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Myeloid derived suppressor cells: The Dark Knight or The Joker in viral infections?

Celeste Goh¹, Sowmya Narayanan¹, and Young S. Hahn¹

¹Department of Microbiology, Beirne B. Carter Center for Immunology Research, University of Virginia, Charlottesville, VA, USA

Summary

Myeloid derived suppressor cells (MDSCs) are immature cells of myeloid origin, frequently found in tumor microenvironments and in the blood of cancer patients. In recent years, MDSCs have also been found in non-cancer settings, including a number of viral infections. The evasion of host immunity employed by viruses to establish viral persistence strikingly parallels mechanisms of tumor escape, prompting investigations into the generation and function of MDSCs in chronic viral infections. Importantly, analogous to the tumor microenvironment, MDSCs effectively suppress anti-viral host immunity by limiting the function of several immune cells including T cells, natural killer cells, and antigen-presenting cells. In this article, we review studies on the mechanisms of MDSC generation, accumulation, and survival in an effort to understanding their emergent importance in viral infections. We include a growing list of viral infections in which MDSCs have been reported. Finally, we discuss how MDSCs might play a role in establishing chronic viral infections and identify potential therapeutics that target MDSCs.

Keywords

MDSC; viral infection; immunosuppression

Introduction

Chronic viral infections are an ongoing battle between viruses and the immune response, characterized by the sustained recruitment of immune cells matched by an equally stubborn and unrelenting presence of virus. Forefront among the many reasons for viral persistence are myeloid derived suppressor cells (MDSCs), a heterogenous population of myeloid progenitors and immature myeloid cells that share the ability to suppress immune responses. MDSCs were first described in 1987 in a mouse model of lung cancer as bone marrow-derived cells that inhibited T-cell proliferation (1). Over two decades later, these cells have transformed the field of cancer research, even serving as a marker of disease progression in human cancers (2, 3). Given that tumors are characterized by a constant albeit dysfunctional immune response, it is not surprising that recent studies have begun to identify a parallel role for MDSCs in other chronic inflammatory states. In this review, we describe recent studies on MDSCs in viral infections, paying particular attention to the molecular mechanisms that aid in the recruitment and function of this immunosuppressive population.

MDSCs can be broadly classified into two groups—granulocytic and monocytic (Table 1). As the name suggests, monocytic MDSCs appear similar to monocytes in that they have a

single, large, round nucleus, while granulocytic MDSCs have multi-lobed nuclei resembling those of polymorphonuclear cells (4). Since they are morphologically similar to mature immune cells, MDSCs are also distinguished by the expression of surface markers and distinct mechanisms of suppression. Murine MDSCs differ in their expression of Gr-1, a myeloid lineage marker that is recognized by antibodies to Ly6G and Ly6C: granulocytic MDSCs are defined as CD11b⁺Ly6G⁺Ly6C^{low}, while their monocytic counterparts are CD11b⁺Ly6G⁻Ly6C^{hi} (5).

Although CD11b⁺Gr-1⁺ cells are widely accepted as murine MDSCs, an analogous cell surface signature remains elusive in humans, as they do not express Gr-1 or its homologues. Currently, phenotypic markers for human MDSCs are Lin⁻HLA-DR⁻CD33⁺ or CD11b⁺CD14⁻CD33⁺, the latter of which are sometimes CD15⁺ (6). The lack of clearly defined cell surface markers for human MDSCs makes their study particularly challenging. Notably, the hallmark of all MDSCs is their ability to suppress immune responses, which provides an alternative means of further understanding their roles in normal physiology and disease.

Immunoregulatory mediators and cellular targets for MDSCs

Among the soluble factors enabling the functions of MDSCs are three key mediators: reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS), and arginase-1. Each of these mediators plays a pivotal role in dampening host immune responses, both independently and in concert with each other. Generally, murine granulocytic MDSCs are thought to exert their immunosuppressive effects via ROS, usually generated by NADPH oxidase; monocytic MDSCs produce nitric oxide (NO) via iNOS (4, 7, 8). ROS, particularly hydrogen peroxide, can act on immature myeloid cells to reduce their ability to differentiate into macrophages and dendritic cells (DCs) (9) and catalyzes the nitration of the T-cell receptor (TCR), thereby preventing T cell-peptide-major histocompatibility complex (MHC) interactions. Similarly, iNOS, in conjunction with arginase-1 or limiting concentrations of L-arginine, generates reactive nitrogen-oxide species, which also nitrosylate the TCR, thus resulting in T-cell suppression or apoptosis (10). Both granulocytic and monocytic MDSCs were also reported to deplete L-arginine, which is particularly important for the survival and function of T cells, through the action of arginase-1 (11, 12). Interestingly, the suppression of T cells by MDSCs may represent a mechanism of controlling inflammation, as evidenced by studies where treatment with interleukin-2 (IL-2), a cytokine that is essential for T-cell proliferation and function, increased the numbers of arginase-positive MDSCs in cancer patients (13). Similarly, the effect of T-helper 1 (Th1) and Th2 cytokines on arginase-1 further validates the crosstalk between MDSCs and T cells: arginase-1 expression and activity are enhanced by the Th2 cytokine IL-4, both by itself (14) or in conjunction with IL-13 (15), whereas the Th1 cytokine interferon- γ (IFN- γ) upregulates arginase-1 expression (16).

In contrast to murine MDSCs, human MDSCs are not characterized by such clear differences. Moreover, phenotypically distinct human MDSCs have been reported to use the same mechanisms of suppression, negating the use of cell surface markers to distinguish between subsets. In general, among the MDSCs defined as CD33⁺CD11b⁺HLA-DR^{lo/-}, the CD14⁺ MDSCs are thought to resemble murine monocytic MDSCs, while the CD14⁻ MDSCs are compared to the murine granulocytic subtype (17). Continuing this comparison to the murine paradigm, one would expect that the CD14⁺ monocytic MDSCs would use iNOS and arginase-1, while the CD14⁻ granulocytic MDSCs would use ROS and arginase-1. However, unlike their mouse counterparts, both CD14⁺ and CD14⁻ MDSCs share the same mechanism of suppression as they have both been reported to suppress T-cell proliferation and IFN- γ production using ROS generated by NADPH oxidase (18-20).

Human MDSCs are also capable of producing arginase, as CD14⁺HLA-DR^{low/-} MDSCs from hepatocellular carcinoma patients displayed elevated arginase activity that not only inhibited T-cell proliferation but also induced IL-10-producing Tregs, which further dampen the immune response (21).

Although several studies report that MDSCs inhibit natural killer (NK) cell activity, the mechanisms underlying MDSC-mediated inhibition of NK cell responses are elusive.

CD14⁺HLA-DR^{low/-} MDSCs from hepatocellular carcinoma patients were found to suppress NK cell cytotoxicity and IFN- γ release (22). This suppression was an arginase-1 independent, contact-dependent effect that required the expression of a natural killer (NK) cell receptor, NKP30. In murine studies, MDSCs that expanded in tumor-bearing mice inhibited NK cell cytotoxicity, IFN- γ production, and expression of the activating receptor NKG2D, through membrane-bound transforming growth factor- β 1 (TGF- β 1) (23). Surprisingly, MDSCs were also reported to activate NK cells by inducing the expression of Rae-1, a ligand for NKG2D (24). In this study, the interaction of NK cells with MDSCs from RMA-S tumor-bearing mice resulted in NK cell activation and copious production of IFN- γ . Although intriguing, it is important to note that NK cell development and function are highly dependent on the expression of MHC class I. Therefore, it is likely that the interaction of NK cells with MDSCs from RMA-S tumor bearing mice would alter NK cell function, leading to MDSC-mediated activation rather than suppression. Thus, our current understanding of MDSC biology indicates that MDSCs suppress NK cells just as readily as they suppress T cells.

Not surprisingly, in addition to interacting with T cells and NK cells, MDSCs have also been reported to hamper antigen-presenting cell (APC) functions. The accumulation of MDSCs in cancers is often accompanied by the lack of DC maturation (25, 26). In the tumor microenvironment, MDSCs prevent DCs' ability to uptake antigen, thereby limiting a key contribution of DCs to the immune response (27). MDSCs also reduce the efficacy of DC vaccines by inhibiting the migration and T-cell activation capacity of DCs (28), consistent with their ability to reduce DC and T-cell-stimulating activity (29).

Contrasting reports of the need for cell-cell contact for MDSC-mediated suppression further complicate our understanding of this population. While a more extensive review of this subject can be found elsewhere, a cursory overview of the literature suggests that several suppressor functions of MDSCs are dependent on cell-cell contact (14, 30). Considering that ROS, NO, and iNOS are all soluble, short-lived mediators, such a need for cell-cell contact is not unexpected, as it reduces the distance between these effector molecules and their target cells. However, these cells also produce factors that remain stable in blood and act at long distances, hinting at the existence of cell-contact independent effector functions (Goh and Hahn, unpublished data). Such an ability to use multiple mechanisms of suppression makes MDSCs a versatile and potent population of cells, allowing them to effectively hinder our physiological and synthetic efforts at boosting immune responses within tumors (Fig. 1).

Factors involved in promoting the generation and accumulation of MDSCs

Studies examining the pathogenesis of tumor development have elucidated several mechanisms that direct the generation, recruitment, and accumulation of MDSCs. The tumor microenvironment is a dynamic participant in the recruitment of suppressive immune cells including MDSCs. Tumor and stroma-derived factors induce the generation of MDSCs, their chemotaxis to the tumor site, and their survival within the tumor (31). Moreover, upon their initial appearance at the tumor site, MDSCs then further propagate and contribute to tumor growth by recruiting additional MDSCs and other immunosuppressive populations. Given the similarities in the microenvironments of tumors and of chronic inflammatory sites, it is

likely that viruses that establish chronic infections also change the local inflammatory response, thus recruiting MDSCs in a manner similar, if not identical, to tumors.

Generation of MDSCs

As a collection of myeloid progenitors and immature myeloid cells, MDSCs are induced by factors, including soluble mediators and transcription factors that affect the activation and differentiation of myeloid populations. Here we examine a selective group of mediators demonstrated to induce the generation of MDSCs.

A key mediator of inflammatory responses, prostaglandin E2 (PGE2) is derived from the common arachadonic acid product prostaglandin H2, through a reaction catalyzed by the enzyme prostaglandin synthase. PGE2 has a number of biological actions, both anti- and pro-inflammatory, including a prominent role in the generation of MDSCs. Recent studies demonstrate that administration of exogenous PGE2 can block the differentiation of DCs and redirect myeloid progenitors to adopt features characteristic of MDSCs (32). Additionally, a positive feedback loop between PGE2 and COX-2 induces the transcription of NOS2, indolamine-2,3-deoxygenase, and IL-10, all of which are classically immunosuppressive molecules (33-35). The importance of the PGE2-COX-2 axis to the generation of MDSCs is further accentuated by the significant improvement in prognosis with the administration of COX2 inhibitors in numerous cancers, including colon and ovarian carcinomas (36, 37). Since several tumors have been reported to express high levels of PGE2 (38), it seems likely that the effectiveness of COX2 inhibition on tumor growth is due in part to the decrease in the generation of MDSCs.

While the PGE2-COX-2 loop presents an attractive and readily available target for potential therapies, other factors that trigger the generation of MDSCs may not be as easily inhibited, given their roles in normal physiology. For instance, stem-cell factor (SCF), like PGE2, is also expressed by many human and murine cancers. Blocking SCF/c-kit signaling with anti-SCF small interfering RNA (siRNA) or anti-c-kit blocking antibodies resulted in fewer MDSCs at the tumor sites in mice, which corresponded with decreased tumor-specific T-cell anergy, T-regulatory cell (Treg) generation, and tumor angiogenesis (39). However, given that SCF is a necessary component of hematopoietic homeostasis, it presents a less attractive target than more redundant targets such as PGE2. In addition, MDSCs express high levels of HIF-1 α (40). HIF-1 α , whose expression is triggered by hypoxia, directly affects the functions of MDSCs in the tumor microenvironment, upregulating their iNOS and arginase-1 activities (41).

Tumors are also known to secrete copious amounts of IL-6 and macrophage colony-stimulating factor (M-CSF) (42, 43), both of which play a role in myeloid cell development yet also inhibit myeloid progenitors from differentiating into DCs (44). Multiple tumor cell lines were shown to upregulate expression of M-CSF (45), while IL-6 levels directly correlated with numbers of MDSCs *in vivo* (46). The influence of immune mediators in the generation of MDSCs is further evident in a study where blocking of IL-6 signaling significantly slowed tumor growth (47). This effect is explained in part by a decrease in activated signal transducer and activator of transcription 3 (STAT3), a key player in MDSC accumulation, as described below.

A member of the STAT family of transcription factors, STAT3 is a stronghold of cellular function, as it is downstream of several receptors, including a variety of anti- and pro-inflammatory cytokines. A number of reports pinpoint STAT3 hyperactivity as the culprit in arresting the differentiation of myeloid progenitor cells, particularly DCs, veering them instead towards an MDSC phenotype (48, 49). STAT3 signaling upregulates myeloid-related protein S100A9, which not only prevents DC differentiation but also contributes to

the accumulation of MDSCs (25). Furthermore, STAT3 enhances the immunosuppressive activity of MDSCs by upregulating NADPH oxidase, leading to increased ROS production (19). Not surprisingly, inhibition of STAT3 reduces the presence of MDSCs in tumors (50). Interestingly, the hepatic gp130 protein, an acute phase reactant that signals through STAT3, induces the accumulation of MDSCs as a mechanism of limiting inflammation (51). Thus, as with other strategies of immune evasion, STAT3's role in inducing the accumulation of MDSCs is a physiologically important process that is hijacked by tumors and very likely by chronic viral infections, in order to evade an effective immune response.

While the factors described thus far originate from the tumor itself, MDSC-generated mediators also appear to propagate the accretion of MDSCs. Tumors produce copious amounts of IL-1 β , which initiates the generation of MDSCs (52). In a murine model of IL-1 β -secreting breast cancer, surgical removal of the tumor alone did not curtail recruitment of additional MDSCs (53). In addition, the MDSCs generated during tumor development continued to synthesize IL-1 β even in the absence of the tumor, further propagating their recruitment. Similarly, the S100A8/A9 pro-inflammatory proteins, which also stimulate MDSC recruitment (54), are another class of molecules that are both tumor and MDSC derived (55). S100A9 is a member of the S100 family of calcium-binding proteins and is expressed in granulocytes, monocytes, and macrophages during acute and chronic inflammation. Binding of S100A9 to its receptor RAGE (receptor for advanced glycation end products) enhances arginase expression in a nuclear factor- κ B (NF- κ B)-dependent manner, increasing the suppressive capacity of MDSCs (6, 54, 55). Thus, the multitudes of factors capable of triggering MDSC generation indicate that MDSCs themselves play a prominent role in propagating their accumulation.

Chemotaxis of MDSCs

Considering that a large number of mediators produced by MDSCs act at short distances, it is necessary for these cells to migrate to the site of an ongoing immune response to fully exercise their immunosuppressive effects. MDSCs, or rather immature myeloid cells, are thought to originate in the bone marrow (6) and are increased in the blood, lymph nodes, and tumor sites of cancer patients (4). Egress from the blood to the tumor is dependent on CXCR4, which, not surprisingly, is also necessary for the chemotaxis of mature myeloid cells.

Several tumor-derived factors, such as TGF- β and PGE2, increase expression of chemokine receptors on MDSCs (56-58). TGF- β upregulates microRNA-494 (miR-494) in MDSCs, leading to a degradation of PTEN (phosphatase and tensin homolog) and concurrent increase in the CXCR4 expression (59). PGE2 can also induce the expression of CXCR4 and its ligand CXCL12 in a COX-2 dependent manner, allowing the influx of MDSCs to the tumor microenvironment (60). Moreover, among its many MDSC-related functions, IL-1 β also affects MDSC mobilization and recruitment (61, 62). As MDSCs themselves are able to produce IL-1 β (63), these studies are evidence of self-propagated and self-sustained mechanisms of generating and recruiting MDSCs to the tumor and presumably to other sites of chronic inflammation.

Survival of MDSCs

While the genetic abnormalities of malignant cells allow them to endure the harshness of tumor microenvironments, accessory cells, including MDSCs, have developed mechanisms that aid their survival without resorting to transformation. As mentioned above, TGF- β -mediated increase in miR-494 degraded PTEN in MDSCs, which, in turn, activated the phosphoinositol 3-kinase (PI3K)/Akt pathway, leading to enhanced activity of mammalian target of rapamycin (mTOR) and NF- κ B, both of which promote cell survival (59). Tumor

necrosis factor (TNF) has similar pro-survival properties, in that signaling via the TNF receptor 2 (TNFR2) on MDSCs upregulates c-FLIP [cellular FLICE (FADD-like interleukin-1 β converting enzyme) inhibitory protein] and consequently, inhibits caspase-8 activity (64). Moreover, TNF also activates NF- κ B and upregulates expression of COX-2 and PGE-2 (65), emphasizing the importance of this cytokine to MDSC biology. Yet again, IL-1 β has been implicated in the survival of MDSCs, as it promoted the accumulation of a subset of MDSCs lacking Ly6C (52). Although the exact signals mediating IL-1 β dependent survival of MDSCs are not known, it is likely that they are similar to the enhanced survival effect of IL-1 β on polymorphonuclear cells (66), especially since low levels of Ly6C are characteristic of granulocytic MDSCs.

The mechanisms orchestrating the generation and chemotaxis of MDSCs are just as heterogeneous and numerous as MDSCs themselves (Fig. 2). As more studies examining the appearance of MDSCs and their immunosuppressive function in non-cancer systems begin to emerge, it will be important to confirm if the same mechanisms are responsible for the recruitment of MDSCs in these settings. Findings from such studies will not only inform our understanding of the pathophysiology of malignant and non-malignant diseases but also may provide the basis for the development of targeted treatments with numerous clinical applications.

Epigenetic control of MDSCs

Considering that MDSCs are derived from the same pool of cells that give rise to non-immunosuppressive populations, their distinct ability to suppress other immune cells raises the possibility of changes in epigenetic signatures. A recent study reported that the histone deacetylase-2 (HDAC-2) was instrumental in repressing expression of the retinoblastoma (Rb) gene, which, in turn, converted monocytic MDSCs into granulocytic MDSCs (67). The results of this study present a mechanism for the generation of granulocytic MDSCs, which is especially promising, since HDAC inhibitors have long been explored as therapeutic agents for cancer treatment. However, the granulocytic MDSCs generated in the models used in this study did not acquire an immunosuppressive phenotype by mere repression of Rb; as the authors note, acquisition of suppressive properties was a product of the tumor microenvironment, once again emphasizing the crosstalk between tumors and MDSCs.

The results of this study (67) prompt a slew of questions regarding other epigenetic mechanisms that control MDSC function. In particular, what are the changes in chromosomal modifications brought about by the action of tumor-derived factors on infiltrating MDSCs? For instance, HDAC-11 was found to repress expression of IL-10, a key immunosuppressive cytokine that is copiously produced by MDSCs; conversely, inhibition of HDAC-11 upregulated IL-10 expression (68, 69). Tumor-derived factors could therefore inhibit the expression or activity of HDAC-11, allowing MDSCs to adopt their characteristic immunosuppressive phenotypes. On the other hand, low doses of the DNA methylation inhibitor zebularine were shown to decrease expression of indoleamine 2,3-dioxygenase (IDO), a potent immunosuppressive mediator employed by MDSCs (70). Accordingly, be it methylation or acetylation, epigenetic changes may dictate both the morphology and suppressive functions of MDSCs, highlighting the various levels of regulation that distinguish this population.

MDSCs in viral infection

The molecular events dictating the role of MDSCs in cancer have been extensively studied, as described above, and are detailed in other reviews (71-73). Recently, MDSCs have been reported in a variety of non-tumor pathologies, including bacterial (74), parasitic (75), fungal (76), and viral (18) infections. MDSCs generated during viral infections are

particularly interesting, because many viruses are not only oncogenic but also are capable of establishing chronic infections that result in a dysfunctional inflammatory environment similar to that of tumors. Potent pro-inflammatory cytokines, such as TNF- α and IL-1 β , are elevated in chronic viral infections and as mentioned above, promote the survival and accumulation of MDSCs (61, 64). Moreover, oncogenic viruses, such as hepatitis B virus, human papillomavirus, and Epstein-Barr virus, establish cancers that have a documented increase in MDSCs (29, 40, 77). Whether the influx of MDSCs in these tumors is due to virus-derived factors, chronic inflammation, or simply a consequence of the crosstalk between the tumor and the immune system is an exciting question that remains to be explored.

Similar to the variety of MDSC-recruiting mechanisms employed by cancers, viral infections also utilize diverse pathways to induce local and peripheral accumulation of MDSCs. In addition, more than one subset of MDSCs with different mechanisms of suppression can be found in the same type of cancer or viral infections (18, 78, 79). Here, we elaborate on a short but growing list of viruses that are known to generate MDSCs in murine and human infections.

Hepatitis C virus (HCV)

The bloodborne pathogen HCV is remarkably efficient at persisting in the presence of an ongoing immune response, as it establishes chronic infection in nearly 80% of infected individuals, putting them at an increased risk of developing fibrosis, cirrhosis, and hepatocellular carcinoma. We and others have reported that the HCV core protein plays a critical role in the pathogenesis of hepatitis C, as it can inhibit T-cell activation and proliferation (18, 80, 81), IL-12 production by macrophages (82), and apoptosis of infected hepatocytes (83). We had previously demonstrated that the core protein is also able to activate the STAT3 pathway in APCs (84). As discussed above, STAT3 is known to stimulate generation of MDSCs, prompting us to consider if this were also the case in HCV infection. In fact, we discovered that the core protein is a potent inducer of MDSCs: addition of core to healthy human peripheral blood mononuclear cells (PBMCs) produced a distinct population of CD33⁺CD11b⁺HLA-DR^{lo/-}CD14⁺ cells, which effectively suppressed CD4⁺ and CD8⁺ T-cell proliferation and IFN- γ production in a ROS-dependent manner (18). Furthermore, this population of MDSCs was also found in the blood of hepatitis C patients, confirming that core is able to induce production of MDSCs *in vivo*. Besides the core protein, it is quite likely that other components of HCV that contribute to immune evasion (85) are also able to generate MDSCs in an effort to subvert the immune response. This is further supported by the recent discovery that MDSCs in the blood of chronically infected HCV patients decrease transiently during antiviral therapy (86). Notably, the MDSCs reported in this study suppress T-cell proliferation via an arginase-1-dependent mechanism in contrast to the ROS-dependent suppression we observed in our studies. One explanation for this discrepancy is that slight differences in viral factors from different viral isolates can direct the development of specific MDSC subsets. Nonetheless, our findings thus far indicate that virally derived factors play a direct role in recruiting MDSCs over the course of infection.

Inflammatory mediators generated during infection could also contribute to the recruitment of MDSCs. IL-1 β , which is increased not only upon infection with HCV *in vitro* (87) but also in the blood and livers of HCV-infected patients (88), promotes survival of MDSCs in the tumor microenvironment (52). Consequently, it may play a similar role in generating MDSCs during HCV infection. However, given that IL-1 β is present in nearly every immune response, this effect is unlikely to be specific to HCV and may instead represent a more general mechanism of MDSC generation. Also noteworthy is that HCV-infected patients with genetic polymorphisms in the COX-2 promoter region show different levels of hepatic

inflammation and fibrosis (89). Given that COX-2 affects MDSC accumulation (90), it is plausible that COX-2 plays a role in the generation of MDSCs in HCV infection, perhaps contributing to the transformation of an acute infection into a chronic disease.

Human immunodeficiency virus (HIV)

Intent on crippling the adaptive immune response, HIV joins the list of viruses that are able to generate MDSCs to facilitate their propagation (91). Specifically, HIV's transcriptional transactivator (Tat) protein adds to the immunosuppressive environment by inhibiting MHC class II expression (92), which is characteristically low on human MDSCs. Tat was also shown to convert healthy human PBMCs into CD33⁺CD11b⁺HLA-DR^{-/low} MDSCs (78). These results were further confirmed *in vivo* by studies demonstrating that HIV-1 seropositive patients had increased numbers of CD33⁺CD11b⁺HLA-DR^{-/low}CD14⁺CD15⁻ monocytic MDSCs in their peripheral blood, which suppressed T-cell proliferation via arginase-1. Treatment with highly active antiretroviral therapy (HAART) produced a significant decrease in MDSCs, which was matched by a steep drop in viral load. Interestingly, the authors of this study, Qin *et al.* (78), did not find a notable difference in granulocytic MDSCs in HIV infection. In contrast, Vollbrecht *et al.* (93) reported that HIV patients who did not receive HAART had elevated levels of CD33⁺CD11b⁺CD14⁻CD15⁺ granulocytic MDSCs when compared to healthy controls, which decreased upon treatment with HAART. The difference in subsets of MDSCs generated in the two cohorts of HIV patients cannot be dismissed and might hint at the influence of genetic and/or environmental differences, since the two studies were conducted in geographically and culturally distinct locations. These findings thus add another layer of complexity to MDSCs, substantiating this population as a mysterious and formidable player in immune responses to viral infections.

Vesicular stomatitis virus (VSV)

VSV is a negative-strand RNA virus that can infect a variety of animals, including humans, in whom it typically causes an acute, mild, flu-like disease. Recent years have brought to light the immense therapeutic potential of this virus, as VSV-based vaccines can deliver antigens specific to tumors and other pathogens (94). A recent study reported an increase in splenic MDSCs in C57BL/6 mice infected with VSV (95). Interestingly, MDSCs were generated only during a relatively prolonged infection of 5 days and were decreased when the infection was limited to 1 day, suggesting that MDSCs are recruited only during sustained immune responses. Of course, 5 days is considered acute when compared to the length of chronic viral infections in humans; however, the relative increase in MDSCs from day 1 to day 5 suggests that persistence of the virus in this system may reflect the processes seen in actual chronic viral diseases. The preceding experiments of this study also demonstrated an increase in the proportion of MDSCs among bone marrow-derived DCs upon protracted treatment with polyinosinic-polycytidylic acid [poly(I:C)], a synthetic mimic of double-stranded RNA. These observations, although from a single study, hint that sustained viral presence triggers the production and accumulation of MDSCs. Although the mechanisms underlying this process have not been determined, it is possible that prolonged activation of viral recognition pathways produces signals necessary for induction of MDSCs. Indeed, myeloid differentiation factor 88 (MyD88), a key adapter molecule in Toll-like receptor (TLR) signaling, was found to be essential for the generation of MDSCs in a mouse model of sepsis (96). These results are somewhat not surprising, as TLR signaling through the adapter molecule MyD88 plays a direct role in MDSC expansion (97). Accordingly, it may not be farfetched to suppose that prolonged stimulation of an analogous viral recognition molecule plays a similar role in triggering the production of MDSCs in chronic viral infections.

Vaccinia

A member of the pox family of viruses, vaccinia is a double-stranded DNA virus whose infamy as the etiological agent of smallpox has faded in light of its use as a vaccine for other infectious diseases and vector for gene delivery. Additionally, vaccinia is also a potent stimulant for the production of MDSCs: a rapid increase in MDSCs appears at the site of vaccinia infection in C57BL/6 mice (98). In contrast to VSV, vaccinia-mediated MDSC production peaked within 1 day of infection, although this increase was limited to the site of infection and was absent in the spleen. The disparity in kinetics and location of MDSC accumulation might reflect the difference in route of infection—intravenous infection of VSV (95) versus intraperitoneal inoculation of vaccinia (98). Alternatively, immunogenicity of the viruses and/or heterogeneity of the MDSC subsets generated in each infection may also have influenced the timing and homing of MDSCs. Indeed, the finding that only granulocytic MDSCs produced during vaccinia infection suppressed NK cell responses highlights the importance of MDSC subsets in disease. Although monocytic MDSCs were also increased at day 1 post-infection, they were dispensable for suppression of NK cells. *In vivo* depletion of MDSCs using anti-Gr-1 antibodies, which would target both monocytic and granulocytic MDSCs, decreased viral load, while increasing mortality and IFN- γ production by NK cells (98). The rapidity with which MDSCs are generated during vaccinia infection additionally identifies them as constituents of a normal acute immune response that are recruited to contain inflammation. Further understanding of the physiological role of MDSCs might provide additional means of regulating their contribution to a variety of diseases.

Adenovirus

Adenovirus is yet another DNA virus that can induce granulocytic MDSCs to suppress NK cell proliferation and activation via hydrogen peroxide (99). C57BL/6 mice intravenously infected with adenovirus generated a substantial population of MDSCs, the depletion of which enhanced NK cell activity and viral clearance. Remarkably, infected mice displayed a dramatic increase in splenic granulocytic MDSCs as early as 4 hours post-infection, which gradually decreased to basal levels within 72 h. By contrast, the same subset of cells (CD11b⁺Ly6G⁺Ly6C^{lo}) was present in high numbers in the bone marrow before infection, because the markers used to define murine MDSCs are also characteristic of the majority of immature myeloid cells. Intriguingly, the bone marrow displayed a marked decrease in granulocytic MDSCs and subsequent increase to pre-infection levels that followed a pattern of kinetics opposite to the influx of MDSCs in the spleen. The authors of the study interpreted these results as evidence of migration of MDSCs from the bone marrow to the spleen. If true, it is surprising that granulocytic MDSCs selectively migrated out of the bone marrow, as there was no difference in monocytic MDSCs in the spleen or bone marrow over 72 h post-infection; selective depletion of monocytic MDSCs also failed to improve NK cell function. The most obvious explanation for these results would be a molecular gradient that is chemotactic to granulocytic MDSCs alone. If so, identifying the factors involved in responding to this gradient presents an exciting opportunity to modulate the recruitment of different subsets of MDSCs.

MDSCs as therapeutic targets

The breadth of studies demonstrating the benefit of eliminating MDSCs in tumors cannot be contested. From chemotherapies that increase anti-tumor immunity by countering MDSC-mediated suppression of T cells (100, 101) to tumor vaccines that convert MDSCs to pro-inflammatory cells that limit tumor growth (102), the reduction of MDSCs in the setting of cancer is undoubtedly beneficial. Besides traditional cancer treatments, there are several existing pharmaceutical agents that show promise in targeting MDSCs. Foremost among

these, as discussed above, are COX-2 inhibitors, as the importance of the PGE2-COX-2 axis to MDSC generation cannot be understated. COX-2 inhibitors are well known to reduce the incidence of numerous cancers (103, 104) via transcriptional changes that can downregulate MDSC trafficking to the tumor site (105). While these agents inhibit the generation and recruitment of MDSCs, inhibitors of phosphodiesterase-5 disable the functional machinery of this population by decreasing expression of arginase-1 and iNOS2 (106). Similarly, all-trans retinoic acid (ATRA), originally used in the treatment of acute promyelocytic leukemia, stimulates MDSCs to complete maturation, a process that may be aided by NKT cells; ATRA also induces expression of glutathione synthase, which produces glutathione, a ROS neutralizing agent (107). Differentiation of MDSCs into mature myeloid cells can also be achieved by paclitaxel (108) or potent pathogen-associated molecular patterns, such as CpG oligonucleotides (109). This small but diverse list of agents that can manipulate MDSC populations may rise to a more prominent role as we improve our understanding of the role of MDSCs in cancer and chronic inflammatory conditions.

Conclusion and perspective

Considering that immune responses to viruses are increased upon eliminating MDSCs, it would be an easy conclusion to suppose that MDSCs play an equally harmful role in viral infections as they do in cancer. However, despite the emerging evidence presented in this review, it can be argued that the precise role of MDSCs in the pathogenesis of viral infections, especially chronic viral infections, remains to be defined and may in fact contradict our current understanding of their roles in certain human diseases. MDSCs are known to play a beneficial role in generating tolerance in autoimmune diseases and allograft transplantation (110, 111). Keeping their tolerogenic properties in mind, consider instead the following hypothesis: MDSCs hamper the development of effective immune responses during the acute phase of the immune response, yet limit the damaging effects of persistent inflammation once the infection has become chronic. In other words, MDSCs simply constitute the body's normal response to return to a homeostatic, non-inflammatory state. As such, it is possible that for infections with viruses such as HCV, where a significant proportion of patients do not respond to treatment and fail to clear virus, it may be of some benefit to promote the accumulation of MDSCs. Even though patients will continue to harbor virus, the increase in immunosuppressive cells will limit the damage caused by chronic inflammatory processes, thus slowing (but not stopping) the progression of disease to fibrosis and cirrhosis, both of which are accelerated by inflammatory mediators (112). Although this model is clearly not applicable to all viral infections, other diseases, such as hepatitis B and inflammatory bowel disease, which have a strong inflammatory component, may benefit from a similar approach. Therefore, the obvious benefit of eliminating MDSCs during the acute phase of viral infection might be negated in later phases of the disease. It will indeed be interesting to see if future studies find evidence for a favorable role for MDSCs in the pathogenesis and treatment of rampant inflammatory diseases.

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Fig. 1. Molecular mechanisms of MDSC action on other immune cells

MDSCs suppress T cells, NK cells, and other myeloid cells via a variety of mechanisms. T cells appear to be mainly suppressed via the production of ROS and RNS or via the depletion of L-arginine. On the other hand, MDSC-mediated inhibition of NK cell responses occur through either membrane-bound TGF- β or downregulation of NK cell activating receptor, NKp30. In contrast to the immunosuppression of MDSCs on NK cell responses, MDSCs are also shown to activate NK cells. In addition, MDSCs act on myeloid cells and affect their differentiation in a ROS-dependent manner. MDSCs, myeloid derived suppressor cells; NK, natural killer cell; ROS, reactive oxygen species; RNS, reactive nitrogen species; TGF- β , transforming growth factor- β .

Fig. 2. Factors involved in the generation and accumulation of MDSCs during viral infection
 Upon viral infection, infected cells produce factors, such as IL-6, M-CSF, and PGE2, which prevent the differentiation of MDSCs into mature macrophages and DCs. In particular, PGE2 upregulates COX-2, which increases the production of IDO and IL-10. Additionally, COX-2 acts in a positive feedback loop, generating more PGE2 that propagates immunosuppression. Under hypoxic conditions, upregulation of HIF-1 α augments the immunosuppressive effect of MDSCs by increasing NOS and arginase-1. As a key transcription factor involved in the differentiation of MDSCs, STAT3 is also found to play a role in increasing ROS production by MDSCs. Apart from suppressing other immune cells, ROS prevents MDSC differentiation into mature myeloid cells. Lastly, recruitment of MDSCs to the site of infection is directed by TGF- β produced by virally infected cells, which increases the expression of CXCR4 and its ligand CXCL12. MDSCs also produce factors such as IL-1 β that increase their accumulation. MDSCs, myeloid derived suppressor cells; IL, interleukin; M-CSF, macrophage-colony stimulating factor; PGE2, prostaglandin E; COX-2, cyclooxygenase-2; IDO, indoleamine 2,3-deoxygenase; HIF-1 α , hypoxia-inducible factor-1 α ; NOS, nitric oxide synthase; STAT3, signal transducer and activator of transcription 3; ROS, reactive oxygen species; TGF- β , transforming growth factor- β .

Table 1

Human and murine MDSC phenotypes.

	Granulocytic	Monocytic
Murine	CD11b ⁺ Ly6G ⁺ Ly6C ^{low} or CD11b ⁺ GR-1 ^{high}	CD11b ⁺ Ly6G ⁻ Ly6C ^{high} or CD11b ⁺ GR-1 ^{low}
	Mechanisms: ROS, Arg-1	Mechanisms: Nitric Oxide, Arg-1
Human	Lin ⁻ HLA-DR ^{low/-} CD33 ⁺ CD11b ⁺ CD14 ⁻ sometimes CD15 ⁺	Lin ⁻ HLA-DR ^{low/-} CD33 ⁺ CD11b ⁺ CD14 ⁺
	Mechanisms: ROS, NO, Arg-1 (specificity undefined)	