Mechanisms and Functional Significance of Human Tumor-infiltrating Myeloid Cells

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Abstract

Myeloid cells as the major components of tumor-infiltrating leukocytes play critical roles in anti-tumor immunity. However, emerging evidences have revealed that soluble factors produced by tumor/stromal cells skew myeloid cells toward a tumor-promoting phenotype. Tumor-infiltrating myeloid cells (TIMs) including tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), myeloid-derived suppressor cells (MDSCs), and tumor-associated dendritic cells (TADCs) are considered as the key mediators of tumor microenvironment (TME). TIMs have been shown to play important roles in various aspects of cancer biology and their presence is often linked to altered patient prognosis and survival. Regarding their critical role in TME, TIMs have been proposed as relevant targets of therapeutic strategies aimed at expanding immunostimulatory myeloid cell populations and depleting or modulating immunosuppressive ones. In this review, we briefly describe TIMs subsets and discuss the mechanisms by which TIMs induce immunosuppression, angiogenesis, and metastasis.

Keywords: Tumor-infiltrating myeloid cells -TAMs- TANs- MDSCs- TADCs

Introduction

Myeloid cells including monocytes, macrophages, dendritic cells (DCs), and granulocytes present the major components of innate immune system characterized by their diversity and plasticity. This heterogeneous population of cells exerts their anti-tumor activity through multiple mechanisms such as direct cytotoxicity, phagocytosis, and antigen presentation to adaptive immune cells. However, tumor-derived factors may impair myeloid cells maturation, differentiation, and function. Tumor-infiltrating myeloid cells (TIMs) which have been known for their tumor-promoting and immunosuppressive activities include tumor-associated macrophages (TAMs), tumor-associated dendritic cells (TADCs), tumor-associated neutrophils (TANs), and myeloid-derived suppressor cells (MDSCs). Evidences suggest that persistent stimulation associated with chronic inflammation play an essential part in developing TIMs with pro-tumor properties [1-2]. TIMs play critical roles in numerous essential cancer-related processes, including immunosuppression, angiogenesis, and metastasis. A close association between TIMs accumulation and poor clinical outcome has been reported in many cancer types [3-6]. While therapeutic strategies based on reactivation of pre-existing anti-tumoral T cells or adoptive transfer of tumor-specific T cells have shown promising clinical results, treatment failure and resistance have been observed in a significant number of patients. Targeting of TIMs present within the tumor microenvironment (TME) might provide a novel therapeutic avenue as they are considered to be a major obstacle for many cancer immunotherapies [7].

In this review, we briefly describe the TIMs subsets and discuss the major mechanisms employed by TIMs to induce immunosuppression, angiogenesis, and metastasis.

TIMs Subsets

TAMs

Monocytes and macrophages have been known as one of the main types of phagocytes, derived from bone marrow myeloid progenitor cells. Upon maturation,
monocytes are released into the bloodstream and emigrate into the tissues where they differentiate into macrophages [8].

Two molecular and functionally distinct macrophages subsets have been identified in TME. The classically activated M1 macrophages have a more pronounced pro-inflammatory profile characterized by high expression of antigen-presenting and co-stimulatory molecules, and production of high levels of immunostimulatory cytokines such as tumor necrosis factor α (TNF-α), interleukin (IL)-6, IL-12, and IL-23. The M1 macrophages also promote T-helper-1 (Th1) responses to infection. In contrast, the alternatively activated M2 macrophages have a pro-angiogenic and immunoregulatory phenotype and are stimulated by (T-helper-2) Th2 cytokines such as IL-4, IL-10, and IL-13. The M2 macrophages are characterized by expression of co-inhibitory molecules like programmed death-ligand 1 (PD-L1) and secretion of anti-inflammatory cytokines such as vascular endothelial growth factor (VEGF)-A and VEGF-C and are a major source of proteases including matrix metalloproteinase (MMP)-2 and MMP-9 which contribute to tumor invasion, neoangiogenesis and metastasis [14-17]. The M2 phenotype is thought to be the predominant phenotype of TAMs and in most cases, it indicates a poor prognosis [3-5]. However, some recent studies in human tumors have been shown the more diverse and heterogeneous population of TAMs which cannot be simply categorized as M1 or M2 macrophages phenotypically and functionally [18-19]. While the majority of TAMs originate from circulating monocytes several studies have suggested that a fraction of the TAMs arises from the tissue-resident macrophages which are self-sustained and do not depend on circulating monocytes for maintenance [20].

A unique and small subset of monocytes named Tie-2 expressing monocytes (TEMs) has been shown to be a critical promoter of tumor angiogenesis. TEMs are characterized by the expression of angiopoietin receptor Tie-2. [21].

TANs

Neutrophils are phagocytic, polymorphonuclear cells that make up the most abundant subpopulation of immune cells [22].

In many types of cancers, the elevated numbers of neutrophils in the circulation or a high neutrophil-to-lymphocyte ratio (NLR) have been shown to be associated with poor outcome [4-23]. Similar to the macrophage paradigm; TANs have been categorized into N1 or N2 in tumor-bearing mice. The N1 TANs exhibit a proinflammatory and antitumorigenic phenotype (i.e., TNFα-high and Arginase-low), while N2 TANs are characterized with a protumorigenic and immunosuppressive profile. The N2 TANs express high levels of Arginase (Arg)-1, and facilitate angiogenesis and metastasis via secretion of proangiogenic (i.e., VEGF and Bv8) and matrix remodeling factors (i.e. MMP9). TGF-β has been considered as one of the central signals inducing the N2-protumor phenotype within the TME [23-26]. It is noteworthy that the classification of TANs as N1/ N2 has been described only in murine models of cancer and the phenotype and function of TANs in the TME, particularly in human tumors, have yet to be fully explored. Additionally, for the same reasons described for TAMs, this binary N1/N2 classification system represents an oversimplification for the phenotypic spectrum of TANs in TME [23]. A further complication in TANs studies is their phenotypic and functional similarities with granulocytic-MDSCs (G-MDSCs) since it is not clear whether these are analogous or separate populations [27].

MDSCs

MDSCs can be considered as the most important cell population contributing to the formation of a pro-tumorigenic and immunosuppressive TME. High MDSC levels have been found to act as a negative prognostic factor for many cancers [6]. MDSCs are a heterogeneous mixture of immature myeloid cells that consist of two large groups of cells: the polymorphonuclear or G-MDSC and the monocytes (M-MDSC) groups. In tumor-bearing mice, the G-MDSC can be defined as CD11b+Ly6G+Ly6C+ and M-MDSC as CD11b+Ly6G< Ly6C+. In humans G-MDSC are described as CD11b+CD14+CD15+CD33+CD66b+ HLA-DR+; while M-MDSC are described as CD11b+CD14+CD15+CD33+CD66b+HLA-DR− [28]. A population of “early stage MDSCs” or eMDSCs comprising more immature progenitors are also identified through the Lin− (including CD3, CD14, CD15, CD19, CD56) HLA-DR−CD33+ profile [29]. In humans, MHC class II molecule (HLA-DR) is the marker to differentiate monocytes from M-MDSC however; no marker has been identified allowing for the clear separation of G-MDSC from neutrophils. The only method that can help to distinguish G-MDSCs from mature neutrophils is by using a Ficoll density gradient. While mature normal neutrophils as normal-density neutrophils are separated at the bottom of the density gradient, a subpopulation of neutrophils, termed low-density neutrophils (LDNs) are found in the low density fraction at the interphase of plasma and Ficoll [30-31]. It has been proposed that G-MDSCs with immunosuppressive functions can be found in LDNs fraction. However, subsets of mature LDNs displaying an enhanced pro-inflammatory profile have also been identified [24-31]. Recently, Condamine et al. identified lectin-type oxidized LDL receptor 1 (LOX-1) as a potent marker of G-MDSCs which can be used to separate them from neutrophils [32]. Several studies proposed that N2 TANs with immunosuppressive and tumor-promoting functions are, in fact, G-MDSCs. However, in some other studies, G-MDSCs have been considered a distinct subpopulation of granulocytes which can infiltrate TME and acquire an N2 phenotype [27].

TADCs

Dendritic cells are the most professional antigen-presenting cells activating naive antigen-specific CD4+ and CD8+ T cells. Two major DC subsets have been
recognized in mouse and human tissues: conventional/ myeloid DCs (mDCs) and the plasmacytoid DCs (pDCs). Both subsets originate in bone marrow from macrophage/ DC progenitors; pDCs terminally differentiate in the bone marrow whereas so-called pre-DCs migrate from bone marrow to peripheral organs to terminally differentiate into CD8α+/CD103− cDC1s and CD11b+ cDC2s subsets in mice and CD141+ (or BDCA3+) cDC1s and CD1c− (or BDCA1−) cDC2s in humans [33].

The pDCs are specialized in secreting a large amount of type I interferons and also play an important role in immune tolerance. The cDC1s mainly induce potent CTL responses through presenting internalized exogenous antigens onto MHCII to CD8+ T cells, while cDC2s are specialized in presenting internalized antigens on MHCI to CD4+ T cells and inducing Th2 or Th17 responses [33].

DCs display different phenotype and activity (immunostimulating or immunosuppressive) at the tumor site suggesting the plasticity of these cells in response to a wide spectrum of signals in TME. Although TADCs with significant antigen-presenting capabilities have been identified within the TME, DCs often exhibit impaired antigen-presenting and/or inhibitory functions in advanced solid tumors. It has been proposed that TME keeps the majority of TADCs in an immature state. However, it is important to emphasize that immunoregulatory function of DCs cannot simply be limited to immature DCs since various factors and pathways can influence the DCs polarization, activation status and their capacity to invoke immunostimulating or immunosuppressive responses within TME [34-36].

Mechanism of Immune Suppression and Immune Tolerance by TIMs

Several mechanisms have been considered for the immunosuppressive effects of TIMs including; secretion of various cytokines and enzymes with immunosuppressive activity and expression of surface markers which can be used to suppress antitumor immune responses.

One of the most important events occurring in the TME is tumor-induced suppression of T cell immune responses. MDSCs and macrophages within TME are the major immunoregulatory cells inhibiting T cell function. Both express high levels of inducible NO synthase (iNOS) and Arg-1 leading to enhanced L-arginine catabolism and production of reactive oxygen species (ROS). Since L-arginine is a nutrient required for T cell activation and proliferation, the lack of L-arginine results in downregulation of the expression of TCR/CD3 complexes and inhibition of cytotoxic T-cell responses [37-39]. On the other hand, ROS produced by MDSCs and M2 macrophages exhibits immunosuppressive properties. ROS inhibit T cells by nitrating T-cell receptors and thereby preventing recognition between TCR and MHC-peptide complex [40-41]. ROS also block tumor infiltration of antigen-specific T cells via nitrating T cell-specific chemokines [42]. Both MDSCs and TAMs produce IL-10 that plays a pivotal role in the immunosuppressive function of regulatory T (Treg) cells and inhibition of cytotoxic T-cell responses [38-43]. TGF-β and indoleamine 2,3 dioxygenase (IDO) have been known to be responsible for the development of Tregs by MDSCs [44-45]. Moreover, TAMs directly stimulate recruitment of Tregs to TME through the secretion of chemotactic factors such as CCL17, CCL18, and CCL22 [46-47]. MDSCs can suppress T cell responses through the secretion of S100 calcium-binding proteins A8 and A9 (S100A8 and S100A9). These proteins have been shown to inhibit DCs maturation and to promote MDSCs migration and accumulation [48]. High levels expression of PD-L1 by activated MDSCs and monocytes inhibit cytotoxic T lymphocyte responses [49]. MDSCs and M2 macrophages also impair the cytotoxic capacity of NK cells through different mechanisms [45-50].

TEM has also been shown to exert immunosuppressive effects through the production of immunosuppressive cytokines such as IL-10 and VEGF, inhibition of tumor-specific T-cell proliferation, and expansion of CD4+CD25+Foxp3+ Treg cells [51].

TADCs are another subset of TIMs often exhibiting immunosuppressive and tolerogenic properties within TME. A number of factors such as IL-10 and TGF-β produced by tumor cells and/or TME cells have been shown to inhibit DC maturation and reduce the capacity of DCs in antigen presentation and T cell activation by a variety of mechanisms [35-52-54]. DCs treated with IL-10 have been shown to induce anergy in cytotoxic CD8+T cells [55]. Tumor-produced TGF-β reduces the potency of DCs to present antigen, to stimulate tumor-specific cytotoxic T lymphocyte, and to migrate to draining lymph nodes [56]. It has been shown that TME converts a specific DC subset of immature mDCs to regulatory DCs that secrete TGF-β and selectively promote the proliferation of CD4+CD25+Foxp3+ Treg cells [57]. Several factors such as Arg-1 and IDO produced by TADCs have been considered to play important roles in mediating the suppression of T cells responses [36-58-59]. Treg cells subsequently induce immunosuppression and DC dysfunction through different mechanisms [57, 60]. Expression of inhibitory molecules such as PD-L1 (and its receptor PD-1) and T-cell immunoglobulin and mucin domain 3 (TIM-3) is another mechanism by which DCs exert their immunosuppressive effects. PD-L1 expression on DCs has been shown to suppress antitumor T cell immunity [61-62]. Tumor-infiltrating DCs expressing PD-1 has been found to suppress CD8+ T cell activity and decrease T cell infiltration in advancing tumor in a mouse model of ovarian cancer [63]. PDL-1 expressing DCs have also been shown to induce Treg generation in the presence of TGF-β [64]. TIM-3 prevents DCs activation and maturation and reduces the anti-tumor responses as well as the efficacy of cancer treatments [65].

Tumor-infiltrating pDCs represent another subset of DCs with immunosuppressive and tolerogenic activity favoring tumor progression [66]. Although properly stimulated pDCs have been shown to induce immunogenic anti-tumor responses, pDCs are mostly defective in their functions under TME [35-67-68]. High densities of tumor-infiltrating pDCs were identified as a negative prognostic
The tumor or stromal cells upregulate the expression of and promote angiogenesis [88]. G-CSF produced by found to release ECM-sequestered VEGF and bFGF by neutrophil-derived TIMP-free pro MMP9 has been function of MMP9 through the formation of a complex the bioavailability of VEGF [87]. Neutrophils are a subpopulation of monocytes. TEMs are found in the mouse and human peripheral blood and are recruited into the solid tumors mainly by angiopoietin 2 produced by tumor endothelial cells [21-81]. Angiopoietin 2 also has been shown to upregulate expression of hypoxia-inducible factors 1 and 2 (HIF1 and HIF2) in TAMs leading to the subsequent activation of many genes involved in cell proliferation, angiogenesis, and metastasis [79-80].

TEMs have been reported as a highly proangiogenic subpopulation of monocytes. TEMs are found in the solid tumors mainly by angiopoietin 2 produced by tumor endothelial cells [21-81]. Angiopoietin 2 also has been shown to enhance angiogenesis activity of TEMs through upregulation of several proangiogenic enzymes such as thymidine phosphorylase and cathepsin B [82].

TANs and MDSCs are also potent promoters of tumor angiogenesis. Both have been shown to induce angiogenesis through upregulation of VEGFA, MMP9, BV8, and bFGF. Human neutrophils contain VEGFA-rich granules that can be rapidly released upon stimulation [83-84]. It has been shown that MDSCs upregulate VEGF and bFGF production and promote angiogenesis in a STAT3-dependent manner [85]. The blockade of STAT3 signaling with IFN-β has been found to suppress the production of VEGFA and MMP9 by neutrophils and limit tumor angiogenesis and growth in a mouse tumor model [86]. TANs and MDSCs produce high levels of MMP9. The production of MMP9 by MDSCs has been considered to be essential for their angiogenic properties. Moreover, MMP9 from MDSCs increases the bioavailability of VEGF [87]. Neutrophils are a key source of tissue inhibitor of metalloproteinase (TIMP)-free pro MMP9. TIMP inhibits the angiogenic function of MMP9 through the formation of a complex with it. Proteolytic cleavage of extracellular matrix (ECM) by neutrophil-derived TIMP-free pro MMP9 has been found to release ECM-sequestered VEGF and bFGF and promote angiogenesis [88]. G-CSF produced by the tumor or stromal cells upregulates the expression of proangiogenic factor Bv8 in CD11b+Gr1+ cells which subsequently induces endothelial cells proliferation and tumor angiogenesis [86].

Beside the major role of DCs in immune suppression/tolerance, there is now substantial evidence that immature DCs actively promote tumor angiogenesis [89]. A new population of CD11c+HLA-DR+ leukocyte expressing both endothelial and DC markers has been described in mouse and human ovarian carcinomas. It has been shown that β-defensin promotes tumor vasculogenesis through the recruitment of immature DCs from the peripheral blood in the presence of increased VEGF-A expression. High levels of VEGF-A in TME induce endothelial-like differentiation of DCs and their migration to vessels through VEGF receptor-2 [90]. pDCs derived from human ovarian tumor ascites induce tumor angiogenesis in vivo, through the production of TNFα and IL-8 [91].

TIMs and Tumor Angiogenesis

Tumor angiogenesis is a crucial step in tumor growth and metastasis. Although tumor cells can directly stimulate angiogenesis, many recent studies have shown the crucial role of TIMs in tumor angiogenesis.

M2 macrophages promote angiogenesis through various mechanisms including secretion of several potent proangiogenic factors (i.e., VEGF, TNF-α, IL-1β, IL-8 (CXCL8), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF)) and production of different classes of matrix remodeling factors (i.e., urokinase plasminogen activator (uPA), MMP-2, MMP-7, MMP-9, MMP-12, and elastase) [76]. Hypoxic TME plays an important role in inducing proangiogenic phenotype of TAMs. High TAMs densities have been found in hypoxic and/or necrotic areas of many human tumors [77-78]. Hypoxia has been shown to upregulate expression of hypoxia-inducible factors 1 and 2 (HIF1 and HIF2) in TAMs leading to the subsequent activation of many genes involved in cell proliferation, angiogenesis, and metastasis [79-80].

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TIMs and Tumor Metastasis

Metastasis remains the major cause of death from solid tumors. To metastasize, tumor cells need to migrate to a secondary site and form metastatic nodules [92]. Recent evidences suggest that primary tumors are able to influence the microenvironment of distant organs before the arrival of metastatic tumor cells providing a supportive metastatic microenvironment called premetastatic niche [93]. Both circulating and tumor-infiltrating myeloid cells have been shown to play crucial roles in different aspects of metastasis including premetastatic niche formation, tumor cells intravasation into the blood vessels and extravasation at the secondary site, and finally tumor cells colonization.

Neutrophils represent the central cell population that promotes tumor metastasis. While primary studies have suggested the CD11b+ VEGFR1+ bone marrow-derived immature myeloid as the major component of pre-metastatic niche [94], some recent studies have shown that neutrophils are the major cell type in the pre-metastatic niche that mobilize in response to primary tumor-derived factors. Tumor-derived G-CSF has been shown to be responsible for mobilization of bone marrow-derived CD11b+Gr1+Ly6G+Ly6C+ granulocytes (immunosuppressive neutrophils) and their homing into the lung before the arrival of tumor cells [95]. G-CSF induces expression of BV8 by Ly6G+Ly6C+ cells which is a chemoattractant for homing of bone marrow-derived Ly6G+Ly6C+ cells into pre-metastatic lungs [95-96]. It has been shown that in mammary tumor-bearing mice, upon stimulation with γδ T cell-derived IL-17, G-CSF-induced immunosuppressive neutrophils facilitate lung metastasis of tumor cells via blocking the antitumor functions of CD8+ T cell [97]. Neutrophils have also been considered as the major sources of some pro-metastatic proteins such as MMP9, S100A8, S100A9, and leuokotrienes [96-98]. Neutrophil-released neutrophil extracellular traps (NET) can also contribute to cancer metastasis by trapping of circulating tumor cells [100]. TGF-β produced by TANs has been shown to trigger epithelial-mesenchymal transition (EMT) of tumor cells which, in turn, promote metastasis [101].
MDSCs can also promote tumor metastasis through infiltration into the pre-metastatic niche. Some soluble factors secreted by primary tumor/stromal cells have been shown to induce migration and activation of MDSCs in the pre-metastatic niche. In a mouse model of colorectal cancer, VEGF-A produced by primary tumor cells induced pre-metastatic niche formation and liver metastasis by MDSCs through upregulation of CXCL1 in TAMs which, in turn, recruits CXCR2-positive MDSCs to liver tissue [102]. Recruitment of MDSCs to the pre-metastatic niche in distant organs is also facilitated by expression of S100A8 and S100A9 by myeloid and tumor cells. These chemoattractant proteins stimulate MDSCs migration through activation of Toll-like receptor (TLR)-4 or receptor for advanced glycation end-products (RAGE) on MDSCs [48-103]. It has been reported that VEGF-A, TGFβ, and TNFα released by the primary tumor induce the expression of S100A8 and S100A9 in premetastatic lungs [104]. In 4T1 tumor-bearing mice, Gr-1+CD11b+ cells were shown to infiltrate into the pre-metastatic lungs and promote aberrant vasculature formation and metastasis through the upregulation of MMP9 [105]. Intravenous injection of primary ovarian cancer cells conditioned with MDSCs in NSG mice model induced formation of more metastatic foci in the liver and lungs of mice compared to control animals. MDSCs were found to enhance tumor cells stemless and their metastatic potential through inducing miRNA101 and suppressing the corepressor CtBP2 [106]. Tumor-infiltrating MDSCs induce EMT in cancer cells. TGF-β1, epidermal growth factor (EGF), and hepatocyte growth factor (HGF) signaling pathways have been shown to play a crucial role in EMT induction by MDSC [107].

TAMs are another myeloid cell population that actively participate in metastatic processes. In a mouse model of pancreatic cancer, macrophages resident in the liver (Kupffer cells) induce pre-metastatic niche formation through the uptake of tumor-derived exosomes containing high levels of macrophage migration inhibitory factor (MIF). Upon MIF stimulation these Kupffer cells secret TGF-β that promotes fibronectin production by hepatic stellate cells. This fibronectin-rich environment recruits pro-tumor bone marrow-derived macrophages to the liver premetastatic niche. Blockade of these tumor-derived exosomes has been shown to prevent liver pre-metastatic niche formation and metastasis [108].

Macrophages not only promote metastasis from the primary tumor site but also induce tumor cell invasion and migration within metastatic sites. It has been shown that CSF-1 produced by cancer cells promote TAMs mobility and their secretion of EGF leading to coligation of macrophages and cancer cells towards tumor blood vessels. TAM-derived EGF further activates the EGF receptor in cancer cells which, in turn, accelerates their invasion and the intravasation. Moreover, TAM-derived VEGF-A promotes cancer cell intravasation into the blood vessels [109-111]. TAMs have also been shown to induce invasion and metastasis of breast cancer cells through integrin clustering and enhancing tumor cells adhesion to ECM [112]. IL-4 produced by the cancer cells and/or stromal cells within TME has been shown to promote cathepsin activity in TAMs which, in turn, enhances the invasiveness of cancer cells [113]. High levels of cathepsin S expression in primary tumor samples from breast cancer patients has been shown to correlate with decreased brain metastasis-free survival. Cathepsin S produced by both tumor cells and TAMs promotes blood-brain barrier transmigration via proteolytic cleavage of junctional adhesion molecule (JAM)-B [114]. In the metastatic liver, monocytes/macrophages promote tumor cells migration and invasion through upregulation of S100A8 and S100A9 in cancer cells which subsequently stimulate tumor cell expression of MMP2 and MMP9 [115]. Moreover, theses inflammatory chemoattractants recruit more macrophages and tumor cells to pre-metastatic lungs via upregulation of serum amyloid A3 in a TLR4-dependent manner [116]. CCL2 produced by tumor cells in the metastatic site also induces recruitment of inflammatory monocytes from the blood to the metastatic site where they promote cancer cells extravasation through VEGF-A secretion [117]. Macrophages also promote metastatic colonization through various mechanisms. They enhance tumor cells survival via counter-receptor α4-integrins that bind to VCAM-1 on the surface of cancer cells in the metastatic site [118]. Metastasis-associated macrophages also promote colony formation abilities of cancer cells through the secretion of granulin that provides a fibrotic microenvironment favoring metastasis [119].

While many studies have described the mechanisms employed by various myeloid cell populations to promote metastasis, few have specifically investigated the premetastatic role of DCs in cancer. Infiltration of DCs in metastatic sites has been shown in several studies. DCs promote metastasis by generating an immunosuppressive microenvironment at the metastatic site. In a mouse model of pancreatic ductal adenocarcinoma, a discrete CD11b+ DC subset expressing MGL2 and PD-L2 has been detected in the metastatic microenvironment. These immunosuppressive DCs develop from monocytes in response to tumor-released GM-CSF and facilitate metastasis through the expansion of Treg cells and suppressing CD8+ T cells at metastatic site [120]. In mouse models of breast cancer, bone infiltration of macrophages has been shown to induce pDCs accumulation which, in turn, skews immune response towards Th2 and upregulate Treg and MDSC populations in the metastatic bone. Moreover, osteolytic cytokines secreted by pDCs and CD4+ T cells induce severe bone damage. Depletion of pDC reduced tumor growth and abolished bone metastasis and osteolysis through the activating CD8+ T cells and decreasing Treg and MDSC populations [121]. In addition to inducing suppressor cells, pDCs promote tumor metastasis through their secretions. Soluble factors secreted by pDCs isolated from the primary tumor of breast cancer patients have been reported to induce lymph node metastasis through stimulation of CXCR4 expression by carcinoma cells. The CXCR4/SDF-1 axis was found to be involved in tumor metastasis in several types of cancer [122].

In conclusion, given the heterogeneity and
plasticity of myeloid cells and their ability in supporting various aspects of tumor biology, the effective management of TIMs has been the target of different therapeutic strategies. All of these strategies aimed at expanding immunostimulatory cell populations and depleting or modulating immunosuppressive ones. Moreover, in future therapies, some important hurdles such as variation in abundance of myeloid cells in different tumor types and even in patients with same tumor type should be considered in order to ensure specific and long term immune responses against tumors.

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