Myeloid-Derived Suppressor Cells: Paradoxical Roles in Infection and Immunity

Jun Dai^a Mohamed El Gazzar^a Guang Y. Li^{a, b} Jonathan P. Moorman^{a–c}
Zhi Q. Yao^{a–c}

^aCenter for Inflammation, Infectious Diseases and Immunity, and ^bDivision of Infectious, Inflammatory and Immunological Diseases, Department of Internal Medicine, Quillen College of Medicine, East Tennessee State University, and

^cHCV/HIV Program, James H. Quillen VA Medical Center, Johnson City, Tenn., USA

Key Words

Immunity · Infection · Inflammation · Myeloid-derived suppressor cells

Abstract

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature suppressor cells that are generated due to aberrant myelopoiesis under pathological conditions. Although MDSCs have been recognized for more than 20 years under the guise of different monikers, these particular populations of myeloid cells gained more attention recently due to their immunosuppressive properties, which halt host immune responses to growing cancers or overwhelming infections. While MDSCs may contribute to immune homeostasis after infection or tissue injury by limiting excessive inflammatory processes, their expansion may be at the expense of pathogen elimination and thus may lead to disease persistence. Therefore, MDSCs may be either damaging or obliging to the host by attenuating, for example, antitumor or anti-infectious immune responses. In this review, we recapitulate the biological and immunological aspects of MDSCs, including their generation, distribution, trafficking and the factors involved in their activation, expansion, suppressive functions, and interplay between MDSCs and regulatory T cells, with a focus on the perspectives of infection and inflammation.

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Introduction

Myeloid-derived suppressor cells (MDSCs) have been recognized for more than 20 years since their initial description in patients with cancer [1–3]. They have been identified by several monikers, including ‘natural suppressor cells’, ‘immune myeloid cells’, ‘suppressor macrophages’ and, recently, MDSCs [2, 4]. As opposed to their suppressive functions in chronic inflammation [5], evolving evidence indicates that MDSCs possess the inherent nature of the M1 macrophages seen in acute stages of infection, which express high levels of inducible nitric oxide synthase (iNOS), arginase 1 (ARG1) and reactive oxygen species (ROS), all of which are important mediators of innate immune responses against pathogenic infections [6–10]. However, how these functional mediators can affect aspects of the innate immune response is still an open question.

The immunosuppressive activities of MDSCs have been documented predominantly in cancer patients or tumor-bearing animals and during inflammation or infections, as they have been shown to suppress immune responses against tumors or microbes [6, 7, 11, 12]. There has been active debate as to whether MDSCs are beneficial or deleterious to host immunity against intruding pathogens. We now realize that MDSCs may be helpful to the host under certain circumstances, yet harmful in others. In addition to their roles in suppressing host immune responses, their immunosuppressive properties can be

Fig. 1. The genesis of MDSCs. Long-term multipotential hematopoietic stem cells in the bone marrow give rise to short-term hematopoietic stem cells, which further differentiate into multipotent myeloid progenitors and then common myeloid progenitors. These evolve into IMCs, which under steady-state conditions leave the bone marrow as myeloid precursor cells and migrate to peripheral tissues, such as the spleen and lymph nodes, where they dif-

ferentiate into macrophages, DCs and granulocytes/neutrophils under the influence of specific tissue factors. Under pathological conditions, such as progressive infection/inflammation or growing tumor burden, these IMCs follow a different differentiation pathway to produce MDSCs with suppressive functions. Notably, resolution of infection or tumor permits MDSC development toward the steady-state myeloid development process.

exploited, for example, in suppressing the immune response to a graft transplant. These same immunosuppressive properties may make MDSCs an important component in hindering immune cell homeostasis and in facilitating persistent infections.

MDSCs appear to protect the host from devastating tissue damage during the initial stages of infection by attenuating an overwhelming inflammatory process [13–16]. In the early stages of severe inflammatory conditions such as sepsis, the administration of anti-Gr-1 antibody has been reported to reduce the numbers of MDSCs and to prevent the Th2-polarized immune response and the suppression of CD4⁺ and CD8⁺ T cells during severe sepsis, suggesting that MDSCs may play an immunosuppressive role during sepsis [15]. However, this approach did not improve outcome, perhaps attributed to the nonspecificity of the anti-Gr-1 that also depletes mature neutrophils [15]. Another study has shown that depletion of MDSCs during early severe sepsis reduced survival, suggesting that MDSCs play an immunoprotective rather an immunosuppressive role during sepsis [17]. It should be noted that the inflammatory response to sepsis is a dynamic process, as it shifts from an early severe hyperinflammatory state to a late immunosuppressive state. Thus, data regarding depletion of MDSCs in sepsis and whether they play a protective or

immunosuppressive role should be interpreted with caution. We have recently shown that, in the course of murine sepsis, MDSCs can enhance (proinflammatory) or suppress (immunosuppressive) severe inflammation of early sepsis, depending on the context in which they expand [13]. We have shown that MDSCs derived from early septic mice were proinflammatory, whereas MDSCs derived from late septic mice were immunosuppressive, and they improved survival only during early septic hyperinflammation [13]. This led us to conclude that, at least in sepsis, MDSC phenotype and activity depend largely on the environment in which they expand and function.

MDSC Origin and Distribution

MDSCs primarily include immature myeloid cells (IMCs), in addition to some mature neutrophils and macrophages, with half-lives ranging from hours to days (fig. 1). Numbers of functionally mature myeloid cells must be maintained by a steady-state asymmetrical myelopoiesis. Long-term hematopoietic stem cells in the bone marrow give rise to short-term hematopoietic stem cells, which further differentiate into multipotent myeloid progenitors and then common myeloid progeni-

tors, which evolve into erythroid progenitors and IMCs, respectively. Under steady-state conditions, IMCs leave the bone marrow as myeloid precursor cells and migrate to peripheral tissues, such as the spleen, where they differentiate into macrophages, dendritic cells (DCs) and granulocytes or neutrophils under the influence of specific tissue factors [15]. Under certain pathological conditions, such as progressive infection/inflammation or a growing tumor burden, these IMCs follow a different differentiation pathway to produce MDSCs [6, 7].

MDSCs are the intermediates of the normal myeloid development and differentiation stages. However, immunosuppressive MDSCs do not expand under normal conditions; these myeloid intermediates or IMCs are reprogrammed and acquire their immunosuppressive properties when they expand in response to a growing tumor or infection/inflammation to become functional, immunosuppressive MDSCs. Under normal conditions, IMCs expressing the Gr-1⁺CD11b⁺ phenotypic marker are usually maintained at a relatively low level in murine bone marrow (20–30% of overall myeloid cells), peripheral blood (2–4%), spleen (2–4%), pancreas (1–2%), liver (2–5%) and lymph nodes (<1%) [17, 18]. In peripheral blood of normal mice, the ratio of Gr-1⁺CD11b⁺ IMCs to T cells is 1:5, whereas under stress conditions, this ratio is 2:1, similar to the ratio in the spleen of septic mice. In septic mouse bone marrow, the ratio can reach up to 16:1 [19–21]. Functionally, Gr-1⁺CD11b⁺ IMCs from normal hosts are not immunosuppressive. The varying numbers of MDSCs required to elicit immunosuppressive effects in different *in vitro* models may explain some of the discrepancies regarding MDSC studies [22]. In humans, there are no details regarding the distribution of IMCs in various tissues, and in healthy subjects IMCs with analogous MDSC phenotypes (Gr-1⁺CD11b⁺) do not exert immunosuppressive capability [23–27]. Thus, MDSCs are differentiated from normal IMCs, and they only expand and become immunosuppressive via aberrant myelopoiesis; this generally occurs under certain pathological conditions, such as progressive infection/inflammation or a growing tumor burden.

Aberrant Myelopoiesis and MDSC Expansion

Of note, dysregulated myelopoiesis appears to be a prerequisite for MDSC expansion and is mediated by both myeloid expansion and activation factors [7, 22]. These two differential factors are normally present at inflammatory sites and are derived from products of dying (apoptotic) cells or mediators, such as granulocyte/macrophage-

colony stimulating factor (GM-CSF) and IFN- γ , secreted by immune cells. However, neither growth factor alone nor one-sided stimulating factors can trigger myelopoiesis [22]. Administration of high doses of bacterial lipopolysaccharide to mice has been shown to prime transient and modest expansion of MDSCs [5], whereas *ex vivo* treatment with GM-CSF has been reported to induce MDSC generation from mouse bone marrow in a dose-dependent manner [28, 29]. In these experimental conditions, however, one cannot exclude the potential contamination with other growth factors, because GM-CSF or lipopolysaccharide alone cannot activate colony proliferation.

Without persistent stimulation, it is difficult to maintain a steady-state expansion of MDSCs. Cultures of tumor-derived MDSCs in the absence of tumor-derived stimuli, or transfer of MDSCs into tumor-free recipients, give rise to mature functional myeloid cells [7, 30, 31]. This is supported by the observation that a drop in the MDSC population occurs after experiencing abscess resolution, primary tumor resection and antiretroviral therapy in HIV patients [11, 32]. Notably, overdosage of GM-CSF as an adjuvant for vaccination or treatment triggers counter-regulatory suppressive mechanisms that may conversely dampen its effectiveness due to the possible expansion of MDSCs [33, 34]. Under normal conditions, the body generates physiologically necessary IMCs, which bear MDSC-analogous phenotypes following myelopoiesis to sustain homeostasis. Whether extramedullary myelopoiesis exists in the spleen, liver or lymph nodes under normal conditions remains unknown, but this is highly likely during severe infections, especially in animal disease models [5].

Inflammation leads to increased mobilization of mature myeloid cells, which create niche spaces in the bone marrow reservoir, and excessive production of inflammatory mediators act in concert to skew them from differentiation into mature myeloid cells toward MDSC expansion. A partial interruption or arrest of IMC differentiation into mature myeloid cells leads to the accumulation of MDSCs following their exclusive pathway, which also partially explains why macrophages and DCs do not expand during the generation of MDSCs in late/chronic inflammation [35, 36]. In the early stages of infection, MDSCs appear to serve as part of the innate immune defense mechanism, and their frequency declines due to the mobilization of the myeloid progenitors to replace the consumed mature myeloid cells. With persistent infection during polymicrobial sepsis, MDSCs expressing CD31 surface antigen, a marker that exists on more IMCs [37], expand in the bone marrow and exponentially increase to nearly 70-fold compared to controls (i.e. 37–40% CD31⁺

Fig. 2. Paradoxical roles for MDSCs in early and late phases of infection. Early infection is characterized by the emergence of MDSCs which appear to be involved in innate host responses to infectious pathogens, with expression of proinflammatory mediators and cytokines and the general appearance of a more M1-like phenotype. These cytokines include IL-6, IL-12, and TNF α , amongst others, and several of these factors may contribute to further MDSC expansion. Chronic or late infection is characterized

by the emergence of an M2-like phenotype, with blast-like nuclei and the expression of significant ARG1 and iNOS as well as cytokines such as IL-10 and TGF- β . The milieu generated contributes to an immunosuppressive/anti-inflammatory environment that includes blunted CD4 and CD8 T cell responses and expansion of both natural (nT_{reg}) and induced T_{reg} (iT_{reg}) cells. MIP1 α = Macrophage-inflammatory protein 1 α .

cells of total Gr-1⁺CD11b⁺ MDSCs on day 3 to nearly 80% on day 12 after sepsis onset in mice) [37]. In line with this observation, in late septic mice, Gr-1⁺CD11b⁺ MDSCs represented 40% of the myeloid cells in the spleen, 90% in the bone marrow and 3–4% in the lymph nodes (normally, 2–4% in spleen, 20–30% in the bone marrow and <1% in lymph nodes in naive mice) [5, 13].

In addition to the massive increase in the immature CD31⁺ MDSC subset during sepsis, there is a parallel loss of their ability to differentiate into mature myeloid cells. In a study by Brudecki et al. [13], approximately 38 and 21% of total Gr-1⁺CD11b⁺ MDSCs from day-3 (early) septic mice differentiated into macrophages and DCs, respectively, compared with only 17 and 9% differentiation when these cells were derived from day-12 (late) septic mice. Interestingly, CD31⁺Gr-1⁺CD11b⁺ MDSCs from both early and late septic mice exhibited similarly low levels of the differentiation potential (<4% of CD31⁺ MDSCs differentiated into mature myeloid cells).

This phenotypic shift and loss of the differentiation potential of MDSCs due to inflammation persistence was also accompanied by a shift from a proinflammatory to a

late anti-inflammatory cytokine profile, characterized by early production of TNF α , IL-6 and IL-12, and late production of TGF- β and IL-10 secretion, and with the disappearance of ring-shaped and blast-like nuclei of MDSCs (fig. 2) [15]. These shifts from the M1- to the M2-like macrophage functional phenotype underpin a postinflammatory immunosuppressive state, which also closely correlates with the expansion and phenotypic shift of MDSCs observed in HIV and HCV persistent infections [13, 14, 16, 38–40]. Correspondingly, an increased expression of anti-inflammatory genes encoding inhibitory signaling molecules and suppressive cytokines as well as a decreased expression of proinflammatory genes encoding proteins associated with immune tolerance was observed in these studies [41–44].

MDSC Subsets and Phenotypes

MDSCs are not a defined subset but a heterogeneous population. Their morphology and function differ in different tissues and under different inflammatory condi-

Table 1. Cell surface phenotypic markers for MDSCs

Phenotype	Human		Mouse	
	M-MDSCs	G-MDSCs	M-MDSCs	G-DSCs
CD11b (Mac-1)	+	+	+	+
Gr-1	N/U	N/U	int/low (dim)	high (bright)
Ly6G	N/U	N/U	–	+
Ly6C	N/U	N/U	+	–
MHC-II (HLA-DR)	low/–	low/–	N/U	N/U
CD14	+	–	N/U	N/U
CD15	–	+	N/U	N/U
CD16 (FcγR)	high	int	+	+
CD115 (M-CSF1R)	N/U	N/U	+	+/–
F4/80	N/U	N/U	+	–
CD31 (PECAM1)	N/U	N/U	+	–
Lin	–	–	N/U	N/U
CD120b	N/U	N/U	low	low
CD125	+	+	–	–
CD124 (IL-4αR)	+	+	+	+
CX3 (CR1)	N/U	N/U	low	high
CD33	high	int	N/U	N/U
CD32	N/U	N/U	+	+
VEGFR1	+/–	+	N/U	N/U
CD49d	N/U	N/U	+	–
CD68	N/U	N/U	–	+
CD40	N/U	N/U	+	+
CD80	N/U	N/U	+	+
CD83	–	–	N/U	N/U
CD66b	–	high	N/U	N/U
MHC I	N/U	N/U	int	int
CD54 (ICAM-1)	N/U	N/U	high	low
CD1d	N/U	N/U	+	–
CCR2	N/U	N/U	+	–

N/U = None or unidentified.

tions. Even within the same inflammatory process, they functionally and phenotypically vary over time and usually share the phenotypic spectrum of mature myeloid cells, such as CD11c⁺ (DC) and F4⁺/80⁺ (macrophage) [7]. For this reason, MDSCs are more accurately identified by their immunosuppressive functions rather than cell surface markers. In mice, MDSCs are defined as IMCs that co-express the Gr-1⁺ and CD11b⁺ markers, which are also associated with other surface markers at various stages of myeloid cell maturation (table 1). This MDSC population can be further dissected into two subsets based on the expression of the Gr-1 antigen: CD11b⁺LyG⁺LyC^{–/low} (granulocyte, G-MDSCs) and CD11b⁺LyG⁺LyC^{high} (monocyte, M-MDSCs).

Unlike mice, human MDSCs do not express GR1 antigen, and thus MDSCs are basically defined as two sub-

sets: G-MDSCs and M-MDSCs. The G-MDSC phenotype is identified as Lin[–]CD11b⁺CD33⁺HLA-DR[–] or CD33⁺CD11b⁺CD14[–]CD15⁺HLA-DR[–], whereas M-MDSCs correspond to CD33⁺CD11b⁺CD14⁺HLA-DR^{–/low} [45–52] or CD14⁺HLA-DR^{–/low} [49, 53]. G-MDSCs comprise the dominant percentage (70–80%) of the total MDSC population in tumor-bearing mice or cancer patients, with multilobed nuclei and high side scatter when assessed by flow cytometry [24, 54–56]. In contrast, M-MDSCs represent about 20–30% of the total MDSC population with ring-shaped nuclei and low side scatter. Tumor-associated production of granulocyte CSF in mice might account for the accumulation of G-MDSCs [57].

Investigations in tumor-bearing mice revealed that the two distinctive subsets of MDSCs exert the same level of immunosuppressive effects on CD8⁺ T effector cells through specific cell-to-cell contact and on CD4⁺ T cells via nonspecific humoral immune mechanisms, despite the fact that M-MDSCs have been suggested to be more suppressive than G-MDSCs at the per cell level [23, 55, 58, 59]. G-MDSCs express higher levels of ROS, whereas M-MDSCs produce more iNOS, and both cell subsets express a modest level of ARG1. During bacterial infection or autoimmune encephalomyelitis, for example, these two distinct subsets have been shown to play different immunomodulatory roles [60, 61]. In persistent infections, G-MDSC and M-MDSC numbers are decreased, with emergence of more immature (blast-like) CD31⁺ myeloid cells. In tumor settings, G-MDSCs lose the myeloid differentiation potential, but M-MDSCs retain the potential for further maturation [7]. Although these two subsets functionally and/or phenotypically overlap, it is unclear if they can switch into the other phenotype. Whether specific subpopulations predominate and whether their corresponding functions change with the severity of infection or tumor progression needs further investigation.

MDSC Trafficking and Mobilization

The phenotypic and functional heterogeneity of MDSCs stems, in large part, from the fact that they have been studied in different experimental models, and from the heterogeneity of MDSCs in different tissues and even under similar conditions. Recent studies linked MDSCs to sepsis progression [15]. Makarenkova et al. [62] reported significant increases in the numbers of Gr-1⁺CD11b⁺ MDSCs derived from a rapid influx into the spleen 12–24 h after a traumatic injury, with cells expressing more MHC II, less MHC I as well as less of the

immature myeloid marker CD31. In contrast, Delano et al. [5] observed a transient decline in Gr-1⁺CD11b⁺ MDSCs in the spleen during the first 24 h after sepsis onset but a massive expansion 3–5 days after sepsis. These cells produced copious amounts of the immunosuppressive cytokine IL-10 and were mostly CD31⁺ [15]. These data support the hypothesis that IMCs in the bone marrow are recruited to sites of inflammation to replace damaged or exhausted cells, and then become trapped in the local microenvironment where they acquire their immunosuppressive properties from various inflammatory signals. Human subjects with sepsis exhibit increases in the numbers of neutrophils with an immature phenotype due to delayed apoptosis [63, 64]. Normal neutrophils undergo apoptosis within 24 h after their release from the bone marrow. Aberrant, septic neutrophils produce small amounts of ROS and show impaired bactericidal activity and loss of chemotactic activity [65, 66].

We hypothesize that, with mild or transient endogenous and exogenous insults (scenario 1), such as minimal-to-modest pathogen load, benign neoplasms, trauma or vaccination, IMCs can be recruited transiently at discrete numbers. In this scenario, more mature myeloid cells rather than IMCs are observed, which are more likely to differentiate into mature myeloid cells with less immunosuppressive activities when compared to those cells that arise under severe insults, i.e. MDSCs [19]. An early decline in mature myeloid cells is due to host defense sacrifice or trafficking of IMCs from the bone marrow and their differentiation into MDSCs [6, 7, 20]. We can consider this pathway as a natural host defense response in common, self-limited diseases. In the setting of uncontrolled systemic insults (scenario 2), such as an overwhelming septic infection or a growing tumor burden, inflammatory mediators or immunosuppressive factors derived from infection or metastatic tumor, respectively, can shift myelopoiesis toward accumulation of MDSCs and yet thwart myeloid differentiation [6, 7, 15]. This would lead to an increase in immature phenotype CD31⁺ cells with strengthened immunosuppressive competence [41] along with diminished terminal differentiation potentials and M2 or Th2 polarization – thus dampening circulating proinflammatory cytokines and bactericidal activity [5, 13, 14]. These two scenarios have similarities at the onset (within the first few hours) of the infectious insult in that there is a transient decrease in Gr-1⁺CD11b⁺ IMCs due to differentiation into mature myeloid cells, which are then mobilized by invading pathogens.

Improving survival via reducing inflammation-induced multiorgan dysfunction comes at the expense of

pathogen elimination and the incurrance of secondary insults [13]. An appropriate example for demonstrating suppressive immune responses comparable to MDSC properties is that of tumor-associated macrophages, which directly arise from MDSCs that have migrated to tumor sites, attenuating host antitumor immunity by producing mediators such as ARG1 or iNOS [7, 10, 67, 68]. Whether chronic infections, such as HIV or HCV, promote the expansion of infection-associated myeloid cells like tumor-associated macrophages remains unknown, but we believe that chronic infection may share similar evasion mechanisms as those operating in cancers. Although several factors have been identified that drive MDSC expansion and terminate normal myeloid cell differentiation, including GM-CSF, VEGF, COX-2, IL-10, TGF- β and some S100A proteins [6, 7, 15], it remains unclear how MDSCs traffic to pathologic sites. The answer to this question is further complicated by the lack of specific markers for human MDSCs and the fast-filtering blood compartment [68].

MDSCs in Infection and Tumor

Generally, most tumors derive from endogenous mutation- or chronic inflammation-induced cell transformation, whereas acute infection is an exogenous pathogen invasion, and these distinct etiologies are likely to determine the diverse immune mechanisms that MDSCs deploy to respond to the respective threat. MDSCs subvert both innate and adaptive immune surveillance and prevent the host immune system from eliminating newly transformed or infected cells [69]. MDSC depletion in a tumor-bearing animal model resulted in tumor recession by altering the inflammatory responses, thus allowing for the restoration of antitumor immune responses due to the elimination of immunosuppressive mediators produced by MDSCs and their subsequent effects on T cells [70]. By contrast, depletion of MDSCs increased host mortality in sepsis due to the loss of the intrinsic ability to inhibit early, unremitting proinflammatory cascades, especially in the early stage of sepsis in which proinflammatory cytokines induce an inflammatory storm [17].

It is possible that the net benefit of limiting expansion of MDSCs contributes to the establishment of antitumor immunity, as their expansion and activities negatively affect the host secondary defense system by inhibiting antigen-presenting DC and antigen-specific CD8⁺ T cells to cell-mediated antitumor immunity [6, 7]. In the context of infection, MDSC depletion increases the risk of suscep-

Table 2. Functional protein and cytokine expression in MDSCs

Protein and cytokine expression	Human		Mouse	
	M-MDSCs	G-MDSCs	M-MDSCs	G-MDSCs
S100A8	N/U	N/U	+	+
S100A9	+	+	+	+
ARG1	+	+	+	+
ROS	low	high	low	high
iNOS	high	low	high	low
IL-10	+	–	+	+
IL-13	+	–	–	–
TGF- β	+	–	–	–
SSC	low	high	low	high

N/U = None or unidentified.

tibility to primary or secondary infection as well as the risk of overwhelming inflammation [13, 15, 71, 72]. Severe infections such as sepsis are typically defined by the production of early proinflammatory cytokines such as TNF α and IL-6, and late anti-inflammatory cytokines such as IL-10 and TGF- β (table 2) [13]. Initial proinflammatory cytokines increase pathogen clearance but decrease survival due to incurring drastic inflammatory responses, resulting in multiple organ failure, whereas late anti-inflammation incurs overall immunosuppression and susceptibility to secondary infection [13, 72]. The question remains whether one should manipulate sepsis pathophysiology by employing different approaches against both the early hyperinflammatory response and the late immunosuppression based on a predicted time point. One could envision a selective approach in treating sepsis may require the use of anti-inflammatory therapy to attenuate and resolve early sepsis hyperinflammation in order to prevent multiple organ injury, while employing immunostimulatory therapy to resolve late sepsis immunosuppression once it has developed.

It is more complex in the clinical scenario, as most clinicians believe that immunosuppression, rather than intractable, low-grade inflammation, is the predominant driving force for morbidity and mortality in late-septic patients [73]. Regulation of immune activation by MDSCs based on a patient's differential immune status and disease stage is apparently important but also challenging. During severe inflammation, the host immune system may prevent self-damage from proinflammatory reactions that are induced by an overwhelming pathogen burden, but this comes at the expense of failing to eliminate infection, leading to disease persistence. In compar-

ison, chronic infections share more common features with tumor progression, characterized by immunosuppression in the advanced stages.

MDSC-Suppressive Mechanisms and Interactions with Regulatory T Cells

Functionally, MDSCs generated in the setting of chronic infections or chronic inflammation have more suppressive activities than MDSCs that arise under acute conditions, such as severe systemic inflammation during early murine sepsis [13]. It has been suggested that the accumulation of MDSCs due to accelerated myelopoiesis during chronic inflammation, such as in late sepsis, is not simply an expansion in their numbers or expression of phenotypes, but rather an enhanced suppressive function gained under pathological conditions. Gr-1⁺ MDSCs from tumor-bearing mice injected into healthy mice rapidly lose their immunosuppressive phenotypes [15].

Using a murine model of induced prostate inflammation, Haverkamp et al. [74] reported that MDSC-suppressive functions were only limited to the site of inflammation, suggesting that the robustness of the inflammatory response determines the gradual-grade spreading of immune privilege. In addition, it has been suggested that MDSCs alone or synergistically with T regulatory (T_{reg}) cells can contribute to the progression or latency of HIV infection, and this may explain the lack of efficacy of some immune-based treatments and vaccinations [11, 75–80]. As summarized in the review by Gabrilovich et al. [52], MDSCs can suppress T cell activation and function by several mechanisms, including (A) deprivation of essential nutrients like L-arginine, L-cysteine and tryptophan from the T cell environment; (B) nitrosylation of T cell receptors by oxidative stress; (C) interference with lymphocyte trafficking and viability via inhibitory molecules or receptors, and (D) amplification of immune suppression by inducing T_{reg} proliferation and differentiation.

The role of T_{reg} cells in transplantation and autoimmune diseases has been well studied, where MDSCs have been shown to induce immune tolerance and reduce transplant rejection and also to attenuate self-tolerance in autoimmune diseases [81–85]. MDSC cross talk with macrophages, DCs and other effector immune cells has been reviewed previously [6, 52, 86], whereas their interaction with T_{reg} cells is less-well appreciated.

MDSCs and CD4⁺CD25⁺FoxP3⁺ T_{reg} cells represent two major classes of suppressive cells that play crucial roles in the establishment and maintenance of peripheral

immune tolerance. Both MDSCs and T_{reg} cells have been reported to synergistically inhibit immune effector cell function and maintain tumor tolerance in tumor-bearing mice [87, 88]. One study has shown that primarily G-MDSCs can inhibit natural T_{reg} cell proliferation and prevent inducible T_{reg} cell differentiation from naïve CD4⁺ T cells. However, this study did not exclude the possibility that M-MDSCs might prime T_{reg} cell development [89].

In cancer, the tumor microenvironment can further induce MDSCs to differentiate into tumor-associated macrophages, which appear endowed with more suppressive capability and which can induce IL-10 [85], TGF- β , PE2 [89] and CC-chemokine ligand 22 (CCL22) [90] production to attract and promote T_{reg} cell development and attenuate antitumor immunity rather than directly inhibiting innate immunity via PD-L1 [91] or ARG1 [92]. We speculate that, during the early stages of inflammation as observed in acute sepsis, T_{reg} cells may partially function to inhibit the initial excessive inflammatory reaction before adequate numbers of MDSCs are generated. During early inflammation, IMCs exhibit the same surface markers as MDSCs but are not immunosuppressive. We suspect that these MDSC-like cells may exert normal immune properties for antimicrobial effects at this stage. Later on, with infection persistence, these IMCs aberrantly differentiate into MDSCs, exerting their immunosuppressive functions at a later stage.

Here, we describe two distinct populations and suppressive mechanisms for both MDSCs and T_{reg} cells: the inherent natural population and the acquired inducible population. Because MDSCs are derived from aberrant myelopoiesis under pathologic conditions, their suppressive ability is not an inherent trait, as is observed in natural T_{reg} cells, but rather induced by pathogenic products and inflammatory cytokines so as to induce T_{reg} cells. MDSCs communicate with and orchestrate aspects of the human immune defense system, balancing T_{reg} and effector T cells, whereby persistent pathogens strengthen their immunosuppressive activities. In comparison, natural T_{reg} cells are part of the inherent host defense system, exerting more comprehensive and long-lasting surveillance for the host over self-immune reactions. The suppressive power of T_{reg} cells against host immune responses may serve as an additional mechanism for promoting MDSC expansion and activation under pathological conditions. If we deem ARG1 [92], H₂O₂ and nitrosylation of effector immune cell receptors [93–95] as direct and primary weapons used by MDSCs against effector immune cells [52, 96], then IL-10 [85], TGF- β [89] and ROS [97] are the indirect or secondary mediators that expand the

MDSC immunosuppressive cascade, in conjunction with inducible T_{reg} cell development. Through induction and interaction of MDSCs and T_{reg} cells [88], persistent pathogens (e.g. HIV/HCV) can suppress antigen-specific [19, 94, 98] or nonspecific [34, 99, 100] effector immune cells for their survival benefit, leading to immune tolerance characterized by a relatively benign immune-mediated injury, but at the expense of chronic infection [101, 102].

Conclusion

The discovery of MDSCs and characterization of their immunosuppressive functions have shed new light on the pathogenesis of many inflammatory diseases. This review has focused discussion on MDSCs in infection-driven inflammation, comparing their properties to tumor-driven MDSCs. Notably, MDSCs may serve as a double-edged sword during the early and late stages of infection and inflammation, from boosting innate immunity in early stages to attenuating the immune system through promoting immunosuppression in late stages of infection. How MDSC phenotypes and functional activities shift along with the host early proinflammatory to late anti-inflammatory phase and how they cross-interact with T_{reg} cells require further investigations. Although some suggest that increasing MDSCs during infection may help limit undesirable inflammatory damage, and boosting MDSC proliferation during an uncontrolled inflammatory response may reduce undesirable inflammation [103], MDSC expansion and activity are not an inherent homeostatic mechanism which the immune system can utilize to return to a noninflammatory state. MDSCs are induced under pathologic conditions and may help balance the immune threshold and induce a weak host response to pathogens. The precise mechanisms of how factors derived from the invading pathogens or inflammatory mediators drive the expansion and activation of MDSCs and their trafficking to the sites of tumor or infection to exert suppressive functions are still under investigation. Taken together, elucidating all the biological and functional aspects of MDSCs will contribute to our understanding of the immunobiology of infection and inflammation and eventually help develop prophylactic or therapeutic approaches for inflammatory diseases.

Acknowledgements

This work was supported by an NIH NIDDK grant to ZQY/JPM (R01DK093526) and an NIH NIAID grant to ZQY/JPM (R01AI114748).

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