	Detrimental	[23–25]
<i>Staphylococcus aureus</i>	Mouse	Skin infection	Detrimental	[26]
<i>Pseudomonas aeruginosa</i>	Human	Cystic fibrosis lung infection	Correlative associated with preserved lung function	[27]
<i>Pseudomonas aeruginosa</i>	Mouse	Lung infection (intranasal inoculation)	No significant impact on disease outcome	[28]
<i>Klebsiella pneumoniae</i>	Mouse	Lung infection (intratracheal inoculation)	Beneficial	[29]
<i>Viral infections</i>				
Hepatitis C virus	Humans	Liver infection	Detrimental	[31]
Hepatitis B virus	Humans	Liver infection	Beneficial	[33]
Human immunodeficiency virus-1 (HIV-1)	Humans	Immune cells	Detrimental	[34–36]
<i>Parasitic infections</i>				
<i>Leishmania major</i>	Mouse	Footpad infection	Beneficial	[37]
<i>Trypanosoma cruzi</i>	Mouse	Intraperitoneal infection	General beneficial, but can be also detrimental	[39]
<i>Schistosoma japonicum</i>	Mouse	Percutaneous infection	Unknown	[41]
<i>Fungal infections</i>				
<i>Candida albicans</i>	Humans and mouse	Invasive infection (humans) and intravenous infection (mouse)	Beneficial	[42, 43]
<i>Aspergillus fumigatus</i>	Humans and immunosuppressed mice	Invasive infection (humans) and intranasal infection (mouse)	Detrimental	[42]

more extensive suppressive effect on T-cell responses than those from healthy individuals recently exposed to *M. tuberculosis* [16]. Interestingly, the authors also reported that the frequency of MDSC returned to the levels and maturation status of healthy individuals after successful antibiotic treatment and concluded that MDSC

induced after exposure to *M. tuberculosis* may contribute to the inability of the host to eliminate the bacterium and thus to disease development [16]. Association of MDSC expansion with tuberculosis progression has also been observed in murine models of *M. tuberculosis* infection [17, 18]. Specifically, Tsiganov et al. [17] reported that

tuberculosis progression in mice that developed severe disease was associated with the replacement of Gr-1^{high} Ly6G^{high} conventional neutrophils by a population of Gr-1^{dim} CD11b⁺ cells that suppressed T-cell proliferation and IFN- γ production in vitro via NO-dependent mechanisms and that resembled MDSC. The study of Knaul et al. [18] confirmed that excessive accumulation of MDSC in the lungs of *M. tuberculosis*-infected mice enhanced disease lethality and indicated that MDSC provided a niche for *M. tuberculosis* survival within the infected lungs.

Recruitment of both M-MDSC and PMN-MDSC from bone marrow into infected tissue has also been observed in mice infected with the Gram-negative pathogen *Salmonella enterica serovar Typhimurium*, which is a primary cause of food-borne infection that cause acute inflammatory diarrhea and can often progress to invasive systemic disease [19]. M-MDSC, in particular, were found to regulate T-cell responses during salmonella infection via NO production [19]. The authors suggested that during *S. typhimurium* infection, moderate amounts of M-MDSC provide protection from immune-mediated pathology, while accumulation of a high amount of these cells beyond a certain threshold may exert immunosuppressive functions that prolong the infection [19]. Defining the individual MDSC thresholds for different pathogens and infection types that separate beneficial (protective counter-regulatory) from harmful (overly immunosuppressive) MDSC functions remains a challenging task for the future.

An important role for MDSC has been reported in chronic infections caused by *Staphylococcus aureus*, a pathogen notorious for its capacity to cause difficult-to-treat chronic infections [20]. In murine models of *S. aureus* chronic abscess, gradual decline in the functionality of effector CD4⁺ T cells has been shown to be associated with the progression of infection toward chronicity [21]. Expansion of MDSC was shown to be responsible for the progressive T-cell dysfunction and the failure to eliminate the pathogen [22]. Likewise, a critical role of MDSC in the establishment of chronic *S. aureus* biofilms in infected prosthetic joint was demonstrated by Heim et al. [23]. The authors showed that MDSC inhibited the pro-inflammatory activity of monocytes/macrophages in the infected joints as depletion of MDSC facilitated biofilm clearance by enhancing the proinflammatory functions of recruited monocytes [23]. Furthermore, the recruitment of MDSC to sites of *S. aureus* biofilm was mediated by IL-12 [24], and IL-10 released by recruited MDSC was responsible for the in-

hibition of the antimicrobial effect of monocytes/macrophages [25].

MDSC seems to further play an important role in immunomodulation during skin infections. Thus, it has been shown that cutaneous exposure to bacteria, such as *S. aureus* and specific bacterial products like TLR 2–6-binding diacylated lipopeptides, induce high IL-6 production by dermal cells leading to immunosuppression mediated by the recruitment of MDSC [26].

In other infection settings, the expansion of MDSC seems to be beneficial rather than detrimental to the host. For example, accumulation of PMN-MDSC has been observed in the lungs of cystic fibrosis patients with chronic *Pseudomonas aeruginosa* infection [27]. PMN-MDSC generation was induced through the stimulation of TLR5 in myeloid cells by *P. aeruginosa* flagellin. PMN-MDSC exerted an anti-inflammatory effect by suppressing polyclonal T-cell proliferation and modulation of Th17 responses [27]. The effect of *P. aeruginosa* infection on MDSC generation has also been demonstrated in vivo by another study [28]. A key role for MDSC in the regulation of lung inflammation was also described for acute bacterial pneumonia [29]. Using a murine model of *Klebsiella pneumoniae* acute lung infection, Poe et al. [29] demonstrated that MDSC contributed to resolution of lung inflammation via IL-10 production and efferocytosis of apoptotic cells.

MDSC in Viral Infections

Many viral infections often take a chronic course and one of the underlying mechanisms for viral persistence is the generation of MDSC [30]. Similar to bacterial infections, the elevated levels of proinflammatory cytokines and other inflammatory mediators may be the driven force for the expansion and recruitment of MDSC.

Hepatitis C is a liver infection caused by hepatitis C virus (HCV) that becomes chronic in a high percentage of infected individuals. It is widely accepted that T-cell responses play a pivotal role in the outcome of acute HCV infection and impaired T-cell responses have frequently been reported to be associated with chronic hepatitis C. In this regard, Tacke et al. [31] reported the presence of MDSC in the peripheral blood of individuals with chronic HCV infection. The authors also demonstrated that MDSC-induced, ROS-mediated immunosuppression of T-cells responses may facilitate and maintain HCV persistence [31]. Furthermore, HCV-induced MDSC were also shown to suppress the functionality of natural killer

cells, a cell population critical for controlling HCV infection by inhibiting viral replication and regulating adaptive immunity [32]. In this context, suppression was exerted by limiting the availability of L-arginine via the production of arginase-1 [32].

On the other hand, MDSC have been shown to exert a protective role in chronic infections caused by hepatitis B virus (HBV) [33]. In contrast to HCV, HBV is non-cytopathic for hepatocytes and the liver disease induced by HBV during chronic infection is immune mediated. Pallett et al. [33] reported a transient expansion of arginase-1-expressing PMN-MDSC in the circulation and liver of patients in whom HBV replicates high levels without inducing necroinflammatory liver disease. The authors propose a protective role for PMN-MDSC in maintaining immunotolerance in replicating HBV and ameliorating hepatic tissue damage in chronic HBV-infected patients [33].

Acquired immunodeficiency syndrome, caused by chronic infection with the human immunodeficiency virus-1 (HIV-1), is one of the most devastating pandemics of the 20th century. T-cells loss and dysfunction have been implicated in HIV-1 disease progression and evidence has been provided for a role of MDSC in the suppression of T-cell function in HIV-1-infected individuals. Thus, Vollbrecht et al. [34] reported high frequency of MDSC in HIV-1 infected cases that positively correlated with viral loads and negatively with CD4+ T cell numbers. The authors also found a fast drop in MDSC frequency upon starting antiretroviral therapy and concluded that MDSCs during chronic HIV-1 infections contribute to the impaired T-cell responses characteristic for the progressive disease [34]. Likewise, Qin et al. [35] reported elevated levels of arginase-1 producing M-MDSC in peripheral blood of HIV-1 infected subjects that correlated with disease prognosis, HIV-1 loads and with T-cell loss and activation. Another study demonstrated that expansion of MDSC in HIV-infected individuals was mediated by high levels of IL-6 induced by the HIV envelop glycoprotein gp120 [36].

MDSC in Parasitic Infections

Beyond bacterial and viral infections, the expansion of MDSC has also been observed in different parasitic infections. Thus, it has been reported that although MDSC with a Gr-1^{high}Ly6C^{high}CD11b^{high}F4/80^{int} phenotype, generated during acute infection with the sand fly-transmitted protozoan *Leishmania major*, can suppress

T-cell responses, they are also capable of efficiently killing the parasite by producing high levels of NO and thereby contributing to parasite clearance [37]. Furthermore, treatment of *Leishmania*-infected mice with all-trans retinoic acid, a compound that drives the differentiation of MDSC into mature macrophages, resulted in increased development of lesions as well as increased parasite loads [37]. Although this study demonstrated that MDSC are beneficial in the effective control of *L. major* infection, another study [38] has reported that the mouse genetic background strongly influences the differentiation and function of MDSC during *L. major* infection. In this regard, MDSC derived from *L. major*-infected BALB/c mice exhibited higher parasite number compared with those derived from infected C57BL/6 mice [38].

Chagas disease, caused by the protozoan *Trypanosoma cruzi*, remains a major cause of morbidity and mortality in Latin America. Myocarditis, characterized by a mononuclear cell inflammatory infiltrate, is the most serious and frequent manifestation of chronic Chagas disease and affects approximately 30% of infected individuals. Cuervo et al. [39] demonstrated that MDSC expressing NO and arginase-1 were recruited into the heart of mice infected with *T. cruzi*. The authors further showed that MDSC are beneficial for host defense against *T. cruzi*, as they may regulate the excessive T-cell-dependent inflammation in the heart at the beginning of infection and produce NO required for efficient control of parasite loads in the heart [39]. However, persistent expression of NO in combination with arginase-1 by MDSC can also be detrimental for the host because it can cause extensive L-arginine depletion in plasma [39]. Similar to *L. major*, it has been reported that expansion and function of MDSC during infection with *T. cruzi* are influenced by the mouse genetic background [40]. Thus, a higher number of MDSC, in particular PMN-MDSC, was detected in the spleens and livers of infected BALB/c mice compared with infected C57BL/6 mice [40]. Since BALB/c mice present less inflammation and better survival than C57BL/6 mice after infection with *T. cruzi*, the authors concluded that MDSC seems to play a beneficial effect in infected BALB/c mice by contributing to reduction of parasite replication, enhancing the resolution of infection and preventing pathology associated with excessive inflammation [40].

It has also been proved that MDSC play a role in the pathogenesis of schistosomiasis, a chronic infection caused by a parasitic worm of the genus *Schistosoma* [41]. Specifically, the soluble egg Ag and schistosome worm antigen of *Schistosoma japonicum* was found to in-

duce the accumulation of MDSC in the spleen of infected mice by inducing the NADPH oxidase (NOX) subunits gp91phox and p47phox [41].

MDSC in Fungal Infections

In fungal infections, MDSC and PMN-MDSC in particular, have been shown to be protective in a murine model of systemic *Candida albicans* infection, but not in a model of pulmonary infection induced by the human pathogenic fungus *Aspergillus fumigatus* [42]. The underlying reasons for this differential role in fungal infections remain to be dissected in future investigations, but may be due to (i) yeast (*C. albicans*) versus filamentous (*A. fumigatus*) fungi, (ii) different routes of infection (systemic/intravenously for *C. albicans*; intranasally for *A. fumigatus*) or (iii) different fungal pathogen-associated molecular patterns. MDSC in *C. albicans* infection were induced through a mechanism involving fungal recognition through Dectin-1/CARD9 and the downstream mediators ROS and IL-1 β [42]. The mechanisms underlying the beneficial effect mediated by MDSC in *C. albicans* infection are yet to be fully defined, but seemed to involve several cell types and mechanisms, including dampening of the pathogenic hyper-inflammatory NK and T-cell responses [42]. Further studies demonstrated that generation of MDSC was largely dependent of the *Candida* species and morphotype [43].

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Concluding Remarks

Studies addressing the phenotypes and functions of MDSC in the setting of infection have grown tremendously during the last 2 decades. However, we have only just begun to understand the complex protective and harmful roles of these cells across a diverse range of infectious diseases. We have learned that MDSC are involved in the outcome of nearly every infection from bacteria to fungi, in particular during chronic infection, and also that they can be detrimental or of benefit for the host depending of the type of infection. Therefore, deeper knowledge about the role of MDSC in the different infection settings may eventually assist in designing treatments that will limit immunopathology, while preserving protective responses to these pathogens. Although the modulation of MDSC has emerged as an attractive option for the immunotherapy of different tumors and autoimmune diseases, more caution may be required for therapeutic targeting of MDSC in infection, since MDSC harbor phenotypic markers of both macrophages/monocytes and neutrophils, which are both critical for the control of many infectious pathogens.

Disclosure Statement

The authors have no conflicts of interest to declare.

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