MDSCs in infectious diseases : regulation, roles, and readjustment

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Abstract

Many pathogens, ranging from viruses to multicellular parasites, promote expansion of MDSC, which are myeloid cells that exhibit immunosuppressive features. The roles of MDSC in infection depend on the class and virulence mechanisms of the pathogen, the stage of the disease and the pathology associated with the infection. This work compiles evidence supported by functional assays on the roles of different subsets of MDSC in acute and chronic infections, including pathogen-associated malignancies, and discusses strategies to modulate MDSC dynamics in order to benefit the host.

Keywords: Myeloid regulatory cells, MDSC, Infection, Immunosuppression, Oncogenic viruses, Mye-EUNITER

Précis: We discuss the roles of MDSC in acute and chronic infection, as well as strategies to modulate their dynamics to benefit the host.

Abbreviations

Arg, arginase
Arm, Armstrong
ATRA, *all-trans* retinoic acid
B. fragilis, *Bacteroides fragilis*
C. albicans, *Candida albicans*
C13, clone 13
CCR, C-C chemokine receptor
COST, European Cooperation in Science and Technology
EBV, Epstein Barr virus
ETBF, enterotoxigenic *Bacteroides fragilis*
FV, Friend virus

H. felis, *Helicobacter felis*

H. polygyrus, Heligmosomoides polygyrus

HbsAg, HBV surface antigen

HDT, host-directed therapy

IAV, Influenza A virus

iNKT, invariant NK T

JEV, Japanese encephalitis virus

K. pneumoniae, *Klebsiella pneumoniae*

L. donovani, *Leishmania donovani*

L. major, Leishmania major

LCMV, lymphocytic choriomeningitis virus

LOX, lipoxygenase

M. tuberculosis, Mycobacterium *tuberculosis*

M-MDSC, monocytic MDSC

MR, mannose receptor

MRC, myeloid regulatory cells

mTOR, mammalian target of rapamycin

NADPH, nicotinamide adenine dinucleotide phosphate

NOS, NO synthase

P. aeruginosa, *Pseudomonas aeruginosa*

PcP, *Pneumocystis* pneumonia

PDE, phosphodiesterase

PGE2, prostaglandin E2

PMN-MDSC, neutrophil-like MDSC

ROS, reactive oxygen species

S. aureus, *Staphylococcus aureus*

SIV, simian immunodeficiency virus

T. crassiceps, *Taenia crassiceps*

T. cruzi, *Trypanosoma cruzi*

T. gondii, *Toxoplasma gondii*

TB, tuberculosis

Tfh, T follicular helper

Introduction

Myeloid cells recognize pathogens and orchestrate the development of antimicrobial immunity. Sensing of microbial cues initiates the inflammatory response during infectious diseases. These events contribute to the generation of effective adaptive immune responses, pathogen removal, and a return to homeostasis. However, if uncontrolled or unresolved, inflammation results in immunopathology. Pathogen-derived molecules and inflammatory mediators trigger expansion and/or activation of specific subsets of myeloid cells with regulatory activities, termed myeloid regulatory cells (MRC). This differentially affects the disease outcome, depending on the type and stage of the infection involved. MRC include MDSC with either a monocytic (M-MDSC) or a neutrophilic (PMN-MDSC) phenotype, alternatively activated macrophages, and regulatory dendritic cells. Here, we focus specifically on the functions of MDSC in acute and chronic infections, including diseases triggered by oncogenic microbes.

There are limitations to the ways in which the functions of MDSC can be addressed experimentally. An animal devoid of MDSC does not exist, as these cells are generated by myelopoiesis, which will be discussed in more detail below. There is also a lack of studies using genetically modified animals to evaluate the relative contribution of different MDSC populations in infection. However, recent years have provided a wealth of information on the potential functions on MDSC based on correlative studies, *ex vivo* functional assays and drug-induced differentiation of MDSC.

Identification of MDSC relies on phenotypic markers and requires validation of their suppressive activity by immunological assays (1, 2). Here, we discuss interactions of MDSC with selected pathogens using examples in which MDSC subsets have been characterized through functional assays and not only immunophenotyping techniques. We emphasize the relevance of MDSC for the resolution of inflammation and their function as reservoirs for persistent microbes. We highlight microbial signatures and host pathways regulating MDSC dynamics, as well as MDSC capacity to modulate immunopathology in chronic infections and the implications for microbial-induced tumorigenesis. Finally, we address MDSC-targeted strategies and discuss how these could be employed to treat infectious diseases.

Pathogen and host factors drive MDSC dynamics during infection

Experimental infections and *ex vivo* assays have indicated that selected pathogen-associated molecular patterns trigger expansion of MDSC. In mice, bacterial lipopeptides that bind TLR2/6 (3), LPS (4), which engages TLR4, and flagellin (5), a TLR5 ligand, lead to local or systemic expansion of $Gr1^{+}CD11b^{+}$ MDSC with proven immunosuppressive properties *ex vivo* and *in vivo*. Viral ligands of TLR2, including HCV core protein (6–9) and HBV surface antigen (HbsAg) (10), both of which are secreted from infected hepatocytes, as well as surface HIV-1 gp120 (11), induce increased numbers of M-MDSC that are able to suppress T cell (6–8, 10, 11) and NK cell responses (9). Such PRR ligands can also drive differentiation of monocytes into MDSC (12). In contrast to TLR2/6, 4 and 5 ligands which lead to expansion of MDSC, TLR3, 7 or 9 ligands negatively regulate the functionality of MDSC during infection with influenza A virus (IAV) (13, 14).

Fungal pathogens promote the accumulation of PMN-MDSC by activating C-type lectin receptors, notably the dectin-1/Card9 pathway (15). However, purified β-glucans, which are abundant in *Candida spp.* and *Aspergillus spp*. and represent agonists for dectin-1, have been shown to restrict MDSC expansion upon therapeutic delivery in tumor models (16). For this reason, the precise molecular mechanisms by which fungal pathogens promote MDSC genesis requires further characterization.

Some glycans originating from parasites also increase MDSC frequencies in infected tissues. For instance, intraperitoneal injection with intact glycans purified from *Taenia crassiceps* (*T. crassiceps*) or schistosome oligosaccharides elicits myeloid cell populations that suppress T cell proliferation *in vitro* (17–19). Some of these effects are independent of TLR4 and Th2-type cytokines (18, 19). Moreover, immunization of mice with *Toxoplasma gondii* (*T. gondii*) oocyst lysate antigen leads to increased numbers of PMN-MDSC in the lungs (20). However, the host sensors controlling MDSC accumulation in parasitic infections remain to be unveiled.

Besides PRRs, many other host factors affect MDSC dynamics during infection. Several inflammatory mediators and growth factors, including VEGF, GM-CSF, G-CSF, IL-1β, IL-6, TNF-α and prostaglandin E2 (PGE2) have been identified as inducers of MDSC expansion and/or activation (21–23). Among these, the requirement for IL-6 and STAT3 signaling for expansion of MDSC appears to be critical in several unrelated infections (3, 10, 24, 25). As an example, a significant reduction in splenic MDSC accumulation was observed in IL-6-deficient compared to wildtype (WT) mice during *Trypanosoma cruzi* (*T. cruzi*) infection (24). Likewise, mice deficient in hepatic expression of gp130, the common signaling receptor for the IL-6 family of cytokines, showed reduced frequencies of MDSC during polymicrobial sepsis (25). Furthermore, IL-6-induced hepatic acute phase proteins, namely serum amyloid A and chemokine (C-X-C motif) ligand (Cxcl)1, cooperatively promoted mobilization and peripheral accumulation of MDSC (25).

The growth factors GM-CSF and G-CSF control myelopoesis in the steady state. During dysregulated myelopoesis, increased levels of these factors leads to continuous activation of progenitors, promoting MDSC generation, particularly in chronic infections (23). Recent findings indicate that GM-CSF drives the conversion of murine $Ly6C^{hi}$ and human $CD14^{+}$ monocytes into suppressor cells. This differentiation requires activation of the protein kinase B (PKB)/mammalian target of rapamycin (mTOR)/mTOR complex (mTORC)1 pathway by GM-CSF and subsequent signaling through the IFN-γ receptor/IFN regulatory factor-1 (IRF-1) pathway (26). Anti-apoptotic molecules, such as cellular-Flice-like inhibitory protein (c-FLIP) and myeloid leukemia cell differentiation protein (MCL-1) play a role in the generation of MDSC during cancer (27), but this has not yet been demonstrated during infection. Overall, it seems that growth factors and cytokines present during an infectious insult may interfere with physiological differentiation of hematopoietic progenitors and result in abnormal cell phenotypes, including MDSC.

Interaction with other immune cells during infection may also influence the frequency and suppressive capacity of MDSC. One example is the more prominent expansion of MDSC in mice deficient in invariant NK T (iNKT) cells compared to control mice during infection with IAV (13). MDSC suppressive activity *in vivo* was abolished by adoptive transfer of iNKT cells, suggesting that interaction between iNKT cells

and MDSC modulates MDSC suppressive activity, at least during IAV infection. Whether this pathway operates in other infections remains to be determined.

Taken together, accumulating evidence suggests that selected pathogen sensors and inflammatory mediators mutually or independently activate pathways leading to expansion of MDSC during infection. Additional regulators and the integration of multiple processes that affect MDSC dynamics will presumably be uncovered as research into the biology of these cells in infection is developed.

The outcome of MDSC expansion in acute infection

MDSC subsets appear to exacerbate certain acute infections (Supplementary Table 1) (Figure 1). In viral diseases, MDSC expansion may favor immunosuppression and viral persistence. An example is the inhibition of T follicular helper cells (Tfh) and B cells by MDSC that was observed during infection with a Japanese encephalitis virus (JEV) strain that causes acute encephalopathy (28). Targeting MDSC with retinoic acid reversed suppression and improved the survival of JEV-infected mice. In infection with Friend retrovirus (FV), which is able to persist lifelong in mice despite eliciting a strong acute immune response, expansion of both M-MDSC and PMN-MDSC populations during the late phase of acute infection correlated with $CD8^+$ T cell contraction. Of these MDSC subsets, experiments *in vitro* suggested that only PMN-MDSC could suppress virus-specific $CD8^+$ T cell responses (29), although the specific contribution of this subset was not evaluated *in vivo*. Depletion of MDSC rescued activated $CD8^+$ T cells and minimized viral loads. These observations suggest that MDSC interfere with immune control of the viral load during acute infection, facilitating the subsequent establishment or maintenance of viral chronicity. The expansion of MDSC during acute toxoplasmosis, a parasitic infection, has also been partly associated with immune hyporesponsiveness within the lung (30).

Another scenario in which MDSC expansion may facilitate disease progression is during sepsis. The number of circulating PMN-MDSC in septic patients correlates with the disease severity and with plasma levels of IL-6 (31). In this case, the type of infection may influence the dynamics of different MDSC subsets. M-MDSC were found in all sepsis patients included in a study cohort, whereas PMN-MDSC expanded preferentially in sepsis caused by gram-positive bacteria. Among the neutrophilic subset, a $CD14^{low}$ PMN-MDSC population was skewed towards expression of IL-10 and suppressed T cell proliferation *in vitro* through the production of reactive oxygen species (ROS) (32). In a more recent study enrolling patients from intensive care units, PMN-MDSC were specifically expanded in individuals with sepsis and were responsible for increased arginase (Arg) 1 activity (33). High initial frequencies of PMN-MDSC, but not of M-MDSC, were associated with subsequent nosocomial infections. Depletion of $CD15^+$ cells from PBMC obtained from sepsis patients increased the rate of T cell proliferation, suggesting that PMN-MDSC may have been largely responsible for the sepsis-induced immune suppression.

The observations in humans diverge from findings in murine models of sepsis. Expansion of MDSC during polymicrobial sepsis induced by cecal ligation was demonstrated to be beneficial for the host (25, 34). Murine MDSC suppressed production of IFN-γ by $CD8^+$ T cells and contributed to sepsis-induced Th2 polarization *in vivo* (34). Mice with reduced levels of circulating and splenic MDSC as a consequence of

hepatic gp130 deficiency showed decreased survival after induction of polymicrobial sepsis. The phenotype could be reverted by the adoptive transfer of a heterogeneous population of $Gr1^+CD11b^+$ cells comprising 50% PMN-MDSC (25). Together, these studies support a host-protective anti-inflammatory role for MDSC during polymicrobial infections in mice. The discrepancy between observations emerging from humans and murine models may stem from analysis of distinct phases of sepsis as well as from the distinct features of the MDSC subsets involved.

MDSC may also be beneficial for the host in certain acute pneumonia and parasitic infections. During infection with *Klebsiella pneumoniae* (*K. pneumoniae*) tight control of inflammation is critical for pathogen clearance (35). Accumulation of neutrophils in non-resolving pneumonia causes collateral tissue damage, resulting in acute lung injury. In mice infected with *K. pneumoniae*, MDSC were recruited to the lungs several days post challenge and represented an important local source of IL-10, which correlated with the resolution of inflammation and recovery after infection (35). MDSC were shown to efferocytose apoptotic neutrophils, limit inflammation and prevent tissue damage, thereby facilitating the return to tissue homeostasis. In a murine model of Chagas disease, M-MDSC exhibited protective roles as well. They were detected in myocardic lesions during the acute phase of *T. cruzi* infection and suppressed polyclonal T cell proliferation *ex vivo* through a NO-dependent mechanism (36). Furthermore, higher numbers of MDSC were detected in BALB/c compared to C57BL/6 mice during infection, along with lower levels of inflammatory cytokines, reduced liver injury and increased resistance to infection (24). Moreover, decreased MDSC recruitment in IL-6-deficient mice and MDSC depletion both led to increased inflammation, higher parasite burdens and mortality (24). Thus, MDSC-mediated modulation of the inflammatory response during *T. cruzi* infection allowed efficient parasite clearance while simultaneously limiting overzealous adaptive immune responses and excessive tissue damage. In humans suffering from chronic Chagas disease, increased tyrosine nitration was detected on $CD8^+$ T cells and heightened NO production was shown in peripheral leukocytes (37). Characteristics of MDSC such as activation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and production of NO and peroxynitrites can cause nitration of the TCR and may contribute to their suppressive activity in such conditions. However, whether MDSC expansion influences tyrosine nitration of $CD8^+$ T cells in humans with Chagas disease remains to be established.

MDSC activity in acute infections can culminate in negative or beneficial outcomes, depending on the microorganism involved as well as the pattern and extent of inflammation. Deleterious effects could result from host inability to clear pathogens due to immunosuppression, whereas suppression of inflammatory responses that exacerbate tissue damage could be beneficial to the host.

The versatile roles of MDSC in chronic infection

Many successful pathogens manipulate host immunity by suppressing T cell responses, thereby establishing chronic infections. Chronicity poses dual risks. Firstly, it requires prolonged therapy, which often leads to poor patient compliance and the development of antimicrobial resistance. Secondly, it leads to tissue remodeling and the development of microenvironments favoring pathogen persistence. Even when antibiotic therapy is effective and clears the pathogen, infected tissue often fails to reach *restitution ad*

integrum, leading to the formation of tissue scars. Such tissue changes and nonresolving inflammation are reminiscent of disease processes in cancer (38). In fact, many types of cancer are associated with particular infectious diseases, with several pathogens so far classified as Group 1 carcinogens (39–41). We will discuss how MDSC affect progression of various infections, including tuberculosis (TB), staphylococcal infections, viral hepatitis, immunodeficiency syndromes, chronic parasitic infections and fungal disorders (Supplementary Table 1) (Figure 1). In addition, we will discuss examples in which MDSC-driven effects have been associated with pathogen-induced tumorigenesis.

An example of a chronic bacterial infection in which MDSC play an important role is active TB, which results predominantly from inefficient T cell responses. Increased frequencies of MDSC are present in pleural fluids from patients with pulmonary TB (42–44), and MDSC isolated from the blood of TB patients suppress T cell function (42, 43), secrete abundant IL-1β and IL-6 (42), and correlate with high NO levels (42, 44). Peripheral MDSC increase in cases of recent, but not remote infection, and a reduction in their frequencies is observed after treatment (43, 44), suggesting that expansion of MDSC correlates with increased bacterial burdens. These findings have been recapitulated in the mouse model of TB, in which MDSC are found in multiple tissues in infected mice (45, 46). These cells harbor *Mycobacterium tuberculosis* (*M. tuberculosis*), and may thus provide a niche for *M. tuberculosis* survival. Furthermore, they release both pro-inflammatory (IL-6, IL-1α) and anti-inflammatory (IL-10) cytokines while exerting suppressive effects on T cells (45), including restriction of IFN-γ production via NO-dependent mechanisms (46). MDSC may thus support immune evasion by promoting T cell dysfunction and disease progression. Therefore, MDSC qualify as attractive targets for therapeutic intervention, as well as biomarkers of active TB. In support of this, different strategies used to ablate these cells in mice during infection, either alone (45) or in combination with antibiotherapy (47), have resulted in improved disease outcomes. Similar consequences of MDSC depletion were observed in infection with another bacterium, *Staphylococcus aureus* (*S. aureus*) (48). Gemcitabine delivery depleted PMN- and M-MDSC and restored T cell responses. *S. aureus* is frequently associated with orthopedic biofilms that subvert immune-mediated clearance. MDSC represent the main cellular infiltrate in biofilms, as demonstrated in murine models, and their abundance inversely correlates with T cell activity. Biofilm MDSC, but not spleen cells from infected animals, displayed increased Arg1, NOS2 and IL-10 expression, and antibody-mediated depletion of this population improved bacterial clearance by augmenting pro-inflammatory cytokine release in monocytes and macrophages (48). Hence, MDSC contribute to the chronicity of *S. aureus* biofilm infection.

MDSC may also support oncogenic transformation in infections with bacterial pathogens that can cause colorectal and gastric cancer. In a murine model, infection with *Helicobacter felis* (*H. felis*) caused mobilization of PMN-MDSC to the gastric mucosa and subsequent tissue metaplasia, a precursor of cancer (49). PMN-MDSC were also associated with intestinal metaplasia in human stomach tissue from *Helicobacter pylori*-infected individuals. Similarly, the gut commensal and candidate pathogen enterotoxigenic *Bacteroides fragilis* (ETBF) induced accumulation of MDSC and colon tumorigenesis in a mouse model of colorectal cancer (50). In this study, sorted M-MDSC displayed higher immunosuppressive activity than PMN-MDSC in *ex vivo* assays.

In viral infections, MDSC support the establishment of chronicity. This has been elegantly demonstrated in kinetics experiments with different strains of lymphocytic choriomeningitis virus (LCMV). Comparable levels of expansion of MDSC were observed during the first week of LCMV infection with the Armstrong (Arm) strain, which leads to acute resolving infection, and with clone 13 (C13), which develops into a chronic infection (51). However, only C13 sustained a high number of M-MDSC with suppressive capacity in infected organs. C-C chemokine receptor (CCR)2-deficiency, which diminished mobilization of monocytic cells, or antibody depletion of $Gr1^+$ cells led to enhanced LCMV-specific T cell cytokine responses in C13-infected mice, suggesting that expansion of suppressive M-MDSC facilitates the establishment of chronicity (51). A detailed analysis of MDSC during chronic infection with LP-BM5 retrovirus, which causes murine acquired immunodeficiency, has also provided evidence for M-MDSC-mediated down-regulation of $CD4^+$ T cell and B cell responses (52).

HIV induces concomitant immune-regulatory and inflammatory mechanisms that drive chronic viral persistence and disease progression (53, 54). Several studies have quantified MDSC frequencies in different phases of the HIV infection and investigated their interplay with anti-viral immune responses. In patients with primary or chronic HIV-1 infection, expansion of PMN-MDSC with enhanced expression of PD-L1 was already observed during the early primary immune response against HIV (55). *In vitro*, PD-L1 blockade with specific antibodies attenuated the inhibitory function of patient MDSC co-cultured with $CD8^+$ T cells, suggesting that PD-L1 forms part of their suppressive arsenal. Chronically HIV-1-infected patients showed increased levels of PMN-MDSC that express IL-4 receptor alpha (IL-4Rα). This phenotype positively correlated with the viral load and inversely associated with the $CD4^+$ T cell count, rapidly changing upon anti-retroviral therapy (56). *In vitro*, MDSC inhibited the proliferation of $CD8^+$ T cells from both healthy donors and HIV-controllers (HIV-1-infected individuals able to control plasma viral load in the absence of therapy), and induced expansion of Treg from HIV controllers. Another mechanism proposed for PMN-MDSC-mediated suppression in HIV-1 patients is their capability to inhibit CD3ζ expression by cell-to-cell contact (57). Increased frequencies of M-MDSC have also been detected in HIV-1 patients despite effective anti-retroviral therapy (58). The suppressive activity of these cells is mediated by Arg1 and cell-to-cell contact, yet their specific contribution to disease pathophysiology in comparison to that of PMN-MDSC in HIV-1 infection remains elusive. The simian immunodeficiency virus (SIV)-macaque model recapitulates the pathogenesis of HIV infection in humans and is therefore widely used to study the physiopathology of AIDS. In a recent study, SIV infection induced the expansion of $CD14^{hi}CD16^-CCR2^{lo}$ M-MDSC that efficiently suppressed proliferation of $CD8^+$ T cells, but not of $CD4^+$ T cells (59). Like in humans, antiretroviral therapy of infected macaques led to contraction of MDSC. Low copy numbers of SIV DNA were found in MDSC of infected macaques, indicating that these cells could constitute a viral reservoir. In a follow-up study looking at the chronic phase of SIV infection before and after anti-retroviral therapy, PMN-MDSC expanded after interruption of treatment. At all stages of infection, isolated PMN-MDSC were able to suppress T cell proliferation (60). Despite clear evidence that MDSC are induced in HIV/SIV infection and that they can inhibit T cell responses, further studies are required to better characterize the dynamics and role of different MDSC subsets in the tissues where immune responses and inflammatory processes take place. Because of their immunosuppressive activity, MDSC may constitute a putative reservoir for pathogens and therefore the permissiveness of this population to HIV infection should be considered.

M-MDSC frequencies were also significantly higher in patients with chronic HCV infection compared to healthy donors (6, 7, 61, 62) or patients receiving antiviral therapy (61, 62). MDSC-induced suppression in HCV infection has often been associated with expression of IL-10 and Arg1 (6, 61, 62). M-MDSC frequency was found to positively correlate with HCV RNA levels (7, 61, 62) and Treg expansion (7). Despite strong evidence that MDSC contribute to T cell impairment, which affects viral clearance in chronic HCV infection, one study challenged this notion by reporting no differences in the frequency of M-MDSC and PMN-MDSC in chronically infected HCV patients and healthy individuals and a lack of correlation between these cells and the viral load (63). In chronic HBV infection, the M-MDSC population expands as well (10, 64) and M-MDSC frequencies correlate positively with HbsAg serum levels (10). *In vitro*, MDSC decreased HBV-specific $CD8^+$ T cell responses via PD-1-dependent secretion of IL-10 (64). In a mouse model of chronic HBV infection, forced maturation of MDSC by delivery of all-trans retinoic acid (ATRA) limited viral replication (10). In this model, M-MDSC were more efficient at suppressing T cells than PMN-MDSC (65). Their accumulation in the liver was driven by γδ T-cells and led to $CD8^+$ T cell exhaustion (66). In contrast to the findings in mice, higher PMN-MDSC and not M-MDSC frequencies were found in a chronic HBV cohort (67). PMN-MDSC transiently expanded in acute resolving HBV infection and contracted prior to acute liver injury. In persistent infection, Arg-expressing PMN-MDSC increased predominantly in phases characterized by HBV replication without immunopathology and accumulated in the liver, suggesting that PMN-MDSC may restrict liver inflammation (67). MDSC expansion during HBV infection could therefore prevent immunopathology at the cost of promoting chronicity. Whether distinct MDSC subtypes drive such dual outcomes needs further investigation.

Besides favoring chronicity, MDSC abundance correlates with clinical outcome in several virus-associated malignancies. Epstein Barr virus (EBV) is the most growth-transforming pathogen in humans and, accordingly, is associated with human malignancies, mostly of B or epithelial cell origin (68). In Hodgkin's lymphoma, which is EBV-associated, increased numbers of MDSC in the blood were prognostic of a worse clinical outcome (69). M-MDSC are also present in EBV-associated extranodal natural killer NK/T cell lymphoma (70). In this study, their suppressive function was dependent on NOS2, Arg1 and ROS activities and correlated with elevated expression of immune suppressive cytokines and an increase in Treg. Several viral factors expressed by tumor cells may trigger expansion of functional MDSC, as proposed in studies on EBV-associated nasopharyngeal carcinoma. For example, latent membrane protein 1-mediated glycolysis triggers the activation of p65 and the inflammasome, leading to the production of cytokines critical for MDSC expansion (71).

MDSC also accumulate in chronic parasitic infections, which are commonly associated with the generation of Th2 and Treg responses (72). *Schistosoma japonicum* antigens, for example, enhanced the expansion and suppressive activity of MDSC (73). In this model, immunosuppression was mediated through upregulation of NADPH oxidase subunits and ROS production. MDSC isolated from *Heligmosomoides polygyrus* (*H. polygyrus*)-infected mice, in contrast, used an NO-dependent mechanism for immunosuppression (74). Adoptive transfer of these cells promoted chronic infection with increased worm burdens and egg production.

Like macrophages, M-MDSC may be both classically and alternatively activated depending on their exposure to Th1 or Th2 cytokines and many helminths induce mixed Th1/Th2 responses, at least in certain phases of infection (75). Following implantation with the cestode *T. crassiceps*, IL-4/IL-13 signaling was critical for gradual expansion of MDSC in the peritoneal cavity and acquisition of an alternatively activated phenotype. These cells suppressed T cell proliferation through mechanisms that switched from NO secretion at early stages of infection to a combination of Arg activity, ROS production and generation of peroxisome proliferator-activated receptor gamma (PPAR-γ) ligands via 12/15-lipoxygenase (LOX) activity in the late phase of infection (76). These results suggest that the mechanisms used by MDSC to limit anti-parasitic adaptive responses may depend of the phase of infection.

The role of MDSCs in chronic infection with other pathogens such as protozoan parasites and fungi has also been investigated. During experimental leishmaniasis, resistant C57BL/6 mice accumulated MDSC which suppressed parasite specific T cell proliferation, but not cytokine release (77). MDSC killed *Leishmania major* (*L. major*) parasites in an NO-dependent manner and enhanced parasite clearance in skin lesions despite decreased parasite-specific T cell proliferation, indicating that MDSC enhanced resistance to *L. major* (77). In agreement with these observations, genetically susceptible BALB/c mice exhibit a reduced ability to recruit $CD11b^{+}Ly6C^{hi}$ cells to the site of *L. major* infection compared to resistant C57BL/6 mice (78). Thus, genetic conditioning of MDSC function could contribute to disease resistance in murine inbred strains.

The fungal pathogen *Candida albicans* (*C. albicans*) induces a subset of PMN-MDSC during infection in humans and mice (15). *In vitro*, these cells inhibited T cell proliferation, and phagocytosed and killed fungi. In a mouse model of invasive *C. albicans* infection, adoptive transfer of PMN-MDSC effectively dampened T and NK cell proliferation and improved mouse survival. Notably, different *Candida* species had differential capacities to induce *in vitro* PMN-MDSC expansion and subsequent suppressive activities (79). *Aspergillus fumigatus* also elicits PMN-MDSC (15). However, adoptive transfer of MDSC did not alter viability post-infection in mice. The divergent effects of MDSC in these fungal infections may have been due to the distinct animal models that were employed. *Aspergillus* infection was established in immunocompromised animals, whereas infection with *C. albicans* was performed in immunocompetent mice. MDSC have also been studied in the context of *Pneumocystis* pneumonia (PcP), where they accumulated in the lungs of rodents upon infection and suppressed $CD4^{+}$ T cell proliferation *ex vivo* (80). Their frequency correlated with the severity of disease, and adoptive transfer of these cells into healthy mice caused lung damage. ATRA treatment of PcP-infected rats and mice led to diminished MDSC numbers and an increase in alveolar macrophages, which further underlines the deleterious effects of these cells (81). Co-culture studies have suggested that MDSC disable alveolar macrophage function through PD-1/PD-L1 signaling, extending the known MDSC interaction partners to myeloid cells (82).

In summary, during chronic infection MDSC contribute to microbial persistence and, in such instances, pathogens often trigger generation of and benefit from MDSC expansion. However, MDSC may also promote direct pathogen killing by intrinsic effector mechanisms or prevent excessive tissue damage. Additional investigations are required to identify the precise kinetics of distinct MDSC subtypes and unveil how their tissue or lesion compartmentalization influences the course of different infections. MDSC drive

tissue metaplasia and are associated with a poor prognosis in cancer. Although it is poorly investigated, the genesis of MDSC in such infections appears to be driven by prolonged inflammation, and possibly by microbial moieties. A comprehensive characterization of MDSC in microbial-induced cancers is essential for the design of novel preventive and therapeutic approaches in this subgroup of malignancies.

Targeting MDSC by host-directed interventions for infectious diseases

Various strategies targeting MDSC have been envisaged, depending on the suggested detrimental or beneficial roles of these cells during a particular infection (Figure 2). In several chronic infections in which MDSC expansion limits protective immunity, depletion of MDSC reversed immunosuppression and improved disease outcome (45, 48). In TB and AIDS, such interventions may in addition remove pathogen reservoirs, as MDSC can harbor these microbes (45, 83). MDSC can be targeted via (i) depletion, (ii) maturation-induced ablation, (iii) interference with their pathways of genesis, and (iv) interference with their suppressive activity.

Antibody-mediated depletion of $Gr1^+Ly6G^+$ MDSC-like cells has proven successful in experimental models of TB (45, 84, 85), staphylococcal disease (3, 48) and viral infection (29, 51). Cell depletion is, however, impracticable in humans because MDSC lack unique surface markers and therefore such therapies may affect frequencies and functions of related myeloid populations. Drug-induced depletion of MDSC triggered by cytotoxic agents, including gemcitabine and denileukin diftitox, has been employed as a proof-of-principle in murine models of *S. aureus* infection (86) and as a host-directed therapy (HDT) complementing canonical chemotherapy in TB (47).

Maturation-induced ablation represents a more attractive option to reduce MDSC frequencies. Various classes of drugs can induce differentiation or maturation of MDSC. ATRA, for example, which induces MDSC differentiation to dendritic cells and macrophages, has been successfully employed in TB. ATRA leads to MDSC ablation and restricts bacterial replication (45), most prominently when given as adjunct to TB chemotherapy (87). ATRA also promotes maturation of HBV-induced MDSC, restores proliferation and IFN-γ production of HBV-specific $CD4^+$ and $CD8^+$ T cells from chronically infected patients and prevents viral replication in a mouse model of HBV infection (10). Alternatively, differentiation of MDSC can also be achieved by delivery of β-glucan or low doses of cyclic diguanylate, strategies with proven beneficial effects in cancer (16, 88). Reduction of MDSC can also be accomplished by administration of ceramidase inhibitors, which induce apoptosis though ER-stress and interference with autophagy (89). More recently, activation of liver X receptors has proven efficient in inducing apoptosis of MDSC and has been employed in preclinical models and in human trials for tumor immunotherapy (90). Interference with enzymatic pathways relevant for MDSC-induced suppression represents a complementary intervention for targeting these cells. Phosphodiesterase (PDE) (i.e. PDE5) inhibitors block MDSC suppression by limiting Arg1 and NOS2 expression, and are beneficial as a HDT in TB (91). However, a link to MDSC biology is missing and they may exhibit broad effects on other myeloid cells and additional pathways. Targeting the generation of MDSC is possible with COX2 inhibitors, which block the synthesis of PGE2. These effects may explain the beneficial role of ibuprofen in a TB model characterized by heightened MDSC dynamics (92, 93). In contrast to ablation, drug-induced generation of MDSC has recently been reported. Delivery of

finasteride boosts the genesis of suppressor cells (94) and may be employed in infections in which MDSC are beneficial, for instance in acute sepsis or *Pseudomonas aeruginosa* (*P. aeruginosa*) infection (5, 25, 35). Additional studies deciphering the biology of MDSC in infection are required to advance such HDTs into the clinic and for the discovery of novel ways to target these cells therapeutically.

General conclusions and Future Perspectives

The roles of MDSC in fine-tuning the interplay between host and pathogen are being increasingly recognized. As with most myeloid cell subsets, MDSC are endowed with plasticity and thus the search for specificity and commonalities in MDSC biology in infections has just begun. One of the major challenges when dissecting the roles of different MDSC subsets is that a large amount of research is based on a combination of correlation studies *in vivo* and functional assays *ex vivo*. In a study using genetically engineered mice that underwent depletion of either M-MDSC or PMN-MDSC, M-MDSC were identified as the principle immunosuppressive MDSC population in the tumor microenvironment (27). Before experiments using such genetic tools are performed in infections, including those caused by tumorigenic microbes, current conclusions on the relative contribution of specific MDSC populations during infection need to be taken cautiously.

MDSC have nonetheless emerged as targets for HDTs for infectious diseases. The rapid development of antimicrobial resistance advances these cells in the pipeline for the development of novel therapies against drug-resistant microbes. Therapeutic targeting of MDSC in infections with tumorigenic microbes, and the effect on tissue metaplasia, needs to be evaluated. Apart from their therapeutic potential, MDSC have barely been investigated in the context of vaccination. Living organisms, PAMPs, adjuvants and inflammation trigger MDSC generation. Thus, an understanding of whether and how MDSC affect the success of immunizations is needed. This is particularly relevant for newborns and the elderly, as MDSC frequencies are raised in both age groups (95, 96). Lastly, the value of MDSC as biomarkers and their benefits for stratification of patients further justifies accelerating research focused on biology of MDSC in infection and pathogen-associated malignancies.

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflicts of interes.

Ethical approval and ethical standards

Not applicable.

Informed Consent

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Animal source

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Not applicable.

Figure legends

Figure 1. Suppressive mechanisms of MDSC in infection. MDSC subsets exhibit suppressive activities in various infections. Enzymatic pathways, secreted and cell-surface molecules controlling MDSC function are depicted in the context of specific pathogens. The target cells and consequences of MDSC activities are indicated for each infectious agent. Host beneficial and detrimental effects of MDSC are displayed color-coded, in green and red color, respectively.

Figure 2. Targeting MDSC as part of host-directed interventions against infection. Four different strategies have been so far envisaged to manipulate MDSC: maturation-induced ablation, depletion, interference with their suppressive activity and promotion of their genesis. Specific drugs for each

approach, as well as evidence from particular infectious disease along with the outcome of each immune therapy are summarized. *, successful method for depletion in mouse model.

Abbreviation: Mφ, macrophage.

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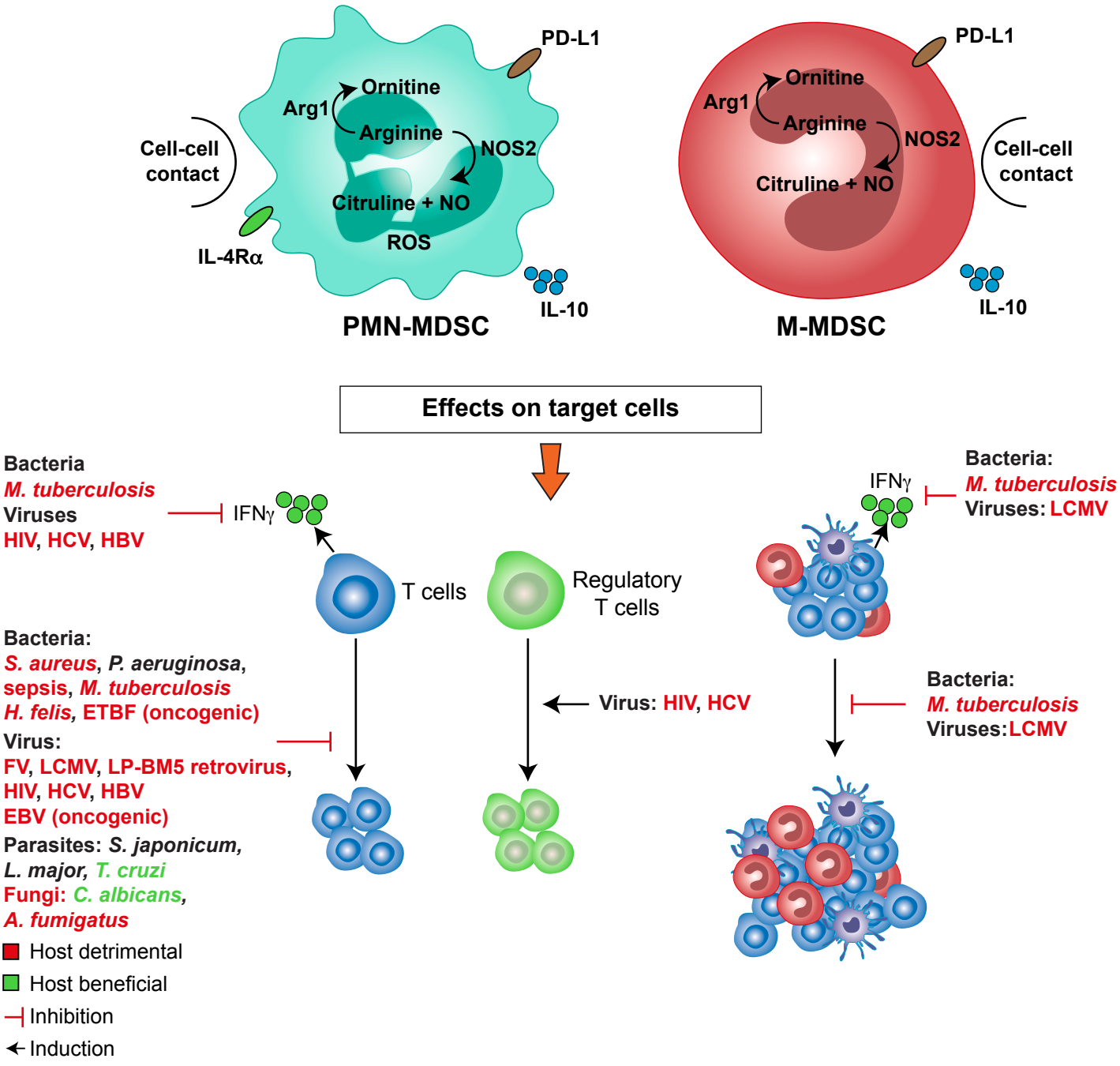
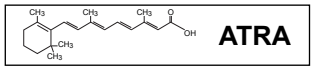

PD-L1
Ornitine
Arg1
Arginine
NOS2
Cell-cell contact
Citruline + NO
ROS
IL-4Rα
IL-10
PMN-MDSC
PD-L1
Ornitine
Arg1
Arginine
NOS2
Cell-cell contact
Citruline + NO
IL-10
M-MDSC
Effects on target cells
Bacteria
M. tuberculosis
Viruses
HIV, HCV, HBV
IFNγ
T cells
Regulatory T cells
IFNγ
Bacteria:
M. tuberculosis
Viruses: LCMV
Bacteria:
S. aureus, P. aeruginosa,
sepsis, M. tuberculosis
H. felis, ETBF (oncogenic)
Virus:
FV, LCMV, LP-BM5 retrovirus,
HIV, HCV, HBV
EBV (oncogenic)
Parasites: S. japonicum,
L. major, T. cruzi
Fungi: C. albicans,
A. fumigatus
Virus: HIV, HCV
Bacteria:
M. tuberculosis
Viruses: LCMV
Host detrimental
Host beneficial
Inhibition
Induction

Maturation-induced ablation



Viruses
HBV
JEV

IFNγ

↑T cell ↑Tfh ↑B cell

Bacteria
M. tuberculosis

Bacterial replication

Fungi
Pneumocystis

↑Alveolar Mφ ↑T cells

Depletion

Abs anti-Gr1 AND -Ly6G*

GEMCITABINE

Bacteria
M. tuberculosis
S. aureus

Biofilm ↑T cell ↑Mφ

Viruses
LCMV
HBV
FV

T cell CD8+

Targeting

MDSC

↑ Enhancing/Restoring of immune response
⊣ Blocking

Blocking of suppressive activity

Abs anti-PD-L1

Viruses
HIV

PMN-MDSC

PHOSPODIESTERASE (PDE) INHIBITORS

Bacteria
M. tuberculosis

ARG1 NOS2

Genesis

BLOCKING

COX2 inhibitors
e.g. Ibuprofen

Bacteria
M. tuberculosis

PROMOTING

Fungi
C. albicans

T cell NK

Bacteria
K. pneumoniae
P. aeruginosa

↑IL-10

Sepsis

IFNγ ↑Th2

Parasites
T. cruzi

↓ Inflammation

↑ Enhancing/Restoring of immune response
⊣ Blocking

Supplementary Table 1. Roles of specific MDSC subsets in acute and chronic infection. Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; HIF, hypoxia-inducible factor; hm, human; LP, lamina propria; mc, macaque; ms, mouse; Mφ, macrophages; PC, peritoneal cavity; PF, Pleural fluid; rd, rodents; Ref, references.

Pathogen / Disease	Host	Acute / Chronic	Location	MDSC Type	Phenotypic markers	Readout functional assays	Suppressive mechanisms	Outcome	Interventions targeting MDSC	Ref
S. aureus	ms	Acute	Skin, LNs, spleen, blood, BM	MDSC	$Gr1^{+}CD11b^{+}$	↓T cell proliferation/ IFNγ production	Cell-cell contact, NOS2	Infection-induced suppression of dermatitis	Depletion (anti-Gr1 Abs)	(3)
		Chronic	Spleen, orthopaedic biofilm	PMN-MDSC	$CD11b^{+}Ly6G^{+/hi}$ $Ly6C^{lo/+}(Gr1^{+})$	↓T cell proliferation/ activation;↓inflammation; ↑infection	Cell-cell contact; Arg1, NOS2, IL-10	Disease exacerbation; restrict biofilm clearance	Depletion (gemcitabine/anti-Ly6G Abs); MDSC transfer	(48, 86)
			Spleen	M-MDSC	$CD11b^{+}Ly6G^{-}$ $Ly6C^{hi}$					
P. aeruginosa	hm	Chronic	Blood	PMN-MDSC	IL-4Rα^{int}CD33^{hi} HLA-DR^{dim}CD66^{hi}	↓T cell proliferation/ IL-17 production	ND	Correlation with active disease	ND	(5)
K. pneumoniae	ms	Acute	Lung	PMN-MDSC	$CD11b^{+}F4/80^{+}$ $Gr1^{int}Ly6G^{int}$ $Ly6C^{lo/-}$	Efferocytosis of apoptotic neutrophils	IL-10	Resolution of inflammation	ND	(35)
M. tuberculosis	ms	Acute	Lung	PMN-MDSC	$CD11b^{+}Ly6G^{+}$ $Gr1^{int}$	↓Splenocyte and $CD4^{+}$ T cell proliferation/ IFNγ production	IL-4Rα	Indicator of active disease and fatality	Ablation (ATRA); depletion (anti-Gr1 Abs); MDSC transfer	(45, 46)
		Acute / Chronic	Lung, BM, spleen, blood	M-MDSC	$CD11b^{+}Gr1^{dim/hi}$ $Ly6G^{-/dim}(F4/80^{+}$ $CD49b^{+}Ly6C^{+}$ $CD117^{+}CD135^{+})$		IL-4Rα, NOS2; cell-cell contact			
	hm	Chronic	Lung, PF, blood	MDSC	$Lin^{-/lo}CD11b^{int/+}$ $HLA\text{-}DR^{-/lo}CD33^{+}$	↓T cell proliferation/ cytokine/CD69 expression	ND	Indicator of active disease	ND	(42, 43)
			Lung, blood	PMN-MDSC	$CD11b^{+}CD14^{-}CD33^{+}CD15^{+}$ $HLA\text{-}DR^{lo/-}$	↓T cell proliferation	NO			(44)
H. felis	ms	Chronic	Stomach	PMN-MDSC	$Gr1^{+}CD11b^{+}$ $Slfn4^{+}Ly6G^{+}Ly6C^{lo}$	↓T cell proliferation	Arg1, NOS2	Correlation with metaplasia	ND	(49)
ETBF	ms	Chronic	Colon tumours	M-MDSC	$CD11b^{+}Gr1^{lo}$ $F4/80^{lo}CD11c^{-/lo}$ $MHCII^{-/+}SSC^{lo}$	Ag-specific $CD8^{+}$ T cell proliferation	NOS2, IDO1	Association with infection-induced colon tumorigenesis	ND	(50)

EBV	hm	Chronic	Blood	M-MDSC	$CD11b^{+}CD33^{+}HLA\text{-}DR^{-}CD14^{+}$	$CD4^{+}$ T cell proliferation	NOS2, Arg1, ROS	Correlation with lower overall survival	ND	(70)
IAV	ms	Acute	Lung	MDSC	$Gr1^{+}CD11b^{+}$	↓Ag-specific splenocyte proliferation	Arg1, NOS2	Suppression of IAV-specific immunity; high viral titer; increased mortality	Transfer of iNKT cells abolish MDSC suppressive activity	(13)
JEV	ms	Acute	Spleen	MDSC	$Gr1^{+}CD11b^{+}$	↓Tfh cell proliferation; ↓neutralizing Abs	ND	Decreased survival	Ablation (ATRA)	(28)
FV	ms	Acute	Spleen	PMN-MDSC	$CD11b^{+}$ $Ly6G^{hi}$ $Ly6C^{lo}$	↓Virus-specific $CD8^{+}$ T cell proliferation and granzyme B production	Arg1, NOS2, PD-L1, CD39	Increased viral load	Depletion (5FU/ anti-Ly6G Abs)	(29)
LCMV	ms	Chronic	Spleen	M-MDSC	$CD11c^{-}CD11b^{+}$ $Gr1^{lo}Ly6C^{hi}$ $F4/80^{+}SSC^{lo}$	↓Splenocyte/T cell proliferation; ↓virus-specific cytokine-producing T cells	ND	Indicator of chronic infection	Depletion (anti-Gr1 Abs); mobilization ($CCR2^{-/-}$ mice)	(51)
LP-BM5 retrovirus	ms	Chronic	Spleen	M-MDSC	$CD11b^{+}Gr1^{+}$ $Ly6C^{+}Ly6G^{-/lo}$	↓T- and B cell proliferation	NOS2	Susceptibility to infection	ND	(52)
HIV	hm	Primary response/ Chronic Chronic	Blood	PMN-MDSC M-MDSC	$HLA\text{-}DR^{lo/-}CD14^{-/+}$ $CD33^{+}CD11b^{+}$ $(CD15^{+}CD124^{+})$ $HLADR^{-/lo}$ $CD11b^{+}CD14^{+}$ $CD33^{+/hi}CD15^{-}$	↓$CD8^{+}$ T cell proliferation/IFN-γ production; Treg expansion ↓T cell proliferation/ IFN-γ production	PD-L1, IL-4Rα, suppression of CD3ζ Arg1; cell-cell contacts	Indicator of viral load; negative correlation with $CD4^{+}$ T cell frequencies	ND	(55-57) (58)
SIV	mc	Acute/ Chronic	Blood Blood, spleen	M-MDSC PMN-MDSC	$CD14^{hi}CD16^{-}CCR2^{lo}$ $CD3^{-}HLA\text{-}DR^{-}CD11b^{+}CD66^{+}$	↓Inflammatory cytokines; ↓$CD8^{+}$ T cell proliferation ↓T cell proliferation	ND	Indicator of active disease; decreased upon antiretroviral treatment	ND	(59) (60)
HCV	hm	Chronic	Blood, liver	M-MDSC	$HLA\text{-}DR^{-/lo}$ $CD14^{+}CD33^{+}$ $CD11b^{+/lo}$	Treg expansion; ↓T cell proliferation/IFN-γ production	IDO1, PD-L1, HLA-DR, IL-10, Arg1	Indicator of viral RNA and liver damage	ND	(6, 7, 61, 62)

HBV	ms	Chronic	Spleen, liver	M-MDSC PMN-MDSC	$CD11b^{+}Gr1^{+/dim}$ $Ly6C^{hi}Ly6G^{-/+}$ ($F4/80^{lo}CD80/86^{lo}$ $MHC\text{-}II^{lo}$) $CD11b^{+}Gr1^{hi}$ $Ly6G^{+}Ly6C^{lo}$	↓T cell proliferation, $CD8^{+}$ CTL function/ IFN-γ synthesis ↓T cell proliferation	NOS2, Arg1 (M-MDSC); CTLA-4/PD-1 on T cells	Indicator of chronic infection	Depletion (ATRA/anti Gr1 Abs); Arg inhibition; MDSC transfer to $TCR\delta^{-/-}$ mice	(10, 65, 66)
	hm	Chronic Acute/ Chronic	Blood Blood, liver	M-MDSC PMN-MDSC	$HLA\text{-}DR^{-/lo}CD33^{+}$ $CD11b^{+}CD14^{+}$ $CD11b^{hi}CD33^{+}$ $HLA\text{-}DR^{-}$ $CD14^{-}CD15^{+}$	↓T cell proliferation, IFN-γ production, CTL activity	PD-1-induced IL-10 synthesis Arg1	Indicator of viral load; negative correlation with liver pathology Indicator of infection without liver injury	ND	(10, 64) (67)
T. crassiceps	ms	Chronic	PC	MDSC	$CD11b^{lo}Gr1^{+}$ $F4/80^{lo}$	↓T cell proliferation; IL-4 induction	NOS2; Arg, ROS, 12/15 LOX	Indicator of infection progression	ND	(47)
H. polygyrus	ms	Chronic	LNs, spleen, LP	MDSC	$F4/80^{-}Gr1^{hi}$ $CD11b^{hi}Ly6G^{+}$ $Ly6C^{+}(CD11c^{-})$	↓Ag-specific $CD4^{+}$ T-cell proliferation/parasite-specific IL-4 secretion	NOS2	Exacerbation of infection	Transfer of $CD11c^{-}Gr1^{+}$ $CD11b^{+}$ cells	(74)
L. major	ms	Chronic	PC Skin	MDSC M-MDSC	$Gr1^{hi}CD11b^{hi}$ $CD11b^{+}$ $Ly6C^{hi}Ly6G^{-}$	↓T cell proliferation	ND NOS2	Enhanced resistance to infection	MDSC transfer; ablation (ATRA) ND	(77) (78)
T. cruzi	ms	Acute	Heart Spleen, liver	M-MDSC MDSC	$CD11b^{+}Ly6C^{+}$ $Ly6G^{-}$ $CD11b^{+}Gr1^{+}$	↓T cell proliferation	NO; L-arginine depletion NADPH oxydase; NO/ peroxynitrite	Protective role Reduced inflammatory cytokines/liver injury; resistance to infection	*In vivo* inhibition of NOS2; L-arginine supplementation Depletion (5FU)	(36) (24)
T. gondii	ms	Acute	Lung	MDSC	$Gr1^{+}CD11b^{+}$	↓Lymphocyte proliferation	NO	Lung defective response	ND	(30)
C. albicans	ms	Acute	Spleen	PMN-MDSC	$CD11b^{+}Ly6G^{+}$	↓T/NK cell activation/Th17 and TNFα cytokine responses	ND	Increased survival and control of infection	MDSC transfer	(15)
	hm	Chronic	Blood	PMN-MDSC	$CD11b^{+}CD33^{+}$ $CD14^{-}CXCR4^{+}$ $CD16^{+}CD66b^{+}$	↓T cell proliferation	ND	ND	ND	

Pneumocystis	rd	Acute	Lung	MDSC	$Gr1^+CD11b^+$ (ms) $CD11bc^+His48^+$ (rat)	↓$CD4^+$ T cell proliferation Impaired alveolar Mφ activation/phagocytosis	Arg1, NOS2 PD-1/PD-L1 signaling	Indicator of infection severity; lung damage	PcP MDSC transfer; ablation (ATRA)	(80-82)
Polymicrobial sepsis	ms	Acute	Liver, spleen, BM, blood, LNs	MDSC	$Gr1^+CD11b^+$	↓Ag-specific T cell IFNγ synthesis; ↑Th2-linked Abs; restrict Mφ IL-6/IL-12 and boost IL-10	Cell-cell contact	Increased survival; Th2 polarization	Depletion (anti-Gr1 Abs); MDSC transfer	(25, 34)
Sepsis	hm	Acute	Blood	PMN-MDSC	$CD11b^{+/hi}CD15^{+/lo}$ $CD66^+CD16^{int/hi}$ $CD45RO^+CD33^{-/+}CD14^{-/lo}$	↓T cell proliferation	Arg; ROS; alter T cell ζ-chain expression	Indicator of severity, $Gram^+$ sepsis and subsequent infections	ND	(31-33)