Regulation of Tumor Metastasis by Myeloid-Derived Suppressor Cells

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Annu. Rev. Med. 2015. 66:97–110

First published online as a Review in Advance on October 9, 2014

The *Annual Review of Medicine* is online at med.annualreviews.org

This article's doi: 10.1146/annurev-med-051013-052304

Keywords

angiogenesis, tumor cell invasion, immune suppression, chemotherapy

Abstract

Accumulation of pathologically activated immature myeloid cells with potent immune-suppressive activity is one of the major immunological hallmarks of cancer. In recent years, it became clear that in addition to their immune-suppressive activity, myeloid-derived suppressor cells (MDSCs) influence tumor progression in a variety of ways. They are directly implicated in the promotion of tumor metastases by participating in the formation of premetastatic niches, promoting angiogenesis and tumor cell invasion. In this review, we discuss recent data describing various roles of MDSCs in the formation of tumor metastases.

INTRODUCTION

PMN: polymorphonuclear neutrophil

DC: dendritic cell

MDSC: myeloid-derived suppressor cell

PMN-MDSC: polymorphonuclear MDSC

M-MDSC: mononuclear MDSC

Myeloid cells are one of the largest groups of hematopoietic cells. They include mature, terminally differentiated cells—polymorphonuclear neutrophils (PMNs) and other granulocytes, macrophages, and dendritic cells (DCs)—as well as relatively immature cells, namely monocytes and granulocytic precursors. During the past decade, it has become clear that the hierarchical system of myeloid cell differentiation is not functional in cancer. Abnormal differentiation of the myeloid compartment is now considered one of the major immunological hallmarks of cancer. As a result, tumor-bearing mice and cancer patients accumulate immunosuppressive macrophages with enhanced ability to promote angiogenesis and tumor cell invasion, as well as ineffective antigen-presenting DCs that can in some cases directly inhibit immune responses. However, the most prominent change in the myeloid compartment in cancer is the expansion of pathologically activated immature myeloid cells with the potent ability to suppress immune responses (1). Although these cells had been observed in tumor-bearing hosts since the 1970s, their true biological role became appreciated only 15 years ago. These cells are now termed myeloid-derived suppressor cells (MDSCs) to reflect their origin and major function (2). It has become clear that MDSCs not only are an important element of negative regulation of immune responses in many pathological conditions, but also contribute greatly to other aspects of tumor growth. In recent years, MDSCs were directly implicated in the promotion of tumor metastasis. We briefly discuss the main features of MDSCs and in more detail review recent data describing important roles of these cells in tumor metastasis.

MAIN CHARACTERISTICS OF MYELOID-DERIVED SUPPRESSOR CELLS

Markers and Subsets of Mouse MDSCs

MDSCs represent a heterogeneous population of myeloid cells at different stages of differentiation (3). In mice, MDSCs are generally characterized by coexpression of myeloid lineage differentiation markers, Gr-1 and CD11b (4). It is now established that MDSCs consist of two major groups of cells with mononuclear and polymorphonuclear morphology. These cells can be identified with a combination of specific markers. Polymorphonuclear MDSCs (PMN-MDSCs) are defined as $CD11b^{+}Ly6C^{low}Ly6G^{+}$ cells and mononuclear MDSCs (M-MDSCs) as $CD11b^{+}Ly6C^{high}Ly6G^{-}$ cells (5, 6). PMN-MDSCs are the largest population of MDSCs in tumor-bearing mice, representing >80% of all MDSCs.

PMNs in tumor-free mice and PMN-MDSCs in tumor-bearing mice have similar morphology and phenotype (4, 7). However, they have many distinctive features. In contrast to PMNs, PMN-MDSCs inhibit antigen-specific T cell responses, and a substantial proportion of PMN-MDSCs express CD244 and the receptor for macrophage colony stimulating factors (M-CSFR). PMNs have significantly higher phagocytic activity, expression of lysosomal proteins, and production of tumor necrosis factor alpha (TNF-α) than do PMN-MDSCs. In contrast, PMN-MDSCs have higher activity of arginase 1 (arg-1) and myeloperoxidase and higher production of reactive oxygen species (ROS) than PMNs. Within 24 h in culture with granulocyte macrophage colony stimulating factor (GM-CSF), PMN-MDSCs acquire all characteristics of PMNs, and these cells become phenotypically and functionally indistinguishable (8).

M-MDSCs share the phenotype and morphology of $CD11b^{+}Ly6C^{high}Ly6G^{-}$ inflammatory monocytes. In contrast to PMN-MDSCs, M-MDSCs are proliferative cells (9). In a tumor site, they preferentially differentiate into immunosuppressive macrophages (10). A substantial

proportion of M-MDSCs, in contrast to monocytes, differentiates into PMN-MDSCs (9). This effect appears to be controlled by epigenetic silencing of retinoblastoma (*rb1*) tumor-suppressor genes. Tumor explant supernatants can induce the differentiation of monocytes into the PMN type of cells in vitro, suggesting that monocytes can be reprogrammed by tumor-derived factors rather than representing a separate developmental pathway (9).

MDSCs in Cancer Patients: The Phenotype and Clinical Relevance

During the past decade, accumulation of MDSCs has been reported in a large number of cancers (11). Historically, human MDSCs were defined as lineage markers (CD3, CD14, CD19, CD56)–negative, HLA-DR-negative, and CD33-positive cells copurified with mononuclear cells on ficoll gradient (2). More recently, the existence of two subsets of cells (similar to murine models) has been reported in cancer patients, and PMN-MDSCs are commonly characterized as $CD11b^{+}CD14^{-}$ cells expressing a granulocytic marker: CD15 or CD66b (12, 13). M-MDSCs are defined by two combinations of markers: $CD11b^{+}CD14^{-}CD15^{-}$ (or $CD66b^{-}$) or $CD11b^{+}CD14^{+}HLA\text{-}DR^{low}$ (14, 15). It is important to point out that, similar to mouse models, PMN-MDSCs represent the majority of MDSCs in most types of human cancer.

Although accumulation of MDSCs in cancer patients is widely appreciated (16), elucidating the clinical relevance of MDSC accumulation remains a work in progress. In recent years, a substantial number of studies have shown a correlation between the level of MDSC accumulation and stage, overall survival, and response to therapy. Accumulation of circulating MDSCs correlated with stage in patients with solid tumors (mainly breast cancer) (17), gastric cancer (18), and colorectal cancer (19, 20). MDSC accumulation in tumor sites (both primary and metastatic) has also been shown to correlate with overall survival and disease-free survival in patients with ovarian cancer (21). An increased level of PMN-MDSCs was detected in patients with pancreatic cancer (22) and renal cell carcinoma (23). Furthermore, in patients with small cell lung cancer, circulating MDSCs negatively correlated with the immune response to cancer vaccine (24). Targeting MDSCs in these patients substantially improved antigen-specific immune responses to vaccination (25). More recently, the clinical relevance of M-MDSC accumulation in cancer patients has been reported. The presence of circulating M-MDSCs was reported to correlate with the stage of hepatocellular carcinoma (26). The accumulation of M-MDSCs has also been reported to correlate with progression-free survival and response to chemotherapy, as well as metastatic burden, in melanoma and non–small cell lung cancer (NSCLC) (27–29).

MECHANISMS OF EXPANSION AND IMMUNE SUPPRESSION

MDSC Expansion

The mechanisms of regulating MDSC expansion are covered in other reviews (4, 30) and are not discussed in detail here. It is important to point out that expansion of MDSCs in cancer is largely driven by soluble tumor-derived factors. These factors include prostaglandins, GM-CSF, macrophage colony-stimulating factor (M-CSF), IL-1β, IL-6, vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), IL-10, IL-12, IL-13, and others (4). Most of these factors activate signaling cascades involving Janus tyrosine kinase (JAK) protein family members, as well as signal transducer and activator of transcription 3 (STAT3) (31). Several downstream targets include S100A8 and S100A9 proteins (32) and CCAAT-enhancer-binding protein beta (C/EBPβ) (33). Other mechanisms include interferon regulatory factor-8 (IRF-8)

(34), myeloid differentiation primary response gene 88 (*MyD88*), NF-κB (35, 36), prostaglandin E2 (PGE2) (37, 38), TNF (39), and more.

MMP: matrix metalloproteinase

MDSC-Mediated Immune Suppression

Numerous studies have established the potent immune-suppressive mechanisms of MDSCs (4). First to be discovered were ROS, arg-1, and nitric oxide (NO). More recently, it was shown that peroxynitrite (PNT), the product of interaction of superoxide and NO, could cause nitration of T cell receptor–CD8 complex, which reduced its binding to the peptide MHC class I complex and rendered T cells unresponsive to antigen-specific stimulation (40). PNT also hampered the recognition of cancer cells by cytotoxic T lymphocytes (41). Accelerated depletion of L-arginine and cysteine in the tumor microenvironment caused by MDSCs resulted in decreased CD3ζ chain expression, diminished production of IL-2 and IFN-γ, and inhibited T cell proliferation (42–44).

The two populations of MDSCs employ different mechanisms of immune suppression. PMN-MDSCs produce high levels of ROS and an undetectable amount of NO, whereas M-MDSCs have high levels of NO but undetectable ROS (5). Both populations use arg-1 for their suppressive activity.

Several studies showed the ability of MDSCs to induce differentiation and/or proliferation of $Foxp3^+$ Tregs; the various mechanisms included TGF-β (45, 46) and CD40 (47). However, one other study showed that MDSC-mediated Treg induction was TGF-β independent but required arg-1 (48). MDSCs also have the ability to recruit Tregs to the tumor site in a CCR5-dependent manner (49). Interestingly, this induction ability of Tregs seems to be restricted to the M-MDSC subset (50). In contrast, PMN-MDSCs did not promote Treg differentiation but actually showed the ability to impair TGF-β-induced Treg generation or proliferation (51).

IL-17 could be involved in the immune-suppressive function of MDSCs in a mammary carcinoma model. IL-17 increased the immune-suppressive function of MDSCs through the upregulation of arg-1, matrix metalloproteinase 9 (MMP-9), indoleamine 2,3-dioxygenase (IDO), and cyclooxygenase 2 (COX-2) (52). Transmembrane but not secreted TNF-α enhanced suppressive activity of MDSCs by upregulating arg-1 and inducible NO synthase (iNOS), promoting secretion of NO, ROS, IL-10, and TGF-β (53).

The nature of immune suppression by MDSCs can be defined by the local microenvironment. MDSCs from tumor tissues suppressed both antigen-specific and nonspecific T cell activity, whereas on the periphery, antigen-specific suppression was more prevalent (10). Exposure of splenic MDSCs to hypoxia resulted in the conversion of these cells to nonspecific suppressors, and hypoxia-inducible factor (HIF-1α) was found to be primarily involved in the observed effects (10).

ROLE OF MYELOID-DERIVED SUPPRESSOR CELLS IN TUMOR METASTASIS

In order to metastasize, tumors need to invade the surrounding tissue, enter the circulation, and seed and proliferate in a distant permissive niche. There is increasing evidence from preclinical and clinical studies that MDSCs play an important role in all steps leading to metastasis. Although the immune-suppressive activity of MDSCs is critically important for the formation of a metastatic niche, these cells employ a number of other mechanisms promoting metastases. In NSCLC patients, circulating $CD14^+HLA\text{-}DR^{low}$ M-MDSCs correlated with extrathoracic metastases (28). An increase in IDO-expressing $CD45^+CD33^+CD14^-CD15^-$ MDSCs in breast cancer tissue also correlated with increased lymph node metastasis in breast cancer patients (54). In patients with melanoma, the development of metastases and poor survival were associated with increases in both circulating $CD11b^+CD14^-CD15^+$ PMN-MDSCs (55) and M-MDSCs (56).

Table 1 Mechanisms of MDSC migration to the tumor site

Chemokine	Receptor	Type of MDSC recruited	References
S100A8/A9	RAGE	MDSC	69–71
CXCL1/CXCL2/CXCL5	CXCR2	PMN-MDSC (not confirmed yet)	58–61
CXCL12	CXCR4	MDSC	62
CCL2	CCR2	M-MDSC	63–65
MIF	CXCR4, CD74	MDSC, M-MDSC	67, 68

Abbreviations: MDSC, myeloid-derived suppressor cell; M-MDSC, mononuclear MDSC; PMN-MDSC, polymorphonuclear MDSC.

MDSC Migration to the Tumor Site or Premetastatic Niche

Several chemokines and chemokine receptors are involved in the recruitment of MDSCs to the tumor site or to the premetastatic niche (**Table 1**). Chemokines CXCL1, CXCL2, and CXCL5 have been shown to recruit MDSCs to the tumor site (57) or to the premetastatic niche (58–60). These chemokines bind to the same receptor, CXCR2. CXCR2 deficiency has been shown to decrease tumorigenesis and tumor growth owing to a strongly reduced accumulation of MDSCs (61). All these CXCR2 ligands are well known for their ability to recruit neutrophils, suggesting that they could mainly be responsible for the recruitment of PMN-MDSCs. However, this specificity remains to be confirmed.

CXCL12, which binds the CXCR4 receptor, has also been suggested to cause accumulation of MDSCs in tumors of patients with ovarian cancer (62). CCL2 and macrophage migration inhibitory factor (MIF), two chemotactic factors for monocytes, have been shown to specifically recruit M-MDSCs to tumors in mice and cancer patients (63–65). Interestingly, MDSCs via PNT release can nitrate CCL2, which prevents the chemokine from recruiting cytotoxic T lymphocytes but does not affect its ability to recruit MDSCs (66). MIF can promote tumor growth, associated with an increased accumulation of M-MDSCs inside the tumor (67). Accordingly, tumors deficient in MIF had lower levels of M-MDSCs (68). Proinflammatory proteins S100A8 and S100A9 are potent chemoattractants for MDSCs and have been implicated in the promotion of tumor growth and metastases by MDSCs (69–71). Further study demonstrated that serum amyloid A3 (SAA3) induced by S100A8/A9 directly attracted MDSCs to premetastatic lungs, stimulated NF-κB signaling in a TLR4-dependent manner, and facilitated metastasis (72). Thus, it appears that MDSC recruitment to tumor sites may represent a vicious circle: MDSCs initially recruited to the tumor site by tumor-derived chemokines can facilitate the recruitment of other MDSCs via release of S100A8/A9 proteins (58).

MDSC Effect on Angiogenesis

Rapid growth of solid tumors results in hypoxia, which induces upregulation of proangiogenic factors such as VEGF, PDGF, basic fibroblast growth factor (bFGF), and angiopoietins (73). Hypoxia can enhance MDSC migration to the tumor site via HIF-1α-mediated production of chemokines (58, 74). Inhibition of MDSC infiltration of the tumor site results in the inhibition of tumor angiogenesis (75). Another important proangiogenic factor secreted by MDSCs in the tumor site is bombina variegata peptide 8 (Bv8), which is upregulated by STAT3 (76). STAT3 can also directly induce the secretion of VEGF and bFGF by MDSCs (77). Bv8 production by PMN-MDSCs has been shown to promote lung metastasis (78). Blockade of Bv8 in combination with VEGF antibody showed an additive effect in inhibiting angiogenesis and tumor growth (79).

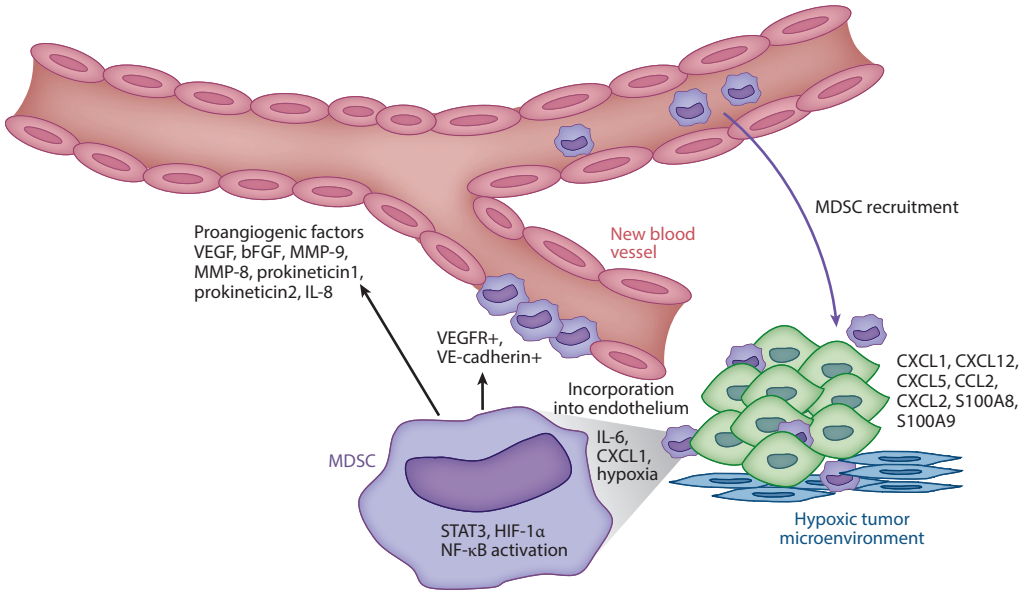

Figure 1

Effect of myeloid-derived suppressor cells (MDSCs) on angiogenesis. MDSCs are recruited to the tumor site by several chemokines and in the tumor microenvironment produce soluble factors promoting angiogenesis. Abbreviations: bFGF, basic fibroblast growth factor; HIF-1α, hypoxia-inducible factor; MMP, matrix metalloproteinase; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

Another important mechanism by which MDSCs can promote tumor neovascularization is by secreting MMP-9. MMP-9 promotes bioavailability of VEGF in the tumor microenvironment (**Figure 1**). There was a report that MDSCs could be directly incorporated into the vascular endothelium by differentiating into endothelial-like cells expressing VE-cadherin and VEGF-R2 (80). However, this observation was not directly confirmed by other studies.

Although VEGF antibody-mediated therapy has had some success in clinics, tumors eventually become refractory to this treatment. Recruitment of MDSCs is a key mechanism that mediates resistance to anti-VEGF therapy. MDSCs were able to promote new vessel growth even in the presence of VEGF antibody (81, 82). MDSCs have also been shown to mediate resistance to the tyrosine kinase inhibitor sunitinib, an antiangiogenic agent, in preclinical models of renal cell carcinoma (83). In patients with renal cell cancer, the clinical response to sunitinib inversely correlated with the presence of circulating PMN-MDSCs. These cells had increased levels of MMP-9, MMP-8, and IL-8, suggesting that MDSCs in sunitinib-resistant tumors could still promote angiogenesis through alternative mechanisms (83). The nature of those mechanisms needs to be elucidated.

Mechanisms of MDSC Effect on Tumor Metastasis

MDSCs' role in the promotion of metastases was extensively investigated in the mouse models of breast cancer and melanoma. In the 4T1 model of breast cancer, accumulation of PMN-MDSCs correlated with increased bone metastasis, and coinjection of MDSCs and 4T1 cells led to increased lung metastasis. MDSCs in 4T1 tumors upregulated the expression of several MMPs, which was critical in mediating invasiveness of 4T1 cells in vitro and in vivo (84). MDSCs also

Table 2 Mechanisms of regulation of tumor metastases by subsets of MDSCs

MDSC subset	Mechanism of action	References
total MDSC (subset is not defined yet)	metalloproteinase	83–85
total MDSC (subset is not defined yet)	induction of stemness of cancer cells in human ovarian tumor cells via microRNA-101	21
PMN-MDSC	EMT via production of HGF and TGF-β	60, 91
PMN-MDSC	production of bv8	77, 78
PMN-MDSC	production of MCP-1	90
PMN-MDSC	TGF-β–TGF-β receptor II interaction	87
M-MDSC	MET via versican release	93
M-MDSC	local immune suppression	70, 92
M-MDSC	production of IL-6	88
M-MDSC	differentiation of osteoclasts—bone metastases	94

Abbreviations: EMT, epithelial-mesenchymal transition; MET, mesenchymal-epithelial transition; MDSC, myeloid-derived suppressor cell; M-MDSC, mononuclear MDSC; PMN-MDSC, polymorphonuclear MDSC.

downregulated protease inhibitors such as the neutrophilic granule protein, an inhibitor of tumor invasiveness and metastasis (85). Each subset of MDSCs might contribute differently to tumor metastasis promotion (**Table 2**).

TGF-β is involved in the regulation of mammary carcinoma metastasis by MDSCs. However, its precise role remains controversial. Deletion of the gene encoding TGF-β receptor II (Tgfbr2) in mammary carcinoma cells increased MDSC infiltration into tumors mediated by SDF-1 and CXCL5. These MDSCs were observed at the leading invasive tumor edge and produced MMPs that contributed to breast tumor cell invasion (84). Inhibition of TGF-β signaling in SMAD4-deficient mouse colon carcinoma also induced MDSC recruitment and tumor invasion, which was dependent on CCL9 (86). In contrast, a recent study demonstrated that the specific deletion of *tgfbr2* in myeloid cells significantly inhibited tumor metastasis (which could be reversed by transfer of wildtype PMN-MDSCs). Tgfbr2 deficiency in myeloid cells decreased arg-1 activity and NO production, which promoted IFN-γ production and improved systemic immunity (87).

MIF was implicated in the promotion of metastases by inducing MDSC accumulation in a mouse breast cancer model (67). MDSCs in the primary tumor and metastatic sites produced IL-6, which conferred invasive potential of breast cancer cells and stimulated distant metastases through persistent activation of STAT3 in cancer cells. Blocking of IL-6 signaling successfully reduced primary tumor growth and lung metastasis (88). MDSCs recruited to premetastatic lungs stimulated the migration of tumor cells by secreting TNF-α, CXCL2, and TGF-β (70). In a mouse mammary tumor model, HIF-1α-dependent kit ligand expression by hypoxic tumor cells mobilized c-Kit^{+} CD11b^{+}Ly6G^{high} PMN-MDSCs to the primary tumor and promoted metastasis (89). PMN-MDSC recruitment to a premetastatic niche was dependent on hypoxic tumor cell–derived monocyte chemotactic protein-1 (MCP-1) (90).

Recently, several studies have shown the role of MDSCs in epithelial-mesenchymal transition (EMT). To disseminate, invade tissues, and metastasize, some tumor cells undergo EMT, in which polarized epithelial cells lose epithelial markers and differentiate to cells with mesenchymal features (91). Abastado and colleagues (60) showed that PMN-MDSCs were recruited to the tumor site in the *ret*-oncogene transgenic mouse model of spontaneous melanoma. Once in the tumor site, PMN-MDSCs produced hepatocyte growth factor (HGF) and TGF-β and induced EMT of primary melanoma cells. The depletion of PMN-MDSCs led to decreased EMT and fewer

EMT: epithelial-mesenchymal transition

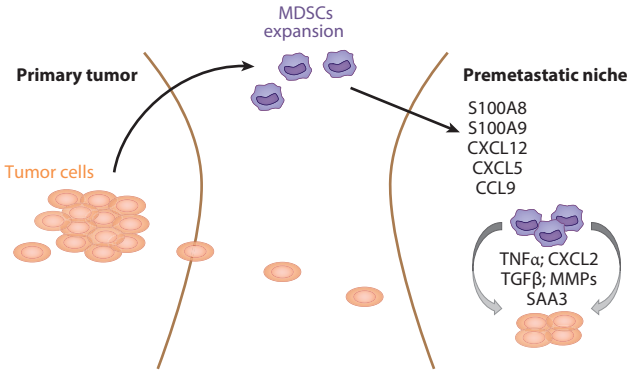

Figure 2

Contribution of myeloid-derived suppressor cells (MDSCs) to the formation of the premetastatic niche. Abbreviations: TNFα, tumor necrosis factor alpha; MMPs, matrix metalloproteinases.

metastatic lesions in mice (60). MDSCs also promote cancer metastasis by inducing stemness of cancer cells or by expanding the cancer stem cell population. In ovarian cancer patients, accumulation of Lin^{-} $CD45^{+}$ $CD33^{+}$ MDSCs correlated with poor survival in metastatic and nonmetastatic disease. MDSCs directly interacted with ovarian tumor cells and induced their stemness. This effect was mediated by upregulation of microRNA-101 in ovarian cancer cells, which in turn targeted CtBP2, a corepressor of stem cell genes. Further, culture of human ovarian tumor cells with MDSCs, before inoculation into immunodeficient mice, led to increases in engraftment and number of metastatic lesions in lung and liver (21). In a mouse model of pancreatic cancer, M-MDSCs directly induced expansion of aldehyde dehydrogenase-1^{+} (ALDH1) pancreatic cancer stem cells. A similar effect was observed with human $CD14^{+}$ $HLA\text{-}DR^{-}$ M-MDSCs (92).

The current concept suggests that MDSCs reach the premetastatic site before the tumor cells. Once in the site, MDSCs condition it to promote tumor seeding. This process involves creating an immunosuppressive microenvironment and secretion of bFGF, IGF-1, IL-10, IL-4, MMP-9, and S100A8/A9 (70, 93) (**Figure 2**). Because most of the metastases are represented by epithelial cells, similar in morphology to the primary tumor, but not mesenchymal cells, it is suggested that EMT is a temporary event and that after arriving in a metastatic site, tumor cells undergo reverse transition from mesenchymal to epithelial phenotype in order to colonize the niche. This process is known as mesenchymal-epithelial transition (MET). In one model, MDSCs were implicated in MET. Mittal and colleagues (94) showed that MDSCs (mainly M-MDSCs), accumulated in the premetastatic lung of MMTV-PyMT spontaneous breast tumor–bearing mice, secrete versican, an extracellular matrix proteoglycan. Versican contributed to MET and the formation of macrometastasis in the lungs (94). MDSCs isolated from the bone marrow of tumor-bearing mice could differentiate into functional osteoclasts, which are closely linked with bone metastasis. NO was crucial for the differentiation of MDSCs into osteoclasts (95).

Despite a body of literature demonstrating the prometastatic role of MDSCs, one recent study suggested that MDSCs had functional plasticity and in some cases could actually inhibit metastasis. Metastatic and nonmetastatic prostate and breast tumors equally induced accumulation of MDSCs in the lung premetastatic site (96). MDSCs from the nonmetastatic tumors produced large amounts of TSP-1, a potent antiangiogenic matrix protein, and inhibited metastasis. Nonmetastatic tumors secreted prosaposin, a potent inducer of TSP-1, and a prosaposin 5 amino acid peptide mimetic was sufficient to cause upregulation of TSP-1 in MDSCs in vivo and inhibit tumor metastasis (96). This is an interesting new mechanism challenging MDSC metastasis-promoting functions.

MET: mesenchymal-epithelial transition

However, more studies confirming the role of TSP-1 and MDSCs in metastasis inhibition in other tumor models are required.

CONCLUSIONS

MDSCs were originally described as cells that potently suppress T cell immune responses in cancer. It is clear now that the effect of MDSCs is much broader. They are known to play an important role not only in cancer but also in chronic infectious diseases and inflammation, autoimmune diseases, trauma, sepsis, etc. At the same time, it has become apparent that the MDSC contributions to tumor progression extend far beyond immune suppression and include regulation of tumor development, progression, and metastasis. MDSCs utilize a variety of different mechanisms not involving immune suppression. One of the most intriguing roles attributed to MDSCs is their contribution to the formation of the premetastatic niche. This may open new therapeutic opportunities to block metastases by targeting MDSCs. However, the mechanisms responsible for MDSC seeding of the tissues and specific regulation of tumor cell seeding in metastatic sites by MDSCs remain rather poorly understood. Understanding the molecular mechanisms that govern the relationship between MDSCs and tumor cells in the premetastatic niche will provide novel opportunities for targeting metastases.

SUMMARY POINTS

1. MDSCs are pathologically activated immune-suppressive immature myeloid cells accumulated in cancer.
2. MDSCs are critical factors in regulation of antitumor immune responses.
3. Two major populations of MDSCs, namely PMN-MDSCs and M-MDSCs, have different effects on immune response.
4. MDSCs promote angiogenesis, tumor cell invasion, and metastases through a variety of different soluble factors.
5. MDSCs play an important role in the formation of the premetastatic niche.
6. M-MDSCs and PMN-MDSCs play different roles in promoting tumor metastases.

FUTURE ISSUES

1. To identify the specific roles of different populations of MDSCs in the promotion of tumor metastases.
2. To determine conditions defining the pro- versus antitumorigenic roles of MDSCs.
3. To identify the precise nature of MDSCs' contribution to the formation of the premetastatic niche.
4. To clarify the possible role of MDSCs as a biomarker of tumor progression and response to therapy.
5. To develop therapeutic approaches for selective elimination of MDSCs in cancer.
6. To understand the mechanisms regulating migration of MDSCs to the site of the premetastatic niche.

7. To elucidate the specific mechanism regulating interaction between MDSCs and tumor cells.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

This work was supported by NIH grants CA 100062 and CA 84488 to D.I.G.

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