

Myeloid-Derived Suppressor Cells

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Abstract

Myeloid cells developed evolutionarily as a major mechanism to protect the host. They evolved as a critical barrier against infections and are important contributors to tissue remodeling. However, in cancer, myeloid cells are largely converted to serve a new master—tumor cells. This process is epitomized by myeloid-derived suppressor cells (MDSC). These cells are closely related to neutrophils and monocytes. MDSCs are not present in the steady state of healthy individuals and appear in cancer and in pathologic conditions associated

with chronic inflammation or stress. These cells have emerged as an important contributor to tumor progression. Ample evidence supports a key role for MDSCs in immune suppression in cancer, as well as their prominent role in tumor angiogenesis, drug resistance, and promotion of tumor metastases. MDSCs have a fascinating biology and are implicated in limiting the effects of cancer immunotherapy. Therefore, targeting these cells may represent an attractive therapeutic opportunity. *Cancer Immunol Res*; 5(1); 3–8. ©2016 AACR.

Introduction

Myeloid cells are a highly diverse population. Mononuclear myeloid cells include terminally differentiated macrophages and dendritic cells (DC), as well as monocytes, which under inflammatory conditions differentiate in tissues to macrophages and DCs. Granulocytic myeloid cells include populations of terminally differentiated polymorphonuclear neutrophils, eosinophils, basophils, and mast cells. Myelopoiesis in response to pathogenic stimuli is a fundamental mechanism protecting the host. It largely manifests in expansion of activated neutrophils and monocytes. Classical activation of these cells takes place as a response to strong signals that usually come in the form of pathogen-associated molecular patterns (PAMP) or danger-associated molecular patterns (DAMP) molecules. This activation is relatively short-lived and results in robust phagocytosis, respiratory bursts, and the release of proinflammatory cytokines. It terminates upon cessation of the stimuli. In contrast, the persistent stimulation associated with chronic infection, inflammation, or cancer involves relatively low-strength signals that induce modest but persistent myelopoiesis. Myeloid cells generated under these conditions, although similar to neutrophils and monocytes in morphology and phenotype, have different genomic and biochemical profiles and functional activity. The main functional characteristic of these cells is their potent ability to suppress various types of immune responses. It is possible that this mechanism evolved as a form of protection from extensive tissue damage caused by an uncontrolled immune response associated with unresolved inflammation.

Reports on the accumulation of immune-suppressive myeloid cells associated with tumor progression were published sporad-

ically beginning in the early 1970s (1). During the 1980s and early 1990s, work from the laboratories of Diana Lopez, Jim Talmadge, M. Rita Young, and Hans Schreiber demonstrated that various types of myeloid cells could inhibit immune function in cancer. However, the specific nature and biological significance of these cells remained largely unclear. The field started changing in the late 1990s when the Gr1⁺CD11b⁺ cellular phenotype was suggested as defining the immune-suppressive myeloid cells in spleens of mice and when these cells were shown to be phenotypically similar but functionally distinct from monocytes and neutrophils (2, 3). The observations of the accumulation in spleens and tumors of large numbers of these cells with potent immune-suppressive activity were readily reproducible in most murine tumor models. However, it quickly became apparent that CD11b⁺Gr-1⁺ cells were heterogeneous. Different phenotypic criteria and multiple mechanisms of action were used to define these cells. In 2007, in an attempt to unify different descriptions of these cells, the name myeloid-derived suppressor cells (MDSC) was proposed (4). This name was based on the myeloid origin of the cells and their main functional trait—potent immune-suppressive activity. In the following years, interest in these cells skyrocketed with almost 2,500 articles published in less than 10 years. MDSCs were implicated in various aspects of immune regulation, not only cancer, but also in diseases that involve chronic inflammation, infection, autoimmune diseases, trauma, graft versus host disease, etc. Evidence of the clinical significance of MDSCs in cancer has emerged, and MDSCs have become an important part of the tumor immunology field. However, as often happens with teenagers, MDSCs periodically have an identity crisis and a difficult relationship with the more established cells in the field. Only recently have MDSCs entered a more mature age where their identity and place among other myeloid cells have become clear.

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Main Phenotypic and Functional Characteristics of MDSCs

MDSCs consist of two large groups of cells termed granulocytic or polymorphonuclear (PMN-MDSCs), which are phenotypically

and morphologically similar to neutrophils, and monocytic (M-MDSCs), phenotypically and morphologically similar to monocytes. Therefore, phenotypic criteria alone are not sufficient to identify cells as MDSCs. In most types of cancer, PMN-MDSCs represent more than 80% of all MDSCs. In addition to these two main populations, MDSCs include a small group (less than 3%) of cells with myeloid colony-forming activity, representing a mixture of myeloid progenitors and precursors. In mice, MDSCs were mostly described in bone marrow, peripheral blood, spleen, liver, lung, or tumors of various organs. PMN-MDSCs can be defined as $CD11b^+Ly6G^+Ly6C^{lo}$ and M-MDSCs as $CD11b^+Ly6G^-Ly6C^{hi}$, with other markers under investigation. In humans, MDSCs were mostly described in blood and tumors of various organs with a number of studies describing these cells in bone marrow. Criteria for the phenotypic characterization of these cells by flow cytometry are now relatively well defined (5, 6). Among peripheral blood mononuclear cells (PBMC), PMN-MDSCs are defined as $CD11b^+CD14^-CD15^+$ or $CD11b^+CD14^-CD66b^+$, and M-MDSCs as $CD11b^+CD14^+HLA-DR^{-/lo}CD15^-Lin^-$ (including CD3, CD14, CD15, CD19, and CD56) $HLA-DR^-CD33^+$ cells contain mixed groups of MDSCs comprising more immature progenitors. The term "early-stage MDSC" (e-MDSC) has been proposed for this latter population (7).

In humans, M-MDSCs could be separated from monocytes based on the expression of the MHC class II molecule HLA-DR. Until recently, the only method allowing for separation of neutrophils from PMN-MDSCs in humans was gradient centrifugation using a standard Ficoll gradient. PMN-MDSCs are enriched in the low-density fraction (PBMCs), whereas neutrophils are high density cells (8). Recently, we identified lectin-type oxidized LDL receptor 1 (LOX-1) as a marker of PMN-MDSCs in humans (9). If confirmed in further studies, LOX-1 expression on neutrophils could be used for direct identification of PMN-MDSCs in blood and tissues. In mice, the phenotypic distinction between neutrophils and PMN-MDSCs in the same mouse is difficult. Several different markers were suggested, but thus far none of them allow for definitive identification of PMN-MDSC.

Immune suppression is a main feature of MDSCs. Although MDSCs are implicated in the suppression of different cells of the immune system, the main targets of MDSCs are T cells. The main factors involved in MDSC-mediated immune suppression include arginase (ARG1), iNOS, TGF β , IL10, COX2, indoleamine 2,3-dioxygenase (IDO) sequestration of cysteine, decrease of L-selectin expression by T cells, and many others. It is now clear that M-MDSCs and PMN-MDSCs utilize different mechanisms of immune suppression. M-MDSCs suppress T-cell responses both in antigen-specific and nonspecific manners, utilizing mechanisms associated with production of NO and cytokines, as reviewed in ref. 10. PMN-MDSCs, on the other hand, are capable of suppressing immune responses primarily in an antigen-specific manner. Induction of antigen-specific T-cell tolerance is one of the major characteristics of these cells (11, 12). Reactive oxygen species (ROS) production is essential for this ability. Reaction of NO with superoxide generates peroxynitrite (PNT), which directly inhibits T cells by nitrating T-cell receptors and reducing their responsiveness to cognate antigen-MHC complexes (13). PNT also reduces the binding of antigenic peptides to MHC molecules on tumor cells (14) and blocks T-cell migration by nitrating T-cell-specific chemokines (ref. 15; Fig. 1).

The large number of different immune-suppressive mechanisms described for MDSCs does not imply that these mechanisms are simultaneously operational. The prevalence of a particular immune-suppressive mechanism depends on the type of MDSC expanded, as well as on the stage of the disease and the site where the suppression is occurring. It is likely that at any given time a suppressive mechanism by MDSCs dominates and that this mechanism could change throughout the progression of the disease.

Besides immune-suppressive mechanisms, MDSCs promote tumor progression by affecting the remodeling of the tumor microenvironment and tumor angiogenesis, via production of VEGF, bFGF, Bv8, and MMP9 (16–18). MDSCs have been implicated in the formation of premetastatic niches (19–22) and the promotion of metastases by infiltrating primary tumors (23, 24). $CD11b^+Gr1^+$ cells oppose cellular senescence in a model of spontaneous prostate cancer by antagonizing IL1 α -mediated senescence (25). In contrast, another report indicates that $CCR2^+$ myeloid cells, represented largely by monocytic cells, support senescence in a model of liver cancer (26).

Major Mechanisms Regulating MDSC Accumulation and Differentiation

Accumulation of MDSCs is a complex phenomenon. We have previously proposed a two-signal model describing this process (27). This model asserts that accumulation of MDSCs requires two distinct, although partially overlapping, types of signals: The first is responsible for the expansion of the immature myeloid cells associated with inhibition of their terminal differentiation, and the second is responsible for the pathologic activation of these cells, converting immature myeloid cells to MDSCs.

The first group of signals is mostly driven by tumor-derived growth factors and involves such factors as STAT3, IRF8, C/EBP β , Notch, adenosine receptors A2b signaling, and NLRP3, as reviewed in ref. 27. The retinoblastoma protein 1 (Rb1) has also been implicated in the ability of some M-MDSCs to differentiate to PMN-MDSCs. Whereas $Rb1^{hi}$ M-MDSCs mainly give rise to macrophages and DCs, the vast majority of $Rb1^{lo}$ M-MDSCs differentiate toward PMN-MDSCs (28). The accumulation of $Rb1^{lo}$ $Ly6G^+$ PMN-MDSCs has been confirmed in the PyMT transgenic model of breast cancer (29).

The second group of signals is mediated by factors produced mostly by the tumor stroma (proinflammatory cytokines, HMGB1) and includes the NF- κ B pathway, STAT1, STAT6, prostaglandin E₂ (PGE₂), and cyclooxygenase 2 (COX2), as reviewed in ref. 27. The endoplasmic reticulum (ER) stress response pathway has been implicated in the suppressive activity of MDSCs. The ER stress response is an evolutionarily conserved mechanism developed to protect cells from various stress conditions, including hypoxia, nutrient deprivation, low pH, etc. MDSCs isolated from tumor-bearing mice and cancer patients overexpress several markers of ER stress, including transcription factors sXBP1 and CHOP, and display an enlarged ER, one of the hallmarks of ER stress (30). Administration of an ER-stress inducer to tumor-bearing mice increases the accumulation of MDSCs and their suppressive activity (31). Induction of ER stress with thapsigargin converts human neutrophils to immune-suppressive PMN-MDSCs (9). CHOP is implicated in the suppressive activity of MDSCs at the tumor site. CHOP-deficient MDSCs not only lose the ability to suppress T cells that had been stimulated in an antigen nonspecific manner, but can even stimulate T cells (32).

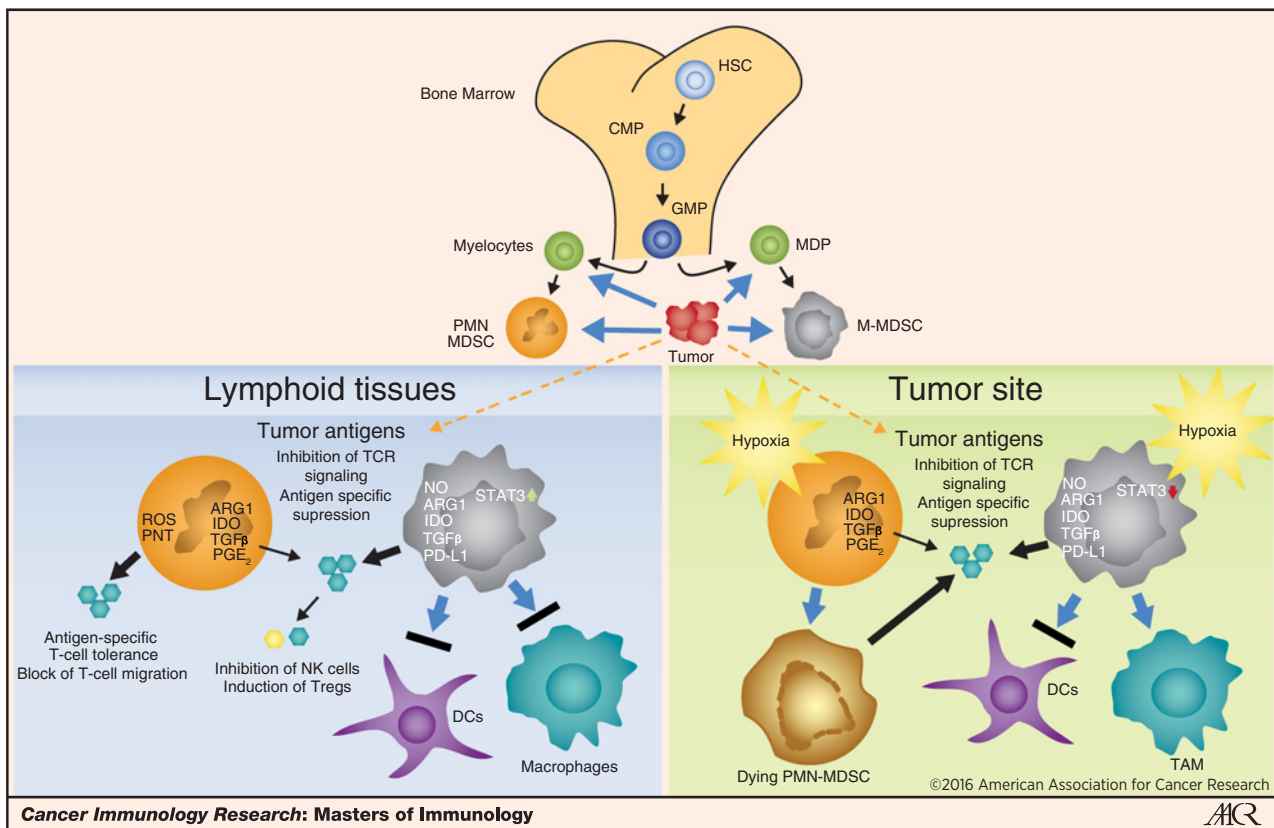


Figure 1.

Development and function of MDSCs. Tumor-derived factors affect different stages of myeloid cell differentiation, resulting in the generation of pathologically activated M-MDSCs and PMN-MDSCs. PMN-MDSCs and M-MDSCs migrate to lymphoid organs and to tumor sites. The function and fate of these cells are different in different sites. In peripheral lymphoid organs, PMN-MDSCs retain a high level of various ROS and cause antigen-specific T-cell suppression/tolerance. M-MDSCs produce large arrays of different factors that enable these cells to suppress not only antigen-specific, but also nonspecific T-cell, responses. M-MDSCs maintain highly activated STAT3 that prevents their quick differentiation to DCs or macrophages. At the tumor site, largely due to the effect of hypoxia, STAT3 activity in MDSCs is dramatically reduced. This results in rapid differentiation of M-MDSCs to TAMs. ROS levels in PMN-MDSCs are substantially reduced, but upregulation of ARG1 and other factors responsible for nonspecific T-cell suppression are increased. The same happens with M-MDSCs. PMN-MDSCs are dying rapidly. Factors released by dying cells can also contribute to immune-suppressive mechanisms. CMP, common myeloid progenitor; HSC, hematopoietic stem cells; GMP, granulocyte-macrophage progenitor; MDP, macrophage/dendritic cell progenitors.

However, CHOP-deficient MDSCs retain the ability to suppress the T-cell response generated from an antigen-specific stimulation (33). More studies will be necessary to clarify the role of the specific mechanisms of ER stress responses in MDSC function.

In tumor tissues, M-MDSCs rapidly differentiate to tumor-associated macrophages (TAM; refs. 34, 35). Downregulation of STAT3 activity in tumor-associated M-MDSCs has been implicated in this phenomenon. This effect was controlled by hypoxia-inducible activation of the CD45 phosphatase in these cells.

The Place of MDSCs among Other Myeloid Cells

MDSCs are pathologically activated myeloid cells. This raises the question of whether MDSCs are really different from neutrophils and monocytes. In many studies, cells with typical MDSC features were called monocytes and neutrophils, and cells were called MDSCs even in the absence of those features. Accumulated data allow us to draw a conclusion about the

specific nature of MDSCs. This conclusion is based on several lines of evidence.

- Immune-suppressive activity is an intrinsic feature of MDSCs. Mature neutrophils or monocytes cannot be converted to potent immune-suppressive cells *in vitro* (at a potency similar to MDSCs) by simply activating them with PAMPs and DAMPs or proinflammatory cytokines. In some cases, neutrophils actually promote antitumor response (36).
- Human PMN-MDSCs have a genomic expression profile that distinguishes them from neutrophils in the same patient, whereas neutrophils from healthy donors and cancer patients have very similar gene expression (9). Mouse MDSCs are also characterized by specific proteome (37–39) and transcriptome (40, 41) profiles.
- Phenotypically, M-MDSCs can be distinguished from TAMs by increased relative expression of F4/80, low to intermediate expression of Ly6C, low or undetectable expression of S100A9 protein, low expression of IRF8, and increased expression of

the CSF receptor CD115 (42). Most of the published data indicate that cells with the phenotype of inflammatory monocytes (CD11b⁺Ly6C^{hi}Ly6G⁻) in tumors have potent immune-suppressive activity and thus can be attributed to M-MDSCs (43).

- There are a number of biochemical features that clearly differentiate MDSCs from their control counterparts. These features include high arginase and iNOS expression and activity, high and persistent levels ROS, including superoxide, myeloperoxidase, hydroxyl peroxide, and PNT. PMN-MDSCs and M-MDSCs also can be distinguished from neutrophils and monocytes by their elevated ER stress response. More details are provided in a recent review (7).

Thus, MDSCs represent a relatively stable, distinct state of functional activity of neutrophils and monocytes. Although the PMN-MDSCs concept is widely accepted, there are number of studies that use different approaches to the nomenclature of tumor-associated neutrophils (TAN), based on the concept of phenotypic plasticity of TANs, which is modulated through distinct micro-environmental signals, at different stages of tumor progression (36, 44). In these reports, neutrophils with immunosuppressive and tumor-promoting functions are called N2, as opposed to antitumor, N1, neutrophils (8, 9). Although this point of view definitely has some rational basis, it is difficult to envision that short-lived, terminally differentiated PMN could be effectively polarized in tumor tissues. It is more likely that N1 cells represent activated bona fide PMN cells, whereas N2 cells are, in fact, PMN-MDSCs. Indeed, potent immune-suppressive activity by TANs has been reported a number of times, which supports these cells as PMN-MDSCs (45–47).

Better characterization of MDSCs in recent years has shed new light on MDSC biology. Evidence now links the accumulation of immature myeloid cells with an MDSC-like phenotype during chronic inflammation to the early stages of tumor development. Exposure of mice to cigarette smoke causes the accumulation of these cells in lungs and spleens (48). However, only after the development of lung cancer did these cells become immune-suppressive MDSCs. Nevertheless, their depletion increased survival (48). In a model of skin carcinogenesis, the accumulation in the skin of mice of immature myeloid cells without suppressive function promoted tumor development (49). This suggests that cells with an MDSC-like phenotype may play a significant role in tumor development and progression via mechanisms not necessarily related to their ability to suppress tumor-specific immune responses. It is possible that accumulation of MDSCs is a gradual process. Myeloid progenitors and precursors affected by low-strength pathologic signals coming from the developing tumor gradually acquire changes leading to their pathologic activation. Bona fide MDSCs are the last stage of this process. Cells at intermediate stages (MDSC-like cells), though not possessing potent immune-suppressive activity, may actively contribute to tumor progression and metastases. Future study will determine whether this concept is correct.

Basic Strategies to Therapeutically Target MDSCs

Ample evidence supports a close association between MDSC accumulation and clinical outcome in cancer patients (50, 51). A

meta-analysis of the studies of 442 patients with various solid tumors revealed that the association of MDSCs with poor overall and progression-free survival is highly significant (52). MDSCs are implicated in resistance to anticancer therapies, including sunitinib (53), cisplatin, and other chemotherapeutics in lung cancer (54–56), and doxorubicin and melphalan in multiple myeloma (57). The level of MDSCs is associated with patient responses to CTLA-4/ipilimumab (58, 59) and PD-1 (60, 61) inhibition.

The fact that MDSCs play an important role in the regulation of tumor growth has stimulated the search for a way to therapeutically target these cells.

MDSCs can be eliminated with relatively low doses of gemcitabine and 5-fluorouracil chemotherapy (62–64). Targeting the TRAIL receptor can be a potent and selective method of MDSC depletion (30). Peptibodies consisting of S100A9-derived peptides conjugated to antibody Fc fragments have shown potential in eliminating MDSCs in mouse models (65).

MDSCs can be functionally inactivated by targeting their suppressive machinery. Clinical reports indicate that head and neck and multiple myeloma cancer patients treated with the PDE-5 inhibitor tadalafil had fewer circulating MDSCs, lower iNOS and arginase expression in these cells, and a greater number of spontaneously generated tumor-specific T cells (66–68). Nrf2 is a transcription factor that plays an important role in cellular protection against free radical damage. Synthetic triterpenoid reduces both the production of ROS by MDSCs and their suppressive activity, by upregulating Nrf2 (69). Inhibition of COX-2 downregulates the production of immune-suppressive PGE₂, and nitroaspirin downregulates NO production (70, 71). Class I HDAC inhibitor entinostat has an inhibitory effect on MDSCs (72), although the mechanism behind the effect remains unclear.

MDSC expansion and differentiation can be targeted by all-trans-retinoic acid (ATRA) (73). In lung cancer patients, immune responses to a p53 vaccine were improved if the patients received a short course of ATRA (74). STAT3 inhibition can induce MDSC differentiation into immunogenic DC (75, 76). Phospholipid phosphatidylserine (PS)-targeting antibody decreases the frequency of MDSCs in tumor-bearing mice, although mechanism by which this occurs is also unclear (77).

Conclusions

MDSCs are a critical factor regulating immune responses under many pathologic conditions and have now become a prominent fixture of tumor immunology. However, their biological role can be established only if methods to selectively target these cells are developed. This requires specific markers of these cells to be identified, which would be possible if the molecular mechanisms governing the development of these cells were better characterized. Hopefully, the next couple of years will bring new and exciting data addressing those challenges.

Disclosure of Potential Conflicts of Interest

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