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Brief Reviews

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Myeloid-Derived Suppressor Cells: Immune-Suppressive Cells That Impair Antitumor Immunity and Are Sculpted by Their Environment

Suzanne Ostrand-Rosenberg* and Catherine Fenselau†

Myeloid-derived suppressor cells (MDSC) are a diverse population of immature myeloid cells that have potent immune-suppressive activity. Studies in both mice and humans have demonstrated that MDSC accumulate in most individuals with cancer, where they promote tumor progression, inhibit antitumor immunity, and are an obstacle to many cancer immunotherapies. As a result, there has been intense interest in understanding the mechanisms and in situ conditions that regulate and sustain MDSC, and the mechanisms MDSC use to promote tumor progression. This article reviews the characterization of MDSC and how they are distinguished from neutrophils, describes the suppressive mechanisms used by MDSC to mediate their effects, and explains the role of proinflammatory mediators and the tumor microenvironment in driving MDSC accumulation, suppressive potency, and survival. ***The Journal of Immunology*****, 2018, 200: 422–431.**

The term myeloid-derived suppressor cells (MDSC) was coined in 2007 to encompass a collection of nonmacrophage cells of myeloid origin that have potent immune-suppressive activity and are phenotypically characterized by a constellation of markers, none of which are unique to MDSC (1). The name was chosen because the cells encompass a range of immature cells whose unifying characteristics are their myeloid origin and their ability to suppress T cell activation and T cell function. Natural suppressor cells, which have a similar function, were reported in the 1980s (2–5), and reviewed previously (6). Such suppressor cells were largely ignored by immunologists until the late 1990s and early 2000s, when it became apparent that antitumor immunity was suppressed by cells of myeloid origin (7–12). As investigators became more aware of MDSC and tested for them in both cancer patients and mice with tumors, MDSC were increasingly recognized as a major spoiler of antitumor immunity because they accumulate in virtually all individuals with cancer (13, 14). This review will describe the basic features of MDSC and how they are identified, and will then examine some of the recent studies that have provided significant insight into how MDSC are induced and inhibit antitumor immunity, and how they are molded by the tumor microenvironment.

MDSC are immature myeloid cells

MDSC encompass a range of myeloid cells that are developmentally immature and in different stages of myelopoiesis. They are phenotypically defined by a constellation of markers. Because none of these markers are unique to MDSC, and some overlap with other cell populations, phenotyping in combination with assessing immune-suppressive activity is the optimal strategy for identifying MDSC. Because there has been considerable discussion about the nomenclature, phenotype, and function of this cell population, an international group of investigators in the field recently recommended nomenclature and characterization standards for MDSC (15). An international consortium of 23 laboratories has also been organized to test human MDSC with the goal of harmonizing staining and gating procedures for analysis of human MDSC (16). The phenotypes reported in these studies are used in the following descriptions and are shown in Fig. 1.

Initial studies identified two major subtypes of MDSC in mice, monocytic MDSC (M-MDSC) and granulocytic polymorphonuclear MDSC (PMN-MDSC) (17). M-MDSC are mononuclear and PMN-MDSC are polymorphonuclear. Both types express the myeloid lineage marker CD11b and the granulocytic marker Gr1. Gr1 includes two distinct molecules, Ly6C and Ly6G. M-MDSC have a lower level of expression of Gr1 and express Ly6C, whereas PMN-MDSC have higher levels of Gr1 and express Ly6G. The expression of additional markers varies depending on the tumor system. Functionally, mouse M-MDSC are also characterized by their high levels of NO and inducible NO synthase, whereas PMN-MDSC contain higher levels of reactive oxygen species (ROS).

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Abbreviations used in this article: Arg1, arginase 1; CHOP, C/EBP homologous protein; DC, dendritic cell; ER, endoplasmic reticulum; HDAC11, histone deacetylase 11; HMGB1, high mobility group box protein 1; IRF8, IFN-inducible regulatory factor 8; MDSC, myeloid-derived suppressor cell; M-MDSC, monocytic MDSC; Nrf2, NF erythroid 2–related factor 2; PMN-MDSC, polymorphonuclear MDSC; RAGE, receptor for advanced glycation end products; RORC1/RORγ, retinoic acid–related orphan receptor; ROS, reactive oxygen species; STAT3, signal transducer activator of transcription 3; VEGF, vascular endothelial growth factor.

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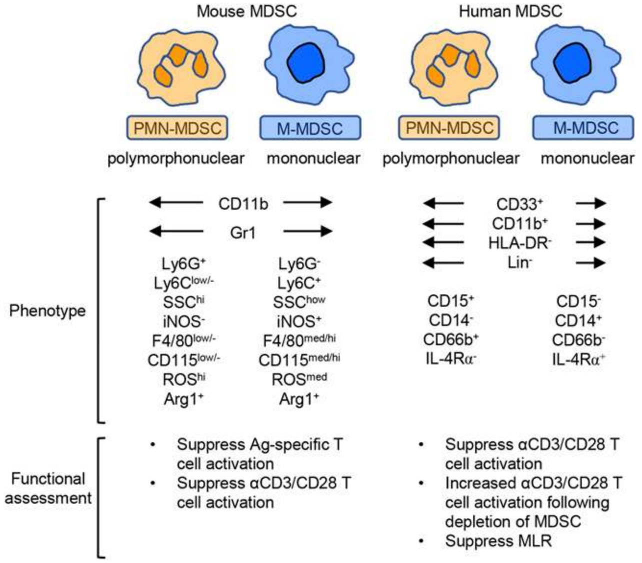

FIGURE 1. Phenotype and immune-suppressive functions of mouse and human M-MDSC and PMN-MDSC. Lin$^-$ indicates cells are negative for CD3, CD19, CD20, and CD56.

There are also two types of human MDSC. Both types express CD11b; however, there is no equivalent to the mouse Gr1 marker. Instead, human M-MDSC are characterized by their expression of CD14 and PMN-MDSC by their expression of CD15 and CD66b. Both types also express the general myeloid maker CD33 and lack linage markers for lymphocytes and NK cells. Because these markers are also expressed by monocytes, MDSC are distinguished from monocytes by their absence of HLA-DR.

Because human peripheral blood leukocytes are frequently cryopreserved prior to testing, the effects of these treatments on MDSC have been examined. PMN-MDSC are particularly sensitive to cryopreservation (18, 19). Likewise, both arginase 1 (Arg1) and ROS are lost with freezing (18). Given these constraints, phenotypic analysis of human MDSC is only accurate if fresh blood samples are tested. Mouse MDSC are typically assessed immediately after being harvested, so freezing is usually not performed; however, mouse M-MDSC and their functions are stable when frozen at liquid nitrogen temperatures.

PMN-MDSC and neutrophils share some common features but are functionally and phenotypically distinct

Defining PMN-MDSC as a distinct population has met with controversy among some investigators because PMN-MDSC and some types of neutrophils have a similar phenotype, and share a multilobed nuclear morphology and some common protumor functions (20–22). Although neutrophils traditionally may have antitumor activity, investigators have ascribed immune-suppressive activity to another group. The latter have been termed N2 neutrophils, whereas the former are N1 neutrophils (23, 24). The controversy over identification is whether N2 neutrophils are MDSC or vice versa. Multiple clinical studies have documented that patients with a variety of solid tumors who have a high baseline level of neutrophils in the blood or in the tumor mass have a poor prognosis and do not respond to medical interventions (reviewed in Refs. 25, 26). Because most studies use only markers shared by PMN-MDSC and neutrophils, it is not possible to retrospectively discern if neutrophils or PMN-MDSC were assessed.

However, there are definitive differences between classical neutrophils and PMN-MDSC. The transcriptomes of mouse neutrophils, tumor-associated neutrophils, and PMN-MDSC differ. Although neutrophils lack immune-suppressive activity, their mRNA repertoire is more similar to PMN-MDSC, whereas the transcriptome of tumor-associated neutrophils and PMN-MDSC are less related (27). The predominant differences are in cytokine and MHC Ag presentation transcripts. At the proteomic level, mass spectrometry studies also revealed that MDSC express a distinct profile (28–31), with S100A8 and S100A9 being prominently expressed by MDSC (28, 32).

PMN-MDSC and neutrophils also differ in their expression of at least some cell surface markers. For example, human neutrophils undergoing endoplasmic reticulum (ER) stress, as occurs within solid tumors, become immune-suppressive PMN-MDSC and express the lectin-type oxidized low-density lipoprotein receptor 1, *OLR1* (33). Similarly, tumor-induced MDSC from C57BL/6 mice express CD115 and CD224, whereas neutrophils express neither of these plasma membrane molecules (34). The latter study also demonstrated that whereas mouse PMN-MDSC expressed more Arg1, myeloperoxidase, and ROS, neutrophils produced more TNF-α and lysosomal proteins, and were more phagocytic.

Whether PMN-MDSC are a type of neutrophil or a distinct granulocyte population remains to be resolved. The distinction is relevant for semantic and categorization purposes. However, a goal of immunotherapy is to neutralize or eliminate immune suppression, so an in-depth understanding of the functional properties of relevant immune-suppressive cells is essential, and whether the cells are called PMN-MDSC or neutrophils may be less important.

Environmental conditions within tumors drive MDSC accumulation and suppressive potency

MDSC are generated in the bone marrow from myeloid progenitor cells and then traffic through the circulatory system where they can mix with circulating malignant cells of hematopoietic origin, or migrate into solid tumors. Tumor-produced growth factors are responsible for increasing the generation of M-MDSC and PMN-MDSC, and recruiting them from the bone marrow (and in mice also from the spleen) to solid tumors, and for sustaining their levels in blood. However, once in the tumor microenvironment most M-MDSC differentiate into immune-suppressive tumor-associated macrophages (35, 36).

The tumor microenvironment is a complex and evolving milieu of tumor cells and host cells, and there is extensive cross-talk between and among cell populations. This cross-talk reciprocally molds the phenotype and function of both MDSC and host tumor-infiltrating cells (37). Fig. 2 shows the growth factors and tumor microenvironment elements that regulate MDSC induction and accumulation and are discussed below.

Growth factors regulating myelopoiesis are important molecules for inducing the accumulation and suppressive activity of MDSC. Cancer patients frequently have abnormal or emergency myelopoiesis due to dysregulated production of hematopoietic growth factors. Vascular endothelial growth

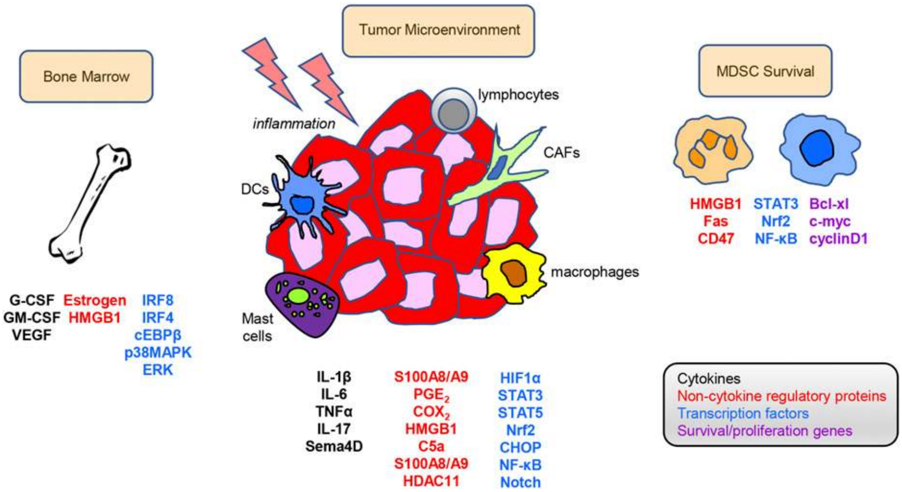

FIGURE 2. Cytokines, immune regulatory molecules, and transcription factors control the development, accumulation, suppressive potency, and survival of MDSC. Growth factors, hormones, and transcription factors that regulate myelopoiesis induce the expansion of MDSC in bone marrow. Within the proinflammatory tumor microenvironment a variety of cytokines and noncytokine regulatory proteins are produced by tumor cells and tumor-infiltrating host cells (e.g., DCs, lymphocytes, macrophages, mast cells, and fibroblasts) and increase MDSC suppressive potency by activating transcription factors and signal transduction pathways in MDSC. Survival of MDSC is mediated by many of the same factors and conditions that induce the accumulation of MDSC plus cell surface receptors and genes that prevent or limit apoptosis.

factor (VEGF) is predominantly thought of as a growth factor that supports tumor progression by promoting neoangiogenesis. It is frequently present and upregulated by hypoxia in the tumor microenvironment. Studies in non–small-cell lung cancer patients demonstrated that VEGF is a chemoattractant for MDSC (38–40), and mouse studies have demonstrated that MDSC produce VEGF (41). GM-CSF and G-CSF, important growth factors that regulate myelopoiesis, also drive the accumulation and suppressive function of MDSC in both mice (42–45) and patients (46) with cancer.

Emergency myelopoiesis, which is controlled by the C/EBPβ transcription factor, often accompanies the chronic inflammation that exists in many solid tumors, and is also present in other inflammatory conditions, including infections, autoimmunity, obesity, and stress. These conditions have led to the understanding that chronic inflammation is a major driving force for MDSC, and the hypothesis that one of the mechanisms by which inflammation drives cancer risk and tumor progression is through the suppression of antitumor immunity (47). Studies with tumor-bearing mice have shown that a variety of proinflammatory mediators can drive MDSC.

IL-6 and IL-1β are potent proinflammatory mediators that have been linked to the induction and progression of multiple cancers. Early studies using knockout mice and gene overexpression demonstrated the role of these molecules in driving both the accumulation and suppressive potency of mouse MDSC (48–51). IL-6 is likely downstream of IL-1β because MDSC induction is restored in IL-1R–deficient mice by provision of IL-6 (49). TNF-α, another potent proinflammatory mediator that is commonly found in the tumor microenvironment, also increases the quantity and suppressive activity of MDSC (52). Drug inhibition of TNF-α during early stages of inflammation allows immature myeloid cells to exit the MDSC state and differentiate into dendritic cells (DC) and macrophages. It also reverses the downregulation of the TcRζ chain in T cells that is characteristic of MDSC-mediated T cell suppression (53, 54).

PGE_2 and cyclooxygenase 2, the enzyme that generates PGE_2 from arachidonic acid, are key proinflammatory mediators that are produced by many mouse and human cancer cells. In vitro studies using PGE_2 receptor inhibitors, PGE_2 receptor knockout mice, and nonsteroidal anti-inflammatory drugs that block PGE_2 established that in mice PGE_2 drives the differentiation of MDSC from bone marrow progenitor cells (55–57). PGE_2 also drives the differentiation of MDSC from human hematopoietic stem cells (58), and for M-MDSC the induction is via the p38MAPK/ERK pathway (59, 60). PGE_2 drives the suppressive potency of MDSC by increasing their content of Arg1 (61).

IL-17 is another cytokine that is present in the environment of many solid tumors and regulates the accumulation and suppressive activity of MDSC. Studies in IL-17–deficient tumor-bearing mice demonstrated that IL-17 increases intratumoral levels of MDSC and raises their intracellular levels of Arg1, cyclooxygenase 2, and the immune-suppressive molecule IDO (62). PMN-MDSC and total MDSC levels are increased in colorectal cancer by the production of IL-17, TNF-α, and GM-CSF by γδ T17 cells (63).

Other mediators that are major contributors to an inflammatory tumor microenvironment have also been shown to induce MDSC. The proinflammatory calcium-binding proteins S100A8 and S100A9 are particularly active. These proteins function as a heterodimer (S100A8/A9) and are ubiquitously present in the microenvironment of most tumors. They are also present in the plasma membrane of tumor-induced mouse MDSC as shown by spectral counting and mass spectrometry (28). S100A8/A9 are regulated by signal transducer activator of transcription 3 (STAT3) and NF-κB, and their overexpression results in an increase in MDSC at the expense of fewer DC and macrophages (64, 65). MDSC themselves produce S100A8/A9, which increases MDSC suppressive activity and serves as a chemoattractant for MDSC. The heterodimer acts by binding to the N-glycan motif of the receptor for advanced glycation end products (RAGE) (65). Interestingly, TNF-α also drives the suppressive activity of MDSC by increasing S100A8/A9 levels that signal through RAGE (53).

Recent studies have identified even more factors that regulate MDSC levels and activity. High mobility group box protein 1

(HMGB1) is present in the nucleus where it forms a scaffolding for DNA, but when released from cells, functions as a damage associated molecular pattern molecule or alarmin. As for S100A8/A9, HMGB1 is ubiquitously present in the tumor microenvironment and RAGE is one of its plasma membrane receptors. HMGB1 drives the differentiation of MDSC from bone marrow progenitor cells, increases MDSC production of IL-10, enhances MDSC cross-talk with macrophages, and promotes MDSC-mediated downregulation of L-selectin expression on naive T cells.

Using head and neck squamous cell carcinoma cells, the induction of human MDSC has also been ascribed to semaphorin 4D, a proangiogenic cytokine that is produced by several types of cancers (66). Inhibition of semaphorin 4D in the supernatants of cultured head and neck squamous cell carcinoma cells resulted in decreased levels of MDSC with reduced content of Arg1, TGF-β, and IL-10, and concurrent restoration of T cell activation.

Estrogen also induces both mouse and human MDSC. In mouse tumor models in which the tumor cells are nonresponsive to estrogen, estrogen has been shown to dysregulate myelopoiesis and drive the accumulation and suppressive activity of MDSC (67). Estrogen mediates its effects by binding to its receptor on myeloid progenitor cells in bone marrow and subsequently activating the STAT3 pathway and enhancing JAK2 and SRC. These findings suggest that estrogen antagonists may decrease tumor progression and enhance antitumor immunity even in individuals whose tumor cells do not express estrogen receptors.

Complement has also been shown to modulate the antitumor immune response. Tumor progression has been demonstrated in mice carrying TC-1 cervical carcinoma to be reduced after knockout of complement proteins C3 or C4, and complement component C5a was found to drive accumulation of MDSC (68).

Because of the extensive redundancy in MDSC inducers, depletion of one mediator may be compensated by the presence of other mediators. As a result, elimination of a single inducer may reduce the levels and suppressive potency of some MDSC, but is unlikely to eliminate all MDSC.

MDSC survival

Circulating and tumor-infiltrating M-MDSC and PMN-MDSC have a short in vivo lifespan of ~1–2 d. PMN-MDSC also do not survive longer in vitro, whereas M-MDSC are viable in vitro for several days. Higher levels of inflammation result in more circulating MDSC, suggesting that inflammation may prolong the half-life of MDSC (49). Mass spectrometry studies identified Fas pathway and caspase network proteins in MDSC induced under a heightened inflammatory milieu, and cellular studies with Fas agonists demonstrated that inflammation increases MDSC resistance to Fas-mediated apoptosis (29, 69, 70). As described above, HMGB1 is a proinflammatory mediator that is ubiquitously present in the tumor microenvironment. In addition to driving the development of MDSC, HMGB1 also regulates MDSC survival by rendering MDSC more autophagic. MDSC in the blood have a default autophagic phenotype, and tumor-infiltrating MDSC are more autophagic due to the inflammatory tumor microenvironment (71).

Although ROS are toxic to most cells, MDSC are largely resistant to both their internal content of ROS and the ROS they release extracellularly. NF erythroid 2–related factor 2 (Nrf2), a transcription factor that regulates a battery of genes that ameliorate oxidative stress, enhances MDSC resistance to ROS. Studies with Nrf2-deficient mice demonstrated that Nrf2 reduces oxidative stress and apoptosis of tumor-infiltrating MDSC, thereby increasing the half-life of MDSC within solid tumors. Interestingly, these studies also demonstrated that there is a strong homeostatic regulation of MDSC and that when the half-life of tumor-infiltrating MDSC is decreased, there is a compensatory increase in the rate of MDSC production in the bone marrow so that steady-state levels of MDSC in the blood are maintained (72).

MDSC use a variety of mechanisms to promote tumor progression

MDSC mediate both immune- and nonimmune-suppressive mechanisms (Fig. 3). They promote tumor growth by facilitating neovascularization through their production of VEGF, and by driving invasion and metastasis through their production of matrix metalloproteases (41). Arg1 and ROS are the classic molecules used by MDSC to prevent T cell activation and function. Arg1 depletes arginine, an essential amino acid for T cell activation and function, whereas ROS kills target cells by causing oxidative stress. Because these mechanisms have been recently comprehensively reviewed in other publications (73–77), they will not be further described in this review.

MDSC also use other mechanisms to inhibit innate and adaptive immunity. They sequester cysteine, another essential amino acid for T cell activation and function (78), polarize macrophages toward a tumor-promoting phenotype by downregulating macrophage production of the type 1 cytokine IL-12 (79, 80), inhibit NK-mediated tumor cell lysis (81), and induce and recruit T regulatory cells (82–84). MDSC mediate these suppressive mechanisms by cell-to-cell contact with either T cells, macrophages, or NK cells, and these events predominantly occur in the tumor microenvironment. However, MDSC also inhibit T cell activation and function via a systemic mechanism involving MDSC-mediated downregulation of L-selectin (CD62L) on circulating naive T cells (85). L-selectin is essential for naive T cell extravasation from blood vessels and entry into lymph nodes and subsequent T cell activation in lymph nodes. Recent in vivo imaging studies have confirmed that while circulating in the blood, MDSC downregulate T cell expression of L-selectin, and this downregulation prevents naive T cells from entering lymph nodes and becoming activated (86).

MDSC also contribute to the process of malignant transformation and tumor progression through nonimmune-suppressive mechanisms. In a mouse model of epidermal carcinogenesis, immature myeloid cells with the phenotype of MDSC accumulated in the skin prior to the onset of malignancy. The MDSC secreted CCL4, which chemoattracted Th17-producing $CD4^+$ T cells and resulted in increased papilloma formation. Depletion of either CCL4 or the $CD4^+$ T cells prevented the effect, demonstrating that MDSC indirectly drive epidermal carcinogenesis (87). MDSC also promote tumor progression by endowing breast cancer cells with stem-like characteristics. They mediate this effect through their production of IL-6, which activates STAT3 in

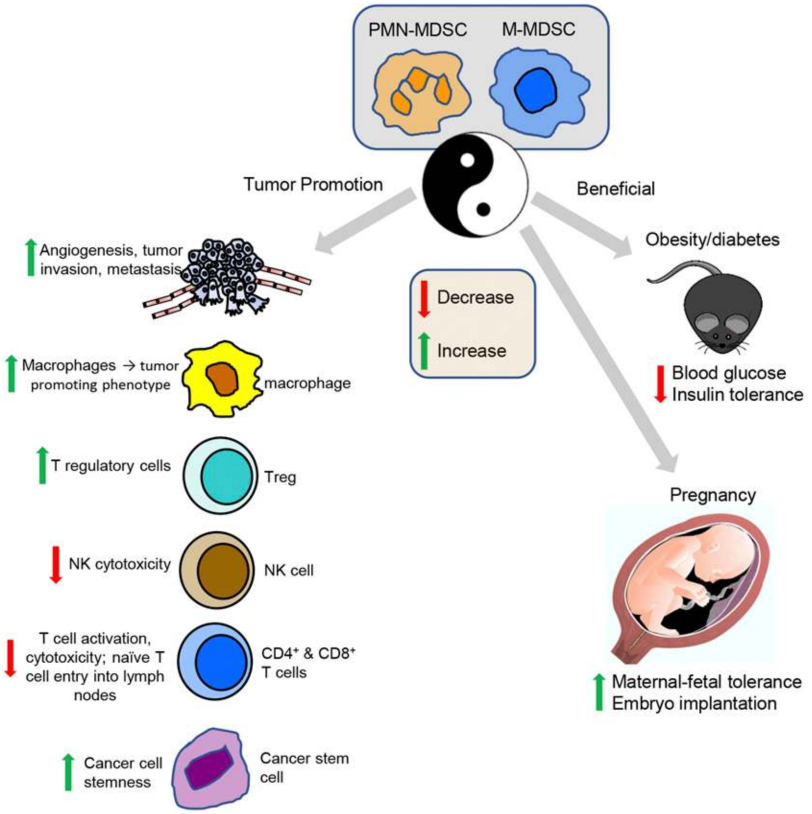

FIGURE 3. MDSC use a variety of immune and nonimmune mechanisms to promote tumor progression, but have beneficial effects in other settings. In individuals with cancer, MDSC inhibit adaptive antitumor immunity by suppressing $CD4^+$ and $CD8^+$ T cell activation and function, and by driving and recruiting T regulatory cells. They inhibit innate immunity by polarizing macrophages toward a type 2 tumor-promoting phenotype and by inhibiting NK-mediated cytotoxicity. MDSC also promote cancer cell stemness, facilitate angiogenesis, and drive tumor invasion and metastasis. Beneficial effects of MDSC include their lowering of blood glucose levels and reduction of insulin tolerance in obese individuals, and their maintenance of maternal-fetal tolerance and embryo implantation during pregnancy.

cancer cells, and by their production of NO, which activates the Notch pathway and sustains STAT3 activation (88). MDSC of ovarian cancer patients increased cancer cell stemness by driving miRNA101 expression in the cancer cells. miRNA101, in turn, downregulated the corepressor gene C-terminal binding protein-2, resulting in increased expression of cancer stem cell genes (89).

Cancer stem cells reciprocally effect MDSC. In a mouse model of glioblastoma, cancer stem cells were found to secrete macrophage migration inhibitory factor, which increased the suppressive potency of MDSC by increasing Arg1 levels via a CXCR2-dependent pathway (90).

MDSC accumulation and function are regulated by multiple transcription and epigenetic factors

MDSC are regulated through multiple and overlapping signal transduction pathways, demonstrating their ability to be induced and function by varied environmental conditions. This section will briefly review the more prominent pathways (see Fig. 2). A more in-depth description can be found in a recent review (91).

During normal myelopoiesis in healthy individuals, the common myeloid progenitor cell gives rise to DCs, macrophages, and granulocytes (neutrophils, basophils, and eosinophils). However, under the influence of tumor-produced factors including proinflammatory cytokines, myeloid cells deviate from their normal differentiation pathway and become immune-suppressive MDSC. Early studies identified STAT3 as a key player in the accumulation of mouse MDSC (92). Multiple subsequent studies confirmed the role of STAT3 (93). Established inducers of MDSC such as G-CSF, GM-CSF, and IL-6 act by turning on STAT3 (94). Given the critical role of STAT3, drugs that prevent STAT3 activation such as sunitinib have been used to limit the accumulation of MDSC in both mice and humans carrying tumors (95–97).

STAT3 promotes MDSC accumulation and function through multiple mechanisms. It facilitates the survival of both mouse and human MDSC by upregulating the proliferation gene cyclin D1 and the antiapoptotic genes Bcl-xl and c-myc (98, 99). It also induces S100A8/A9 expression, which drives the accumulation and differentiation of MDSC (64). Phosphorylation of STAT3 drives MDSC suppressive potency by increasing the expression of gp47 and gp91, two subunits of NADPH oxidase. NADPH oxidase generates superoxide by reducing oxygen (100). When superoxide reacts with NO, peroxynitrite is produced. Peroxynitrite released by MDSC nitrates the TcR and MHC class I, thereby perturbing T cell recognition and preventing both T cell activation and T cell function (101, 102). MDSC that are deficient for $gp91^{phox}$ lack suppressive activity and differentiate to DC and macrophages (100). Phosphorylation of STAT3 is also likely to be responsible for the increased suppressive potency of MDSC within hypoxic regions of solid tumors because these regions contain activated hypoxia-inducible factor-1 α, which activates STAT3 (35, 36).

IFN-inducible regulatory factor 8 (IRF8) is another transcription factor that is important in MDSC accumulation. In contrast to STAT3, which promotes MDSC accumulation, IRF8 deters PMN-MDSC accumulation. IRF8 is activated in the GMP stage of myelopoiesis. It diverts differentiation away from granulocytic lineages and blocks the accumulation of MDSC because it prevents STAT3 activation and thereby limits the level of ROS. As a result, IRF8-deficient mice have high levels of PMN-MDSC (103, 104), and overexpression of IRF8 in the myeloid lineage reduces MDSC accumulation (105, 106). Similar to IRF8, IRF4 expression also decreases

MDSC levels in tumor-bearing mice, and myeloid-specific deletion of IRF4 produces an increase in MDSC (107).

Additional transcription factors and their receptors are also involved in regulating MDSC levels. C/EBPβ preferentially regulates M-MDSC because mice deficient for this transcription factor have reduced levels of M-MDSC (108). Likewise, elements of the ER stress pathway also contribute to MDSC accumulation. MDSC of both tumor-bearing mice and cancer patients contain elevated levels of C/EBP homologous protein (CHOP), an indicator of ER stress (109), and induction of ER stress in tumor-bearing mice increased the levels of tumor-infiltrating MDSC and increased their suppressive potency by upregulating Arg1 and inducible NO synthase (110). MDSC levels are reduced and the remaining MDSC lose their immune-suppressive function and become APCs in CHOP-deficient mice, indicating that CHOP is a positive regulator of MDSC (111). CHOP mediates this effect by impairing C/EBPβ signaling in MDSC, which, in turn, decreases MDSC production of IL-6. Translocation of NF-κB from the cytosol to the nucleus also enhances MDSC suppressive function. Studies have shown that such activation is MyD88 dependent and occurs in conjunction with TLR2- or TLR4-mediated signaling (112–114). The retinoic acid–related orphan receptor (RORC1/RORγ) directs emergency myelopoiesis in individuals with cancer, and ablation of RORC1 in hematopoietic cells reduces the accumulation of MDSC, and prevents tumor development. RORC1 is active in both mouse and human MDSC (and in macrophages) and acts by promoting C/EBPβ and suppressing negative regulators Socs3 and Bcl3 (115).

Accumulation and function of mouse MDSC are also regulated by an epigenetic mechanism. Production of the type 2 cytokine IL-10 is a key distinguishing characteristic of MDSC and contributes to the ability of MDSC to polarize immunity toward a tumor-promoting phenotype. Histone deacetylase 11 (HDAC11) regulates IL-10 production, and HDAC11-knockout mice have higher levels and more suppressive MDSC, suggesting that HDAC11 is a negative regulator for the development of MDSC (116).

Collectively, these studies demonstrate that MDSC are regulated by a variety of mechanisms and through multiple signal transduction pathways.

MDSC-derived exosomes are immune suppressive

In individuals with cancer, body fluids and the local tumor microenvironment contain an abundance of exosomal vesicles derived from tumor cells. These vesicles contain proteins, RNAs, and miRNAs, and act as intercellular messengers. Many of these vesicles contribute to the immune suppression common in cancer patients (117, 118), and in mouse models, tumor-derived exosomes have been shown to induce MDSC (119).

In addition to exosomes shed by tumor cells, host cells in the tumor microenvironment also generate exosomes, and recent studies demonstrated that MDSC-derived exosomes mediate some of the immune-suppressive effects attributed to their parental cells. Using mass spectrometry and bottom-up proteomic analysis, >400 proteins were identified in exosomes derived from mouse tumor-induced MDSC (120). Spectral counting demonstrated a greater abundance of 63 of these proteins if the MDSC developed in a more inflammatory tumor microenvironment, indicating that the level of inflammation impacts MDSC content. Chemotactic assays indicated that >90% of the MDSC-associated proinflammatory S100A8/A9 proteins were carried in exosomes. Functional studies demonstrated that the MDSC-derived exosomes efficiently polarized macrophages toward a type 2 tumor-promoting phenotype and were chemotactic for intact MDSC. Both activities were mediated by S100A8/A9 (120). A more recent proteomic analysis of 1188 proteins indicates that the neutrophil degranulation pathway is enhanced by inflammation in MDSC exosomes (121).

Mass spectrometry studies have also revealed that MDSC-derived exosomes contain ubiquitinated proteins using the conservative requirement that tryptic peptides contain glycinylglycine-modified lysine residues. S100A8/A9 and HMGB1 were among the ubiquitinated species detected (122). In vitro studies using Ab blocking demonstrated that ubiquitinated proteins in exosomes mediate MDSC chemotaxis (121). This latter observation is surprising because although ubiquitinated species are implicated in endosomal trafficking, their function in chemotaxis has not previously been reported.

In addition to delivering their soluble contents to target cells, MDSC-derived exosomes also display plasma membrane glycoproteins that impact target cell communication and function (28). Using cell surface chemistry, 93 N-linked glycoproteins were identified on the surface of parental tumor-induced MDSC (123). Of these glycoproteins, 21 were also present in the membranes of MDSC-derived exosomes, and included CD47, the "don't eat me" molecule, and its two ligands SIRPα and thrombospondin-1. In vitro studies demonstrated that exosomal CD47 served as a powerful chemotactic signal for parental MDSC with thrombospondin-1 being the predominant ligand and SIRPα playing a lesser role (123). Because CD47 protects cells from macrophage phagocytosis (124), MDSC expression of CD47 may be another mechanism sustaining MDSC survival in the tumor microenvironment.

Next-generation sequencing and bottom-up proteomics were used in an integrated study of proteins, mRNA, and miRNA carried in exosomes shed by MDSC (125). Over 40,000 mRNAs were present in the exosomes and ~34% of these mRNAs were more abundant in the exosomes than in parental MDSC. A majority of the mRNA transcripts found were capped and translationally competent. Over 1400 miRNAs were also present and approximately half of these were more abundant in MDSC that developed in a heightened inflammatory environment. In total, 91% of the proteins carried by these immunosuppressive exosomes were also encoded by the mRNA transcripts present, suggesting mechanistic redundancy. The mRNA and miRNA results also suggest that MDSC may amplify and sustain their immune-suppressive activity by transferring nucleic acids that have the potential to be incorporated into the genetic makeup of target cells.

Collectively, the studies with MDSC-derived exosomes demonstrate that MDSC mediate their suppressive effects not only directly but also indirectly via exosomes, thereby increasing the range over which they function.

Conclusions

During the last ~10 y MDSC have come to be recognized as a major obstacle to natural antitumor immunity and to many immunotherapies. This recognition has occurred as clinical studies have demonstrated the presence of MDSC in most cancer patients. The relevance of MDSC as roadblocks of antitumor immunity has been further recognized in the context of checkpoint inhibitor immunotherapy because MDSC are likely a limiting factor for the efficacy of checkpoint inhibition therapy (126–128).

Extensive work in mouse systems, and to a lesser extent in human systems, has demonstrated that MDSC are a heterogeneous population of immature myeloid cells that are induced by multiple myeloid growth factors and that inflammation is a key driving mechanism for enhancing MDSC levels and suppressive potency. Studies have also revealed that MDSC have significant plasticity and undergo cross-talk with their neighboring cells. Accordingly, accumulation and function of MDSC are dependent on and sculpted by their microenvironment. Furthermore, these multitalented cells use a variety of apparently independent mechanisms to impair antitumor immunity and promote tumor growth. Given the critical role that MDSC play as a spoiler of antitumor immunity, many ongoing studies are aimed at discovering therapeutic strategies for neutralizing or eliminating MDSC.

Given the detrimental effects of MDSC, one wonders why such a population of cells would be evolutionarily maintained. Recent work in two conditions provides potential insight into this question (see Fig. 3). During pregnancy, maternal tolerance is essential for maintenance of the allogeneic fetus, and there is evidence that maternal-fetal tolerance is at least partially due to MDSC. PMN-MDSC accumulate in the peripheral blood of pregnant women and in the cord blood of healthy newborns. Within days of giving birth, the level of MDSC in the mother's blood reverts to the levels of nonpregnant women. These MDSC share characteristics with tumor-induced PMN-MDSC in that they suppress T cell activation via Arg1 and ROS, and they polarize immunity toward a type 2 cytokine response (129, 130). Confirmation that these MDSC contribute to maternal-fetal tolerance and are not merely bystanders or passenger cells has been obtained in mice (131). Similar to pregnant women, levels of MDSC increase significantly in the blood of female mice carrying allogeneic fetuses, and MDSC are present in uteri containing viable fetuses. The cells are predominantly PMN-MDSC and suppress T cell activation and impair naive T cell trafficking into the lymph nodes. Knockout and replacement studies demonstrated that the MDSC are essential for successful implantation and maintenance of pregnancy. Low-grade inflammation occurs in the uterus following conception, providing a mechanism for the induction of MDSC during pregnancy.

MDSC also appear to play a beneficial role in the metabolic dysfunction associated with obesity and long-term high fat diet, situations in which low-grade inflammation is chronic (132, 133). Obese *Ob/Ob* mice or mice on a high fat diet for extended periods develop elevated blood glucose levels and insulin tolerance, and their levels of circulating MDSC and MDSC in adipose tissue increase significantly. Tumor progression is more rapid in these mice due to the elevated levels of MDSC. However, MDSC depletion further increases glucose levels and insulin tolerance, indicating that MDSC protect against metabolic dysfunction.

Therefore, although MDSC are detrimental in individuals with cancer because they suppress antitumor immunity and thereby promote tumor growth, they may have evolved because of their protective effects with respect to diet and pregnancy. Additionally, there may be no negative selective pressure on MDSC because cancer is predominantly a disease of individuals beyond reproductive age. We do not at present understand the evolutionary origin of MDSC. However, if the current obesity epidemic continues, and if MDSC continue to limit the metabolic dysfunction associated with obesity, then evolution may favor increasing MDSC levels, and the rates of tumor onset and progression may also increase.

Disclosures

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