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REVIEW

Roles of Myeloid-Derived Suppressor Cells in Cancer Metastasis: Immunosuppression and Beyond

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Abstract
Metastasis is the direst face of cancer, and it is not a feature solely dependent on cancer cells; however, a complex interaction between cancer cells and host causes this process. Investigating the mechanisms of metastasis can lead to its control. Myeloid-derived suppressor cells (MDSCs) are key components of tumor microenvironment that favor cancer progression. These cells result from altered myelopoiesis in response to the presence of tumor. The most recognized function of MDSCs is suppressing anti-tumor immune responses. Strikingly, these cells are among important players in cancer dissemination and metastasis. They can exert their effect on metastatic process by affecting anti-cancer immunity, epithelial–mesenchymal transition, cancer stem cell formation, angiogenesis, establishing premetastatic niche, and supporting cancer cell survival and growth in metastatic sites. In this article, we review and discuss the mechanisms by which MDSCs contribute to cancer metastasis.

Keywords Myeloid-derived suppressor cells · Metastasis · Immunosuppression · Premetastatic niche · Angiogenesis · Apoptosis

Introduction

Cancer cells must be competent to successfully undergone steps of metastasis, i.e. establishing colonies of cells from primary tumor in tissues that are distant from the primary site. The steps of metastasis are as follows: cancer cell must detach from its initial place and invade adjacent tissue, enter blood or lymphatic vessels (intravasation), distribute to remote organ through circulation, extravasate and ultimately make micro and clinically overt macrometastases (Leber and Efferth 2009). One important point about metastatic process is that only a few cells in the primary tumor are capable of surpassing all these stages (Chiang and Massagué 2008). This capability seems to depend on whether cells can attain the alterations which are required for metastasizing or not. Other cardinal features allied to metastasis are the interaction of malignant cells with tumor and metastatic microenvironments and angiogenesis.

Myeloid-derived suppressor cells (MDSCs) are immunosuppressive immature hematopoietic cells that differentiate from hematopoietic stem cells in a variety of pathologic conditions such as cancers and infections. In response to factors released from tumor cells and stroma, white blood cell precursors fail to differentiate into normal immune cells. Then, MDSCs as immature cells leave their site of generation, expand in the whole body and mediate immunosuppression (Marvel and Gabrilovich 2015).

Certain phenotypic features have been used for putting MDSCs into a number of subsets (Bronte et al. 2016).

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Based on their similarity to their normal counterparts, they are divided into two main categories: monocytic-MDSCs (M-MDSCs) and polymorphonuclear-MDSCs (PMN-MDSCs). Murine MDSCs express both CD11b and GR1. Ly6G and Ly6C molecules constitute GR1 marker. The distinction between M-MDSCs and PMN-MDSCs in mouse is made by relative high expression of Ly6C in M-MDSCs and Ly6G in PMN-MDSCs. In human, M-MDSCs can be identified as $CD11b^{+}/CD14^{+}/CD15^{-}/HLA\text{-}DR^{-/Low}$ and PMN-MDSCs as $CD11b^{+}/CD14^{-}/CD15^{+}/HLA\text{-}DR^{-}$ phenotype (Bronte et al. 2016; Wyczechowska et al. 2015).

Both phenotypic and functional criteria need to be met for a cell population to be recognized as MDSCs (Bronte et al. 2016). In fact, many phenotypic features are shared by MDSCs and their counterparts which are non-immunosuppressive, i.e. PMN-MDSCs versus non-immunosuppressive neutrophils and M-MDSCs versus non-immunosuppressive monocytes. This makes their distinction difficult if only morphology is considered. Therefore, the presence of immunosuppressive ability is required for the characterization of MDSCs. However, recent studies have found promising biomarkers for distinguishing these cell types from their mature counterparts. Lectin-type oxidized low-density lipoprotein (LOX)-1 is a transmembrane receptor protein for oxidized low-density lipoprotein. LOX-1 showed discriminatory power in differentiating human PMN-MDSCs from non-immunosuppressive tumor-associated neutrophils both in peripheral blood and tumor tissue (Condamine et al. 2016).

MDSCs can suppress both innate and adaptive immune responses through different mechanisms which will be discussed in the following section. Many clinical studies have demonstrated that higher levels of both circulating and tumor-infiltrating MDSCs are independently associated with poor prognosis in patients with cancer (Choi et al. 2016; Ugel et al. 2015; Zhang et al. 2013a). Recently, it has been discovered that MDSCs play some roles in tumor progression, angiogenesis and metastasis independent of their immunomodulatory activities (Condamine et al. 2015). Mounting evidence of MDSC's contribution to metastasis can bring us the opportunity to develop new therapeutic approaches and enhance patient's survival. A review gathering our understanding about the role of MDSCs in cancer metastasis could pave the way for investigating unanswered questions in this regard and exploiting them for designing new strategies to combat metastasis. The aim of this paper is to review recent knowledge on the involvement of MDSCs in cancer metastasis. In this review, we will discuss the MDSC's contribution to the metastatic process based on each metastasis stage.

Immune Suppressive Activity of MDSCs Helps Tumor Cells to Metastasize

An efficient immune system has the ability to eliminate cancer cells to control tumor growth and progression. Therefore, immunosuppression may accelerate the tumor growth and metastatic process. There are observations proving this concept. In an experimental study, the incidence of metastasis increased with suppressing the immune system by radiation or hydrocortisone acetate (Seshadri et al. 1979). Cancer patients, which were infected by HIV or had received organ transplantation, presented with higher stage than their immunocompetent counterparts (Shiels et al. 2015). Escaping anti-tumor immunity is essential for cancer cells to survive in primary tumor site, circulation, and metastatic environment. Neoplastic cells and their associated stroma employ a variety of mechanisms to circumvent the obstacle of anti-tumor immune responses. Some other cells beside neoplastic cells contribute to anti-tumor immunosuppression, such as MDSCs, tumor-associated macrophages, regulatory T (Treg) cells, natural killer (NK) T cells, mesenchymal stem cells (MSCs) and cancer-associated fibroblasts (Bianchi et al. 2011).

The interplay between MDSCs and tumor microenvironment components, which begins after infiltration of immature myeloid cells to the tumor tissue, promotes the immunosuppressive capability of MDSCs. Cancer cells, bone marrow-derived cells, and mesenchymal cells, such as cancer-associated fibroblasts which reside in the tumor tissue, all directly contribute to activation of MDSCs. When inflammation becomes chronic in the tumor microenvironment whose primary function is control of tumor growth and progression, the physiologically existing mechanisms, that bring homeostasis back to tissues after inflammation, become activated (Umansky et al. 2016). Interferon (IFN)-γ, which is primarily secreted by activated T cells in tumor microenvironment, induces the immunoregulatory molecules PD-L1 (Lu et al. 2016) and CD40 (Pan et al. 2010) in MDSCs. Once MDSCs are activated in tumor microenvironment, they produce molecules that can activate MDSCs in an autocrine manner and maintain the process. Prostaglandin E2 (Obermajer et al. 2011) and S100A8/A9 (Deng et al. 2017; Sinha et al. 2008; Wang et al. 2013) are autoinducers of MDSCs.

MDSCs can suppress anti-tumor immune responses by counteracting both adaptive and innate immune responses. A thorough discussion of the exact mechanisms underlying immunosuppression by MDSCs is out of the scope of this article and their immunoregulatory effects are only briefly addressed (Motallebnezhad et al. 2016).

Depletion of certain amino acids (tryptophan, arginine, and cysteine), which are essential for T-cell proliferation

and function, reduction of T-cell recruitment to tumor tissue, induction of apoptosis in T cells, production of reactive oxygen species and reactive nitrogen species, and interference with antigen presentation can restrain T-cell functions. MDSCs may also promote accumulation of immunosuppressive cells such as Treg cells and tumor-associated macrophages. In addition, MDSCs can impair the function of NK cells to cause immunosuppression (Motallebnezhad et al. 2016; Ugel et al. 2015; Ye et al. 2010). Clinical and pre-clinical studies have shown statistical correlation between higher frequency of MDSCs in blood and tumor tissues, and a lower number and diminished function of cytotoxic and helper T cells, impaired function of NK cells, higher number of Treg cells and increased metastatic burden. Interference with expansion and action of MDSCs, e.g. destroying MDSCs using anti-Gr1 antibody, will reverse the mentioned effects (Condamine et al. 2015; Jiang et al. 2014; Motallebnezhad et al. 2016; Ugel et al. 2015; Zhang et al. 2015a).

Programmed cell death-1/programmed cell death-ligand 1 (PD-1/PD-L1) interaction is altered by MDSCs in tumor microenvironment. PD-1/PD-L1 immune checkpoint pathway is physiologically involved in subsiding prolonged inflammation to prevent tissue damage. In tumor microenvironment, cancer and stromal cells express PD-L1 which binds to PD-1 on the surface of T cell. This interaction results in T-cell exhaustion (Topalian et al. 2015). High PD-1 and PD-L1 expression negatively impact the outcome of cancer patients (Chen et al. 2018; Shen et al. 2017; Wang et al. 2017b). MDSCs are among the stromal cells which express PD-L1 in the tumor microenvironment (Iwata et al. 2016; Noman et al. 2014; Zhang et al. 2017). Macrophage colony-stimulating factor and vascular endothelial growth factor (VEGF) produced by human hepatocellular carcinoma cells induced PD-L1 in MDSCs (Iwata et al. 2016). Hypoxia-induced HIF-1α promoted the transcription of PD-L1 gene in MDSCs (Noman et al. 2014). MDSCs also modulate PD-1/PD-L1 axis by stimulating PD-L1 expression in tumor cells (Zhang et al. 2017) and B lymphocytes (Shen et al. 2018). Another mechanism utilized by MDSCs is upregulating PD-1 expression in T cells. Transforming growth factor (TGF)-β released by MDSCs induced expression of PD-1 in $CD8^+$ T cells (Chen et al. 2018). Figure 1 recapitulates the main mediators of the activation and immunosuppressive functions of MDSCs. As immunosuppression can facilitate cancer metastasis, the immunosuppressive role of MDSCs can be considered as one of the mechanisms to promote metastasis.

Metastasis-promoting Functions Beyond Immunosuppression in the Primary Tumor Site

As already stated, MDSCs can enhance metastatic process by mechanisms besides their immunosuppressive functions. To support this notion, studies in highly immunocompromised models such as non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mice have shown that MDSCs are implicated in cancer cell dissemination even in their defective state of immune system. Administration of anti-Gr1 antibody, which depletes MDSCs, reduces metastatic lesions in these models (Drews-Elger et al. 2014; Mauti et al. 2011; Song et al. 2016). Also, many studies have shown MDSCs play their role in metastasis by different ways including epithelial-to-mesenchymal transition, acquiring stemness features, invasiveness, and angiogenesis (Solito et al. 2017). Therefore, it appears that the role of MDSCs in the promotion of metastasis is beyond their immunosuppressive activity. The following paragraphs are an overview of evidence on non-immunosuppressive mechanisms which MDSCs use in primary tumor site to assist the process of metastasis formation.

Epithelial-to-Mesenchymal Transition

Epithelial-to-mesenchymal transition (EMT) is a process, in which a cell with epithelial phenotype changes to a cell with mesenchymal phenotype. The proceedings underlying this transition include alterations in cell-to-cell and cell-to-matrix interactions of epithelial cells, losing polarity due to some changes in cytoskeleton, as well as reduction in epithelial markers and increase in mesenchymal markers. When cultured epithelial cancer cells undergo EMT, they exhibit enhanced motility and invasive potential (Kalluri and Weinberg 2009). Toh et al. (2011) investigated the role of MDSCs in EMT. They showed that in vivo depletion of PMN-MDSC reduced the number of cells expressing markers of EMT (S100A4 and Vimentin) (Toh et al. 2011).

In another study, MDSCs induced EMT in nasopharyngeal carcinoma (NPC) cells in vitro and when injected subcutaneously with neoplastic cells; a higher number of metastatic lesions were formed compared to the injection of only neoplastic cells. The authors speculated that the mechanism of EMT induction by MDSCs was dependent on TGF-β and nitric oxide (NO) production by MDSCs upon contact with NPC cells. TGF-β and NO led to the upregulation of COX-2 in NPC cells and COX-2 activated β-catenin/TCF-4 pathway (Li et al. 2015). This pathway plays a critical role in EMT (Sanchez-Tillo et al. 2011).

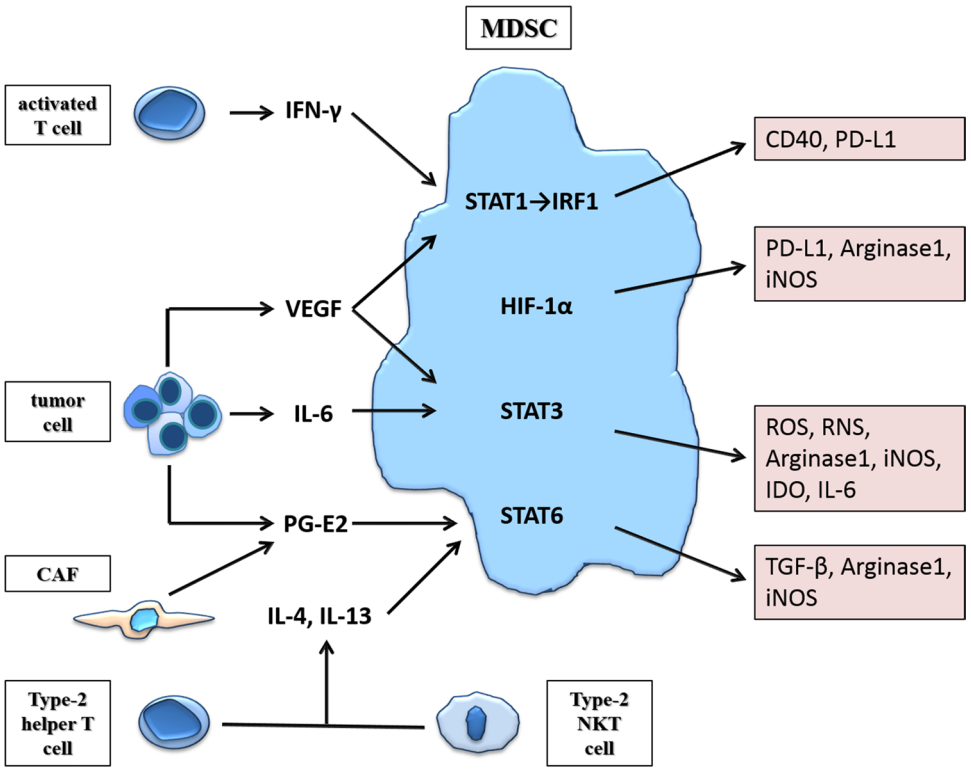

Fig. 1 Activation of myeloid-derived suppressor cells (MDSCs) and the mediators of their immunosuppressive activity. The interaction between tumor microenvironment and MDSCs prevents MDSCs from being differentiated and activates them to exert their immunosuppressive functions. Many cells in the tumor microenvironment contribute to the activation of MDSCs. Tumor-intrinsic factors and signals from other immune cells, matrix-forming cells and cellular components of tumor vasculature modulate the intracellular regulatory pathways of MDSCs. The resultant change in gene expression and cell metabolism is the production of membrane-bound molecules, secretory proteins and extracellular vesicles which suppress anti-tumor immune responses. *CAF* cancer-associated fibroblast, *CD40* cluster of differentiation 40, *HIF-1α* hypoxia-inducible factor-1α, *IDO* indoleamine 2,3-dioxygenase, *IFN-γ* interferon-γ, *IL* interleukin, *iNOS* inducible nitric oxide synthase, *IRF1* interferon regulatory factor 1, *MDSC* myeloid-derived suppressor cell, *NKT* cell natural killer T cell, *PD-L1* programmed cell death-ligand 1, *PG-E2* prostaglandin E2, *RNS* reactive nitrogen species, *ROS* reactive oxygen species, *STAT* signal transducer and activator of transcription, *TGF-β* transforming growth factor-β, *VEGF* vascular endothelial growth factor

In that study, it has been shown that COX-2 is important in the development of MDSCs. Suppression of COX-2 decreased interleukin (IL)-6 production, and consequently inhibited development of MDSC (Li et al. 2015).

In a study by Ouzounova et al. (2017), MDSC-mediated EMT was shown to be dependent on nitric oxide synthase 2 (NOS2). Coculture of M-MDSCs with murine breast cancer cells resulted in an increased expression of EMT markers (IL-6, IL-1A, TGF-β1, and Vimentin), enhanced invasiveness and increased number of cancer stem cells. The observed effects were attenuated by adding an NOS2 inhibitor to the culture medium (Ouzounova et al. 2017). Interestingly, M-MDSCs obtained from animal hosts bearing highly metastatic cancer cell line (4T1) were more efficient in the induction of EMT in cancer cells compared to the M-MDSCs obtained from hosts bearing tumors with much less metastatic potential (EMT6) (Ouzounova et al. 2017).

Moreover, MDSCs secrete IL-28 which promotes EMT, invasiveness, and metastasis through signal transducer and activator of transcription (STAT)3-dependent signaling (Mucha et al. 2014).

Cancer Stem Cell

Resembling normal stem cells, cancer stem cells (CSCs) are capable of self-renewal and asymmetric replication, providing continuous growth of tumor and diverse differentiation (Li et al. 2007; Papaccio et al. 2017). In asymmetric replication, the two daughter cells produced after maternal cell division show variations in differentiation state and fate. For instance, one of them is stem cell, while the other one is a non-stem cell (Yamashita et al. 2010). Theoretically, a cancer cell that has been settled in a distant organ must possess the so-called asymmetric replication ability to form an overt metastatic mass (Li et al. 2007). The exact origin of CSCs has not been elucidated so far. They may be the tumor-initiating cells, which resulted from neoplastic transformation of normal tissue stem cells or their committed

progenies. Another possibility is conferring stemness traits by cells that are not stem cells. Some studies showed that EMT may accompany or result in cancer stem cell formation from cells of no previous stemness potential (Li et al. 2007; Oskarsson et al. 2014). In the first study showing the role of MDSCs in the development of CSC, MDSCs increased the number of CSCs in ovarian tumor tissue. MDSCs rose up miRNA101 level, and in turn decreased the corepressor C-terminal-binding protein-2 (CtBP2). The reduction in CtBP2 expression stimulated stemness (Cui et al. 2013). When M-MDSCs were cocultured with pancreatic cancer cells, tumor cells with stemness properties and evidence of EMT were more abundant than pancreatic cancer cells without MDSCs. Inhibition of phospho-STAT3 was associated with the inability of M-MDSCs to enhance stemness and EMT in tumor cells. Also, IL-6 was partly involved in the increase in number of CSC (Panni et al. 2014).

Angiogenesis

Production of new vessels is a hallmark of cancer (Hanahan and Weinberg 2011). Positive correlation between angiogenesis/lymphangiogenesis and metastatic spread has been seen in many studies (Moserle and Casanovas 2013; Stacker et al. 2002). Newly formed vessels make it possible for tumors to survive, continue development, and metastasize. In addition, increased density of vessels in tumor tissue and the raised permeability of vessels due to their incomplete structure and cytokine effect during angiogenesis can ease cancer cell intravasation (Moserle and Casanovas 2013). MDSCs mediate angiogenesis via production of proangiogenic cytokines, secretion of tissue proteases, downregulation of inhibitors of tissue proteases and directly transforming to endothelial-like cells. MDSCs generate VEGF and fibroblast growth factor (FGF)-2 in a STAT3-dependent manner (Kujawski et al. 2008). $CD11b^+$ $Gr1^+$ cells (immunohistochemically the same as MDSCs) in tumor promote angiogenesis via expression of prokineticin1/Bv8. Bv8 leads to phosphorylation of MAPK in endothelial cells and tube formation. Granulocyte colony-stimulating factor (G-CSF)-mediated upregulation of Bv8 in bone marrow resulted in expansion and differentiation of $CD11b^+$ $Gr1^+$ cells in bone marrow and accumulation of these cells in the tumor (Shojaei et al. 2007a). STAT3 phosphorylation is mandatory for G-CSF-mediated Bv8 upregulation. Phosphorylated STAT3 directly enhances Bv8 transcription by binding to the enhancer of Bv8 gene promoter (Qu et al. 2012). Refractoriness to anti-VEGF therapy is associated with an increase in $CD11b^+$ $Gr1^+$ myeloid cells in peripheral blood and tumor. Increase in Bv8 is an important mechanism in tumor anti-VEGF therapy escape (Shojaei et al. 2007a, b). $CD11b^+$ $Gr1^+$ cells expressing Bv8 were more abundant in anti-VEGF refractory tumors than therapy-sensitive tumors (Shojaei et al. 2009). Development and recruitment of these cells in refractory tumors are inherent in these tissues and are not caused by treatment (Shojaei et al. 2007b). Adding anti-Bv8 to anti-VEGF results in a better control in tumor growth in anti-VEGF refractory tumors (Shojaei et al. 2007a, 2009). MDSCs produce matrix metalloproteinase 9 (MMP9) and to a lesser extent, some other MMPs (Finke et al. 2011; Ko et al. 2010; Murdoch et al. 2008; Yang et al. 2004). MMPs can boost angiogenesis by releasing stored pool of VEGF in extracellular matrix. MMP9 enhances soluble kit ligand (also called stem cell factor) release from bone marrow stromal cells that makes hematopoietic stem cells to enter a proliferative state. One study reported that tumor-infiltrating MDSCs can give rise to vessel formation by incorporating into vessel wall, i.e. MDSCs differentiate to endothelial-like cells and make new vessels (Yang et al. 2004). Supporting experimental evidence is needed to substantiate this route of MDSC-mediated neovasculogenesis.

Interaction with Other Immune Cells

Interplay between MDSCs and other immune cells such as NK cells (Hoechst et al. 2009; Park et al. 2013; Sato et al. 2015), γδ T cells (Oskarsson et al. 2014; Rutkowski et al. 2015; Yan and Huang 2014), macrophages (Beury et al. 2014; Ostrand-Rosenberg et al. 2012; Sinha et al. 2007), B cells (Bodogai et al. 2015; Thorn et al. 2014) and NKT cells (Lee et al. 2012; Lindau et al. 2013) can affect tumor microenvironment.

In some studies, γδ T cells were the main source of IL-17 in the tumor microenvironment. IL-17 works as a chemoattractant for MDSCs. IL-17 also upregulates chemokine production by cancer cells, which enhances MDSC accumulation in tumor. Additionally, IL-17 intensifies the immunosuppressive function of MDSCs. In human colorectal cancer, frequency of γδ T cells in tumor specimens was positively correlated with TNM stage, tumor size and metastasis formation (Yan and Huang 2014). In a murine model of hepatocellular carcinoma, IL-17A produced by γδ T cell had a substantial effect on tumor growth. IL-17A stimulated tumor cells to produce CXCL5, which resulted in the accumulation of MDSCs in tumor. The study also revealed a mutual activation loop between MDSCs and γδ T cells. IL-17A enhances immunosuppressive function of MDSCs and induces MDSCs to secrete IL-1β and IL-23 which activate IL-17-positive γδ T cells (Oskarsson et al. 2014).

The other interplay occurs between MDSCs and NKT cells. NKT cells can convert MDSCs into functional antigen-presenting cells (APC) (Lindau et al. 2013). In the differentiation of MDSCs to APCs, IFN-γ is important, which is secreted by NKT cells (Lee et al. 2012). Moreover, it has been shown that NKT cells can make T cells resistant to the immunosuppressive function of MDSCs (Lindau

et al. 2013). In a study, activation of NKT cells by low-dose glycolipid in surgically-resected breast cancer murine model decreased metastasis. The trial is accompanied by a decreased number and immunosuppressive function of MDSCs in animals (Lee et al. 2012).

The next cells interacting with MDSCs are tumor-evoked regulatory B cells, which are essential for the immunosuppressive activity of MDSCs. Metastasis was highly impaired in B-cell-deficient mice and administration of tumor-primed B cells or MDSCs in a wild-type background to B-cell-deficient mice restored metastasis in a study. In vitro study revealed a direct effect of tumor-B_{reg} in the immunosuppressive ability of MDSCs. This priming was partly dependent on TGF-β (Bodogai et al. 2015). Consistently, immunosuppressive $CD11b^+$ myeloid cells downregulate CD80 expression in B cells of metastatic liver, rendering them less effective stimulators of T-cell proliferation, an important cellular population in eliminating cancer cells (Thorn et al. 2014). B lymphocytes that are cocultured with MDSCs are potent inhibitors of T-cell proliferation and cytokine production. Coculture of MDSCs and B cells also promotes the production of a subset of tumor-evoked regulatory B cells that express the immune checkpoint PD-L1 (Zhang et al. 2017).

Local Invasion

Microscopic analysis of tumor tissues has revealed that MDSCs are more concentrated in tumor invasive fronts (Yang et al. 2008). When MDSCs are cocultured with tumor cells, increased invasiveness of neoplastic cells, examined by in vitro invasion assay, was observed. MMPs produced by MDSCs contribute to tumor migration and invasiveness. When MMPs are inhibited in MDSC–tumor cell coculture, the ability of MDSCs to promote cancer cell invasiveness is abrogated (Yang et al. 2008). MDSCs produced Bv8 that has a direct effect on metastatic breast cancer cells by prokineticin receptor 1 (PKR-1), which fosters migration of cancer cells. Nonmetastatic breast cancer cell lines did not express PKR-1 and did not show increased invasiveness in response to Bv8. When PKR-1 expression was induced in nonmetastatic cancer cell lines, Bv8 administration to medium could increase cancer cell migration (Kowanetz et al. 2010).

MDSCs exhibit diminished expression of neutrophilic granule protein (NGP) during cancer metastasis. NGP is a cysteine protease inhibitor that can inhibit tumor invasion and angiogenesis by inhibition of Cathepsin B (Boutte et al. 2011). TGF-β activated $Ly6C^{high}Ly6G^{high}$ $CD11b^+$ MDSCs potentiates tumor metastasis through stimulation of fibroblast migration. Arousing fibroblast migration was seen to be cytokine mediated. The principal cytokine involved was FGF-2. Coculture of MDSCs with carcinoma cells alone did not enhance tumor metastasis. However, when they were cocultured with both carcinoma cells and fibroblasts simultaneously, carcinoma cells demonstrated higher invasiveness. Inhibition of FGF receptor-3 could completely abrogate the effect of MDSCs on tumor invasiveness (Shawet al. 2015).

IL-6 Trans-Signaling

IL-6 is a proinflammatory cytokine with well-known roles in cancer pathogenesis (Guo et al. 2012). Interaction of IL-6/IL-6 receptor (IL-6R) with the membrane protein gp130 is necessary for intracellular signaling of IL-6. Interestingly, cells lacking IL-6R can also be stimulated by IL-6. This observation can be explained by IL-6 trans-signaling. In this phenomenon, a soluble form of IL-6R binds to IL-6 in biological fluids and this complex associates with membrane gp-130 and lets cells to be affected by IL-6 (Rose-John 2012). IL-6 trans-signaling showed to be important in tumor invasiveness and metastasis in vitro and in vivo. In a murine model, MDSCs related to cancer cell line with high metastatic potential could activate cancer cells by IL-6 trans-signaling. MDSCs produced both IL-6 and a disintegrin and a metalloprotease (ADAM) family proteases. It seems that ADAMs, which are metalloproteases, hydrolyze IL-6R in the surface of MDSCs. The hydrolyzed IL-6R then sheds from the cell surface and mediates IL-6 trans-signaling (Oh et al. 2013).

MDSCs in Metastatic Site

To form a colony of cancer cells in a distant organ, an extravasated cancer cell and its progeny must survive, proliferate and progress in metastatic site. Successful completion of this process is determined by both factors intrinsic to the metastatic cells and the hostile tissue invaded. The metastatic cells must be protected from killing, receive enough blood supply and other environmental supports needed. The term "premetastatic niche" describes changes in the destination organ prior to cancer cell arrival to the site. These changes are in response to factors released by primary tumor and make the site a more suitable place for cancer cell metastasis. A hallmark of premetastatic niche is the accumulation of immunosuppressive and metastasis-promoting leukocytes in the location (Kaplan et al. 2005; Steeg 2016).

MDSCs accumulate in distant metastatic organs during different stages of tumor progression. They are present in distant sites before cancer cell arrival, and they prepare the site to adopt the coming neoplastic cells and then support neoplastic cell growth to form overt metastatic lesions. MDSCs present in distant site can exert their metastasis-promoting function through mechanisms such as immunosuppression (Connolly et al. 2010; Mauti et al. 2011; Sangaletti et al. 2014; Sceneay et al. 2012; Yan et al. 2010), recruitment

of tumor cells to distant site (Erler et al. 2009; Kowanetz et al. 2010; Zhao et al. 2016a), mesenchymal-to-epithelial transition (Gao et al. 2012), increasing cancer cell survival (Yan et al. 2015), enhancing neoplastic cell proliferation (Gao et al. 2012; Zhao et al. 2015, 2016a), angiogenesis (Lim et al. 2015; Yan et al. 2010) and extracellular matrix remodeling (Gao et al. 2012; Sangaletti et al. 2014) (Fig 2).

Many studies have revealed the correlation between the presence of MDSC in distant sites and markers of diminished anti-tumor immunity including decreased T-cell-mediated cytotoxicity (Connolly et al. 2010), IFN-γ production (Yan et al. 2010) and NK cell function (Mauti et al. 2011; Sceneay et al. 2012) and increased Treg generation (Connolly et al. 2010).

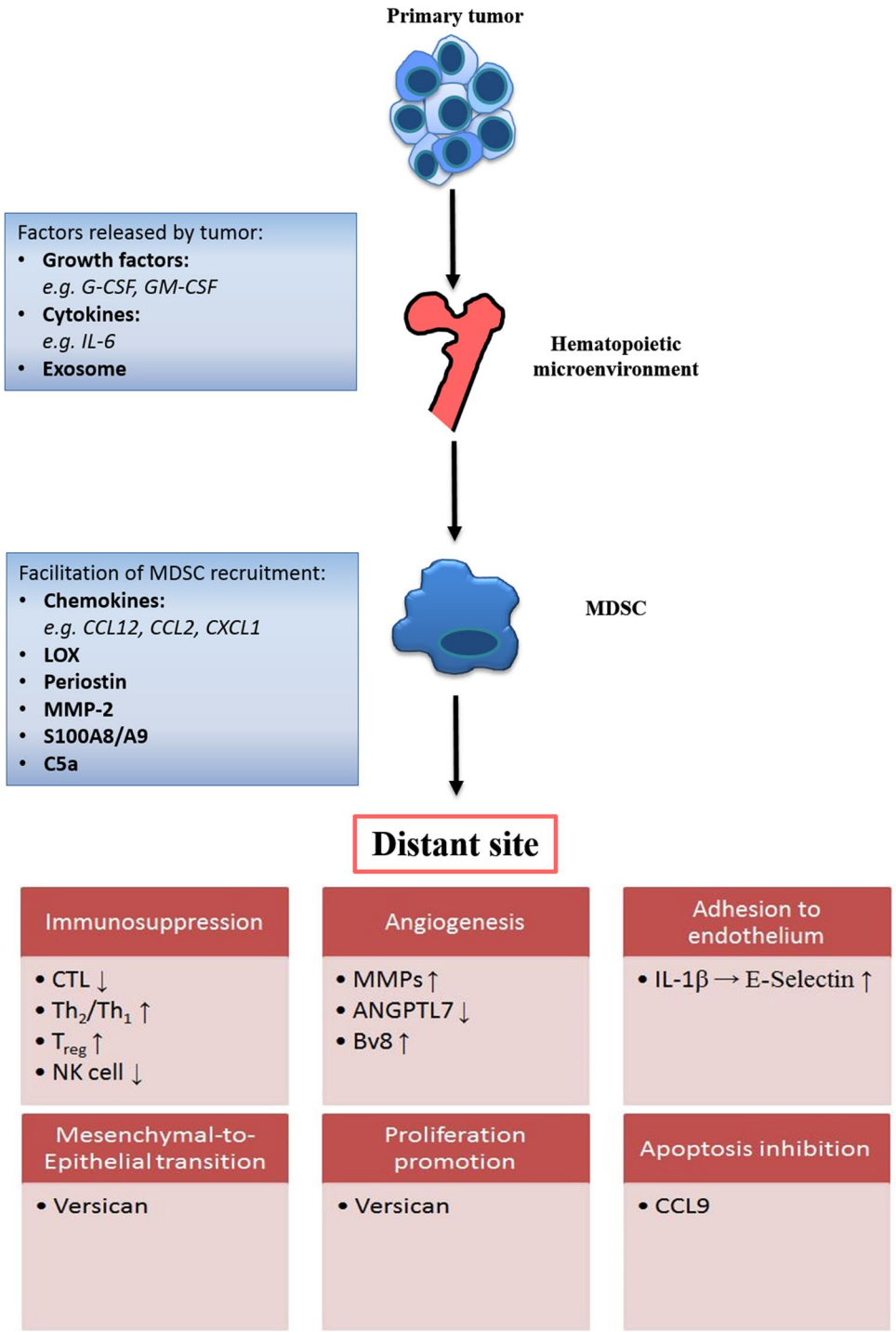

Fig. 2 Accumulation of myeloid-derived suppressor cells (MDSCs) and their metastasis-promoting functions in premetastatic and metastatic microenvironments. Significant changes in myelopoiesis accompany progression of a cancerous lesion. MDSCs arise as a consequence of altered myelopoiesis in response to factors released by neoplastic cells and their associated stroma. These factors can be either soluble molecules, such as growth factors and cytokines, or exosomes which are membrane-surrounded particles. MDSCs enter distant sites where they work in favor of cancer dissemination by means of contributing to immunosuppression, angiogenesis, cancer cell adhesion to endothelium, mesenchymal-to-epithelial transition, enhancing cancer cell proliferation and survival and extracellular matrix remodeling. *ANGPTL7* angiopoietin-like factor 7, Bv8 Bombina variegate 8, C5a complement component 5a, *CCL12* chemokine (C–C motif) ligand 12, *CCL2* chemokine (C–C motif) ligand 2, *CCL9* chemokine (C–C motif) ligand 9, *CTL* cytotoxic T lymphocyte, *CXCL1* chemokine (C–X–C motif) ligand 1, E-Selectin endothelial selectin, *G-CSF* granulocyte-colony-stimulating factor, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *IL* interleukin, *LOX* lysyl oxidase, *MDSC* myeloid-derived suppressor cell, *MMP* matrix metalloproteinase, *NK* cell natural killer cell, Th_1 T helper 1 cell, Th_2 T helper 2 cell, T_{reg} regulatory T cell

M-MDSCs produce versican, an extracellular matrix chondroitin sulfate proteoglycan, in metastatic lungs of breast cancer models and human patients. Knockdown of versican in bone marrow hematopoietic cells led to decreased versican expression in metastatic lung. Although immunohistochemical analysis detected no effect on micrometastasis formation, macrometastases were significantly reduced. Suppressing versican in bone marrow hematopoietic cells did not influence recruitment of MDSCs to lungs, expression of immunomodulatory molecules in lungs and primary tumor growth. The effect of versican on metastatic lesion growth seems to be mediated by its direct promotion of cell proliferation and mesenchymal-to-epithelial transition. Mechanism of versican involvement in gaining epithelial phenotype could be explained by a reduction in phosphorylated Smad2 level after versican administration to the culture medium, as TGF-β-Smad2 pathway induces epithelial-to-mesenchymal transition (Gao et al. 2012).

Fibrocytes are circulating cells with characteristics of both hematopoietic and fibroblastic cells. These cells differentiate to fibroblasts after entering peripheral tissues (Terai et al. 2015). Recent studies give credit to fibrocyte involvement in the pathogenesis of cancer, as they can increase tumor proliferation and mediate tumor fibrosis and immunosuppression (Zhang et al. 2013b; Terai et al. 2015). Knocking out the transcription factor KLF4 in MDSCs impairs breast cancer and melanoma metastasis to lungs. Although there is not enough strong evidence, the study also showed that MDSCs can transdifferentiate to fibrocyte. Interestingly, KLF4 is essential for MDSC differentiation to fibrocytes. It may cause this differentiation by inducing transcription of fibroblast-specific protein (FSP)-1, which is a fibroblast marker. KLF4 deficiency decreases recruitment of a specific subset of MDSCs expressing CCR2 to metastatic lung. The metastatic lungs in bone marrow KLF4$^{-/-}$ hosts also harbors fewer myofibroblasts (Shi et al. 2014). Coinjection of fibrocytes with cancer cells enhances lung metastasis. Fibrocyte administration increases recruitment of M-MDSCs to metastatic lung. Adoptively transferred fibrocytes induce host CCL2 production which stimulates recruitment of M-MDSCs (van Deventer et al. 2013). F-box protein FBXW7 is a tumor suppressor gene that recognizes substrates such as NOTCH, MYC and cyclin E for degradation (Welcker and Clurman 2008). These substrates are important regulators of intracellular signaling, metabolism and cell growth (Dang 1999; Fortini 2009; Hwang and Clurman 2005). In mice with FBXW7-deleted bone marrow, more metastatic lesions developed in lungs after injection of melanoma and Lewis lung carcinoma cells to tail vein than control wild-type mice. Also after orthotropic breast cancer transplantation, number and the average surface of metastatic nodules in lungs were greater for FBXW7-deficient mice than control wild-type mice. Increased recruitment of M-MDSCs and macrophages was observed in metastatic lungs of mice lacking FBXW7 in bone marrow. The infiltration of M-MDSCs and macrophages to metastatic lung was at least partly dependent on the CCL2/CCR2 pathway. The source of CCL2 in this model was bone marrow-derived stromal cells, which expressed FSP similar to fibrocytes. FBXW7 deletion leads to an increase in intracellular NOTCH level which upregulates CCL2 mRNA transcription in bone marrow-derived stromal cells (Yumimoto et al. 2015). Bringing together the information obtained from these studies, cells residing in the metastatic organs cause CCL2 production and recruit MDSCs to the distant site via this cytokine.

Lysosomal acid lipase (LAL) hydrolyzes cholesteryl esters and triglyceride in lysosomes. In a mouse model, more metastasis to lungs occurred following intravenous injection of melanoma cells when myeloid lineage cells were not expressing LAL (Zhao et al. 2015). In another study, LAL deficiency in hematopoietic cells directed myelopoiesis toward overproduction of MDSCs (Zhao et al. 2015). LAL-nonexpressing PMN-MDSCs enhanced cancer cell proliferation more efficiently than LAL-expressing PMN-MDSCs (Zhao et al. 2015, 2016a). *lal*$^{-/-}$ PMN-MDSCs produced more tumor necrosis factor (TNF)-α compared to its *lal*$^{+/+}$ counterpart. Using a TNF-α antagonist abolished the proliferative effect of MDSCs (Zhao et al. 2015). *lal*$^{-/-}$ Ly6G^{+} cells also promote neoplastic cell migration in an in vitro tumor cell migratory assay (Zhao et al. 2016a). *lal*$^{-/-}$ MDSCs, compared to lal$^{+/+}$ MDSCs, are more potent in inducing proliferation of bone marrow MSCs. Bone marrow MSCs have a role in facilitating cancer metastasis (Zhao et al. 2016b). Two major signaling mechanisms have been related to the role of lal$^{-/-}$ MDSCs in tumor progression. mTOR pathway is overactivated in *lal*$^{-/-}$ PMN-MDSCs and its inhibition impairs the metastasis of melanoma cells (Zhao et al. 2015). Metabolites formed upon LAL action activate PPARγ. PPARγ downstream gene expression is altered in *lal*$^{-/-}$ PMN-MDSCs. Coinjection of melanoma cells with PPARγ pretreated *lal*$^{-/-}$ PMN-MDSCs resulted in less extensive metastasis than coinjection with untreated *lal*$^{-/-}$ PMN-MDSCs. PPARγ ligand administration reduced intracellular levels of activated forms of mTOR pathway components, suggesting that effect of PPARγ on *lal*$^{-/-}$ PMN-MDSCs function may be at least partially dependent on mTOR pathway (Zhao et al. 2016a) though more investigation is required to investigate the exact interaction between these two pathways in the function of MDSCs.

CD11b^{+} Gr1^{+} myeloid cells, which infiltrate metastatic liver, downregulate angiopoietin-like 7 (ANGPTL7) in cancer cells. ANGPTL7 is an antiangiogenic factor and its overexpression decreases the size of metastatic lesion (Lim et al. 2015).

MDSCs are also involved in complications of metastasis to target organs. MDSCs are contributors to osteolytic bone disease in breast cancer and multiple myeloma models (Binsfeld et al. 2016; Olechnowicz and Edwards 2014; Sawant et al. 2013). They differentiate to osteoclasts in response to RANKL (Olechnowicz and Edwards 2014; Sawant et al. 2013). The exact mechanism underlying differentiation of MDSCs to osteoclasts in metastatic bone environment is not clearly described. In a study, NO level was elevated during the process and differentiation was shown to be NO dependent (Sawant et al. 2013).

Premetastatic Niche Formation

The fact that bone marrow-derived cells exist in distant organs before metastasis formation was proved about a decade ago (Kaplan et al. 2005). A recent study tracked hematopoietic lineage cell mobilization to premetastatic sites. Bone marrow hematopoietic stem cells and multipotent progenitor cells started increased proliferation in response to factors released by primary tumor during a period of time when no tumor cell could be found in distant tissues. The expanded bone marrow-derived cells entered bloodstream and then mobilized to multiple tissues. After intravenous injection of hematopoietic stem/progenitor cells of tumor-bearing mice to tumor-bearing and healthy control mice, some evolved into MDSCs in recipient tissues. Transforming to MDSCs was more efficient in tumor-bearing mice in comparison with healthy mice, indicating the importance of tumor-derived factors in this process (Giles et al. 2016).

$CD11b^+$ $Gr1^+$ myeloid cells infiltrate premetastatic lungs of mice bearing 4T1 breast cancer. These MDSCs inhibited IFN-γ production and alternatively increased Th2 induction in the premetastatic lung (Yan et al. 2010). Therefore, MDSCs may provide an immune-permissive environment for malignant cells in the premetastatic site.

MDSCs produced MMP-2 and MMP-9 in the premetastatic niche in lung. MMPs promoted the generation of aberrant and leaky vessels in the premetastatic lung tissue. Deletion of host MMP-9 abolished the formation of aberrant vessels in the premetastatic lung and decreased lung metastasis; however, it did not significantly affect primary tumor growth (Yan et al. 2010).

MDSCs help circulating cancer cells to find their way to the distant site. In a murine model of melanoma, M-MDSCs produced IL-1β which upregulated E-selectin on the endothelium of premetastatic lungs. E-selectin contributes to the adhesion of circulating cancer cells to the endothelium of the target organ (Shi et al. 2017).

In another study, the chemokine CCL9 was expressed in premetastatic lungs of murine breast cancer and melanoma models more than healthy controls. Both culture of $CD11b^+$ $Gr1^+$ myeloid cells in tumor-conditioned media and coculture of these cells with tumor cells in one media resulted in the production of CCL9 by myeloid cells. These data suggest that cell-to-cell contact is not necessary for CCL9 induction in $CD11b^+$ $Gr1^+$ cells; therefore, presumably released factor(s) partly mediates this effect, but contact between MDSCs and cancer cells is also a stimulator of CCL9 expression as more efficient CCL9 induction occurs in coculture experiment. CCL9 knockout in $CD11b^+$ $Gr1^+$ myeloid cell did not influence primary tumor growth but decreased tumor metastasis to lung. Tumors with higher metastatic potentials expressed more CCR1, the only receptor known for CCL9, compared to tumors with lower metastatic potentials. Neoplastic cells of metastatic nodules expressed higher levels of CCR1 than their primary tumor counterparts. CCL9 deficiency did not affect cancer cell extravasation. CCL9 promotes neoplastic cell survival and renders them more resistant to apoptosis-inducing conditions (Yan et al. 2015).

Mechanisms underlying accumulation of MDSCs in premetastatic sites are not fully understood. Chemokines and chemokine receptors have been shown to be involved in recruitment of MDSCs to premetastatic sites. Lung tissue-derived CCL12 attracts M-MDSCs to premetastatic lungs of mice (Shi et al. 2017). Anti-CCL2 antibody attenuates the mobilization of M-MDSCs into premetastatic lungs and consequently impairs lung metastasis (Eisenblaetter et al. 2017). CXCL1 regulates infiltration of PMN-MDSCs in premetastatic liver in a murine model of colon cancer. VEGF-A produced by colorectal carcinoma cells is required for CXCL1 production (Wang et al. 2017a).

Hypoxic tumor cells in primary site secrete lysyl oxidase (LOX) into circulation (Erler et al. 2009). Also, MDSCs infiltrating to the primary tumor tissue produce TGF-β and make myofibroblasts producing LOX (Connolly et al. 2010). Lysyl oxidase lodges in distant tissues and crosslinks collagen type IV. Implantation of tumor cells with silenced *lox* gene dramatically abrogates accumulation of $CD11b^+$ myeloid cells and c-Kit^+ myeloid progenitor cells in premetastatic sites. The effect of LOX on metastasis formation seems to be dependent on MMPs produced by recruited myeloid cells. Collagen crosslinking increases MMP-2 production by myeloid cells. This induction seems to be dependent on direct contact of myeloid cells with cross-linked collagens. MMPs thus intensify myeloid cell invasion in premetastatic site. Moreover, the peptide fragment generated from collagen cleavage by MMPs further recruits cancer cells to the site (Erler et al. 2009). A study showed a temporal relationship between collagen crosslinking in lungs, $CD11b^+$ cell recruitment to lungs and cancer cell metastasis (Wong et al. 2011).

The matricellular protein *periostin* is involved in infiltration of MDSCs to premetastatic lungs. Periostin is almost absent in the intact lung but it is increased in lungs of

tumor-bearing mice before cancer cell arrival. Hosts lacking periostin showed significantly fewer metastatic nodules in lungs after inoculation of breast cancer cells orthotopically. In agreement, considerably fewer MDSCs accumulate in premetastatic lungs in periostin-deficient mice. Periostin is required for LOX-mediated establishment of the premetastatic niche (Wang et al. 2016). The mentioned role may be explained by an independent observation that showed periostin binds to bone morphogenetic protein (BMP)-1 and enables BMP-1 to post-transcriptionally modify and activate LOX (Maruhashi et al. 2010).

STAT3 is the most recognized transcription factor in regulating expansion, recruitment and function of MDSCs (Motallebnezhad et al. 2016). Both the primary tumor cell and myeloid STAT3 are crucial for establishing premetastatic niche and cancer metastasis to lung. STAT3 inhibition in myeloid cells later in disease course reduces metastasis, indicating STAT3 is also required for premetastatic and metastatic niche preservation (Deng et al. 2012).

Bv8 is highly produced by $Ly6G^+$ $Ly6C^+$ granulocytes in lungs of mice with breast cancer in both premetastatic and metastatic phases. G-CSF is produced by carcinoma and host cells in primary and metastatic tumor. Anti-G-CSF antibody completely abrogates accumulation of $Ly6G^+$ $Ly6C^+$ cells in blood and premetastatic lungs, in concert with the decreased Bv8 level in lungs. Anti-G-CSF antibody also impairs cancer metastasis (Kowanetz et al. 2010).

Carbonic anhydrase IX (CA9) is a transmembrane enzyme overexpressed in hypoxic tumor cells of different cancer types (Supuran and Winum 2015). In a breast cancer murine model, CA9 was required for G-CSF-mediated accumulation of PMN-MDSCs in premetastatic lungs and its silencing inhibited cancer metastasis to lungs. The study revealed that CA9 induction of G-CSF production was dependent on NF-κB activation (Chafe et al. 2015).

Exosomes released by cancer cells are the other contributors to formation of premetastatic niche (Costa-Silva et al. 2015; Wen et al. 2016). They are membrane-surrounded particles containing protein, DNA, and coding and non-coding RNA. These particles are released from cells to their outside. Then other cells can take them up, thus providing a means for intercellular communication (Zhang et al. 2015b). Demonstrating their role in metastasis, after intravenous administration of exosomes derived from highly metastatic breast cancer, bone marrow-derived cells in the lung tissue showed uptake of these exosomes. Repeated administration led to the increased number of bone marrow-derived cells and increased frequency of PMN-MDSCs in the lung tissue (Wen et al. 2016).

Decrease in metastasis formation in lung and liver of breast cancer-bearing mice was observed in the case of C5a receptor deficiency in host. Administration of C5a receptor antagonist disrupts accumulation of MDSCs in premetastatic lungs and lessens the production of immunosuppressive cytokines TGF-β and IL-10 (Vadrevu et al. 2014).

S100A8/A9 produced in primary tumor microenvironment or premetastatic sites may be a key molecule in potentiating metastasis to lung and liver (Hiratsuka et al. 2006, 2008; Ichikawa et al. 2011). S100A8 and S100A9 are two members of a calcium-binding protein superfamily. Their principal active form is S100A8/A9 heterodimer, also named Calprotectin. It binds to glycosaminoglycans, receptor for advanced glycosylation endproducts (RAGE) and toll-like receptor 4 (TLR4) (Pruenster et al. 2016). In murine models of breast cancer, S100A8/A9 molecule is increased in premetastatic lungs as the tumor progresses. The increase in S100A8/A9 level is concomitant with the recruitment of MDSCs to premetastatic lungs (Eisenblaetter et al. 2017; Vrakas et al. 2015). During colorectal carcinoma progression, $CD11b^+$ $Gr1^+$ MDSCs accumulate in the premetastatic liver. Their accumulation was abrogated in S100A8/A9 null mice or by administration of anti-carboxylated glycan antibody (Ichikawa et al. 2011). S100A8/A9 is a chemoattractant for MDSCs. Treatment of tumor-bearing mice with S100A8/A9 neutralizing antibodies decreases the accumulation of MDSCs in the body (Sinha et al. 2008). Furthermore, S100A8/A9 enhances migratory ability of MDSCs (Zheng et al. 2015). MDSCs themselves are a source of S100A8/A9 in cancer patients (Zheng et al. 2015). $CD11b^+$ $Gr1^+$ cells expressed S100A8 and RAGE two- to threefolds more in tumor-bearing mice than tumor-free ones (Sinha et al. 2008). Coexpression of these molecules in MDSCs may indicate an autoregulatory loop, which is remarked in some other studies (Deng et al. 2017; Sinha et al. 2008; Wang et al. 2013). Hiratsuka et al. (2008) showed that S100A8/A9 stimulates pulmonary endothelial cells and macrophages to produce serum amyloid A3 (SAA3). SAA3 binds to TLR4 on myeloid cells, activates NF-κB pathway and recruits myeloid cells to premetastatic lungs. It can also enhance migration of malignant cells via a TLR4-mediated signaling. SAA3 further augments its production in a TLR4-mediated manner (Hiratsuka et al. 2008). Another study showed that expression of this protein is increased in M-MDSCs, but not in PMN-MDSCs, during cancer progression, leading to M-MDSCs viability by a TLR2-dependent mechanism. Interfering with endogenous production of SAA3 in M-MDSCs diminished their viability. SAA3 increased the immunosuppressive ability of M-MDSCs again in a TLR2-based manner (Lee et al. 2014).

Recruitment of bone marrow-derived cells to the distant organ is not the only prerequisite for accepting cancer cells as new residents of the organ. The recruited myeloid cells must also be able to modify the destination site in some ways to grant disseminated cell survival and progression. Injection of conditioned media from both weakly and highly metastatic cancer cell lines leads to infiltration of

$CD11b^+$ myeloid cells to lungs. Myeloid cells recruited in response to conditioned media from cancer cells with lower metastatic potential produce significantly higher thrombospondin-1 which impairs metastatic process by constraining cancer cell proliferation (Catena et al. 2013).

Conclusion

Growing research over the past decade has expanded our understanding on interactions between tumors and the immune system enormously. Tumors can hide from the immune system, suppress its anti-tumor functions or manipulates its components to foster malignant propagation.

Despite appreciable advancements made in cancer treatment, patients with metastatic disease are finally condemned to death mainly due to lack of enough efficacious therapies. Unraveling the pathogenesis of metastasis can enrich the armamentarium in fighting against this fatal process.

Here, we reviewed evidence for contribution of myeloid-derived suppressor cells in cancer metastasis. As these cells can promote metastasis affecting various aspects of this process including immunosuppression, epithelial–mesenchymal transition, cancer stem cell formation, angiogenesis, invasion, premetastatic niche formation, cancer cell survival and growth in the metastatic site, these cells can be considered a promising target for metastasis treatment. Besides, MDSCs are involved in other aspects of cancer progression and they are a major determinant of responsiveness to some anti-cancer therapies or treatment failure. Strategies for targeting MDSCs can be directed to interfering with development of MDSCs, trafficking to primary and distant tissues, viability, intrinsic and extrinsic regulation of function and their effectors. Since MDSCs are immature cells, propelling these cells to more differentiated stages of development without tumor-promoting function or even tumor suppressive effect can be another favorable means. There are several ambiguities about MDSCs that can become clarified more. Our knowledge of exact mechanisms, signaling pathways and intercellular and cell-to-matrix communications involved in metastasis-promoting functions of MDSCs are still rudimentary. Another issue that has not been investigated so far is the participation of MDSCs in establishing or maintaining cancer stem cell niche environment in the metastatic site and mechanisms of dormancy. The related knowledge can be translated to new therapies as well.

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Compliance with ethical standards

Conflict of interest The authors declare they had no conflicts of interest.

References

Beury DW, Parker KH, Nyandjo M et al (2014) Cross-talk among myeloid-derived suppressor cells, macrophages, and tumor cells impacts the inflammatory milieu of solid tumors. J Leukoc Biol 96:1109–1118

Bianchi G, Borgonovo G, Pistoia V et al (2011) Immunosuppressive cells and tumour microenvironment: focus on mesenchymal stem cells and myeloid derived suppressor cells. Histol Histopathol 26:941–951

Binsfeld M, Muller J, Lamour V et al (2016) Granulocytic myeloid-derived suppressor cells promote angiogenesis in the context of multiple myeloma. Oncotarget 7:37931–37943

Bodogai M, Moritoh K, Lee-Chang C et al (2015) Immunosuppressive and prometastatic functions of myeloid-derived suppressive cells rely upon education from tumor-associated B cells. Cancer Res 75:3456–3465

Boutte AM, Friedman DB, Bogyo M et al (2011) Identification of a myeloid-derived suppressor cell cystatin-like protein that inhibits metastasis. FASEB J 25:2626–2637

Bronte V, Brandau S, Chen SH et al (2016) Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. Nat Commun 7:12150

Catena R, Bhattacharya N, El Rayes T et al (2013) Bone marrow-derived Gr1 + cells can generate a metastasis-resistant microenvironment via induced secretion of thrombospondin-1. Cancer Discov 3:578–589

Chafe SC, Lou Y, Sceneay J et al (2015) Carbonic anhydrase IX promotes myeloid-derived suppressor cell mobilization and establishment of a metastatic niche by stimulating G-CSF production. Cancer Res 75:996–1008

Chen X, Wang L, Li P et al (2018) Dual TGF-beta and PD-1 blockade synergistically enhances MAGE-A3-specific CD8(+) T cell response in esophageal squamous cell carcinoma. Int J Cancer. https://doi.org/10.1002/ijc.31730

Chiang AC, Massagué J (2008) Molecular basis of metastasis. N Engl J Med 359:2814–2823

Choi HS, Ha SY, Kim HM et al (2016) The prognostic effects of tumor infiltrating regulatory T cells and myeloid derived suppressor cells assessed by multicolor flow cytometry in gastric cancer patients. Oncotarget 7:7940–7951

Condamine T, Ramachandran I, Youn JI et al (2015) Regulation of tumor metastasis by myeloid-derived suppressor cells. Annu Rev Med 66:97–110

Condamine T, Dominguez GA, Youn JI et al (2016) Lectin-type oxidized LDL receptor-1 distinguishes population of human polymorphonuclear myeloid-derived suppressor cells in cancer patients. Sci Immunol 1(2):aaf8943

Connolly MK, Mallen-St Clair J, Bedrosian AS et al (2010) Distinct populations of metastases-enabling myeloid cells expand in the liver of mice harboring invasive and preinvasive intra-abdominal tumor. J Leukoc Biol 87:713–725

Costa-Silva B, Aiello NM, Ocean AJ et al (2015) Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver. Nat Cell Biol 17:816–826

Cui TX, Kryczek I, Zhao L et al (2013) Myeloid-derived suppressor cells enhance stemness of cancer cells by inducing

microRNA101 and suppressing the corepressor CtBP2. Immunity 39:611–621
Dang CV (1999) c-Myc target genes involved in cell growth, apoptosis, and metabolism. Mol Cell Biol 19:1–11
Deng J, Liu Y, Lee H et al (2012) S1PR1-STAT3 signaling is crucial for myeloid cell colonization at future metastatic sites. Cancer Cell 21:642–654
Deng Z, Rong Y, Teng Y et al (2017) Exosomes miR-126a released from MDSC induced by DOX treatment promotes lung metastasis. Oncogene 36:639–651
Drews-Elger K, Iorns E, Dias A et al (2014) Infiltrating S100A8 + myeloid cells promote metastatic spread of human breast cancer and predict poor clinical outcome. Breast Cancer Res Treat 148:41–59
Eisenblaetter M, Flores-Borja F, Lee JJ et al (2017) Visualization of tumor-immune interaction - target-specific imaging of S100A8/A9 reveals pre-metastatic niche establishment. Theranostics 7:2392–2401
Erler JT, Bennewith KL, Cox TR et al (2009) Hypoxia-induced lysyl oxidase is a critical mediator of bone marrow cell recruitment to form the premetastatic niche. Cancer Cell 15:35–44
Finke J, Ko J, Rini B et al (2011) MDSC as a mechanism of tumor escape from sunitinib mediated anti-angiogenic therapy. Int Immunopharmacol 11:856–861
Fortini ME (2009) Notch signaling: the core pathway and its post-translational regulation. Dev Cell 16:633–647
Gao D, Joshi N, Choi H et al (2012) Myeloid progenitor cells in the premetastatic lung promote metastases by inducing mesenchymal to epithelial transition. Cancer Res 72:1384–1394
Giles AJ, Reid CM, Evans JD et al (2016) Activation of hematopoietic stem/progenitor cells promotes immunosuppression within the pre-metastatic niche. Cancer Res 76:1335–1347
Guo Y, Xu F, Lu T et al (2012) Interleukin-6 signaling pathway in targeted therapy for cancer. Cancer Treat Rev 38:904–910
Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144:646–674
Hiratsuka S, Watanabe A, Aburatani H et al (2006) Tumour-mediated upregulation of chemoattractants and recruitment of myeloid cells predetermines lung metastasis. Nat Cell Biol 8:1369–1375
Hiratsuka S, Watanabe A, Sakurai Y et al (2008) The S100A8-serum amyloid A3-TLR4 paracrine cascade establishes a pre-metastatic phase. Nat Cell Biol 10:1349–1355
Hoechst B, Voigtlaender T, Ormandy L et al (2009) Myeloid derived suppressor cells inhibit natural killer cells in patients with hepatocellular carcinoma via the NKp30 receptor. Hepatology 50:799–807
Hwang HC, Clurman BE (2005) Cyclin E in normal and neoplastic cell cycles. Oncogene 24:2776–2786
Ichikawa M, Williams R, Wang L et al (2011) S100A8/A9 activate key genes and pathways in colon tumor progression. Mol Cancer Res 9:133–148
Iwata T, Kondo Y, Kimura O et al (2016) PD-L1(+)MDSCs are increased in HCC patients and induced by soluble factor in the tumor microenvironment. Sci Rep 6:39296
Jiang J, Guo W, Liang X (2014) Phenotypes, accumulation, and functions of myeloid-derived suppressor cells and associated treatment strategies in cancer patients. Hum Immunol 75:1128–1137
Kalluri R, Weinberg RA (2009) The basics of epithelial–mesenchymal transition. J Clin Invest 119:1420–1428
Kaplan RN, Riba RD, Zacharoulis S et al (2005) VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. Nature 438:820–827
Ko JS, Rayman P, Ireland J et al (2010) Direct and differential suppression of myeloid-derived suppressor cell subsets by sunitinib is compartmentally constrained. Cancer Res 70:3526–3536
Kowanetz M, Wu X, Lee J et al (2010) Granulocyte-colony stimulating factor promotes lung metastasis through mobilization of Ly6G+ Ly6C+ granulocytes. Proc Natl Acad Sci USA 107:21248–21255
Kujawski M, Kortylewski M, Lee H et al (2008) Stat3 mediates myeloid cell–dependent tumor angiogenesis in mice. J Clin Invest 118:3367–3377
Leber MF, Efferth T (2009) Molecular principles of cancer invasion and metastasis (review). Int J Oncol 34:881–895
Lee JM, Seo JH, Kim YJ et al (2012) The restoration of myeloid-derived suppressor cells as functional antigen-presenting cells by NKT cell help and all-trans-retinoic acid treatment. Int J Cancer 131:741–751
Lee JM, Kim EK, Seo H et al (2014) Serum amyloid A3 exacerbates cancer by enhancing the suppressive capacity of myeloid-derived suppressor cells via TLR2-dependent STAT3 activation. Eur J Immunol 44:1672–1684
Li F, Tiede B, Massagué J et al (2007) Beyond tumorigenesis: cancer stem cells in metastasis. Cell Res 17:3–14
Li ZL, Ye SB, OuYang LY et al (2015) COX-2 promotes metastasis in nasopharyngeal carcinoma by mediating interactions between cancer cells and myeloid-derived suppressor cells. Oncoimmunology 4:e1044712
Lim SY, Gordon-Weeks A, Allen D et al (2015) Cd11b(+) myeloid cells support hepatic metastasis through down-regulation of angiopoietin-like 7 in cancer cells. Hepatology 62:521–533
Lindau D, Gielen P, Kroesen M et al (2013) The immunosuppressive tumour network: myeloid-derived suppressor cells, regulatory T cells and natural killer T cells. Immunology 138:105–115
Lu C, Redd PS, Lee JR et al (2016) The expression profiles and regulation of PD-L1 in tumor-induced myeloid-derived suppressor cells. Oncoimmunology 5:e1247135
Maruhashi T, Kii I, Saito M et al (2010) Interaction between periostin and BMP-1 promotes proteolytic activation of lysyl oxidase. J Biol Chem 285:13294–13303
Marvel D, Gabrilovich DI (2015) Myeloid-derived suppressor cells in the tumor microenvironment: expect the unexpected. J Clin Invest 125:3356–3364
Mauti LA, Le Bitoux MA, Baumer K et al (2011) Myeloid-derived suppressor cells are implicated in regulating permissiveness for tumor metastasis during mouse gestation. J Clin Invest 121:2794–2807
Moserle L, Casanovas O (2013) Anti-angiogenesis and metastasis: a tumour and stromal cell alliance. J Intern Med 273:128–137
Motallebnezhad M, Jadidi-Niaragh F, Qamsari ES et al (2016) The immunobiology of myeloid-derived suppressor cells in cancer. Tumour Biol 37:1387–1406
Mucha J, Majchrzak K, Taciak B et al (2014) MDSCs mediate angiogenesis and predispose canine mammary tumor cells for metastasis via IL-28/IL-28RA (IFN-λ) signaling. PLoS One 9:e103249
Murdoch C, Muthana M, Coffelt SB et al (2008) The role of myeloid cells in the promotion of tumour angiogenesis. Nat Rev Cancer 8:618–631
Noman MZ, Desantis G, Janji B et al (2014) PD-L1 is a novel direct target of HIF-1alpha, and its blockade under hypoxia enhanced MDSC-mediated T cell activation. J Exp Med 211:781–790
Obermajer N, Muthuswamy R, Lesnock J et al (2011) Positive feedback between PGE2 and COX2 redirects the differentiation of human dendritic cells toward stable myeloid-derived suppressor cells. Blood 118:5498–5505
Oh K, Lee OY, Shon SY et al (2013) A mutual activation loop between breast cancer cells and myeloid-derived suppressor cells facilitates spontaneous metastasis through IL-6 trans-signaling in a murine model. Breast Cancer Res 15:R79
Olechnowicz SW, Edwards CM (2014) Contributions of the host microenvironment to cancer-induced bone disease. Cancer Res 74:1625–1631

Oskarsson T, Batlle E, Massagué J (2014) Metastatic stem cells: sources, niches, and vital pathways. Cell Stem Cell 14:306–321
Ostrand-Rosenberg S, Sinha P, Beury DW et al (2012) Cross-talk between myeloid-derived suppressor cells (MDSC), macrophages, and dendritic cells enhances tumor-induced immune suppression. Semin Cancer Biol 22:275–281
Ouzounova M, Lee E, Piranlioglu R et al (2017) Monocytic and granulocytic myeloid derived suppressor cells differentially regulate spatiotemporal tumour plasticity during metastatic cascade. Nat Commun 8:14979
Pan PY, Ma G, Weber KJ et al (2010) Immune stimulatory receptor CD40 is required for T-cell suppression and T regulatory cell activation mediated by myeloid-derived suppressor cells in cancer. Cancer Res 70:99–108
Panni RZ, Sanford DE, Belt BA et al (2014) Tumor-induced STAT3 activation in monocytic myeloid-derived suppressor cells enhances stemness and mesenchymal properties in human pancreatic cancer. Cancer Immunol Immunother 63:513–528
Papaccio F, Paino F, Regad T et al (2017) Concise review: cancer cells, cancer stem cells, and mesenchymal stem cells: influence in cancer development. Stem Cells Transl Med 6:2115–2125
Park YJ, Song B, Kim YS et al (2013) Tumor microenvironmental conversion of natural killer cells into myeloid-derived suppressor cells. Cancer Res 73:5669–5681
Pruenster M, Vogl T, Roth J et al (2016) S100A8/A9: from basic science to clinical application. Pharmacol Ther 167:120–131
Qu X, Zhuang G, Yu L et al (2012) Induction of Bv8 expression by granulocyte colony-stimulating factor in CD11b+ Gr1+ cells: key role of Stat3 signaling. J Biol Chem 287:19574–19584
Rose-John S (2012) IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6. Int J Biol Sci 8:1237–1247
Rutkowski MR, Stephen TL, Svoronos N et al (2015) Microbially driven TLR5-dependent signaling governs distal malignant progression through tumor-promoting inflammation. Cancer Cell 27:27–40
Sanchez-Tillo E, de Barrios O, Siles L et al (2011) beta-catenin/TCF4 complex induces the epithelial-to-mesenchymal transition (EMT)-activator ZEB1 to regulate tumor invasiveness. Proc Natl Acad Sci USA 108:19204–19209
Sangaletti S, Tripodo C, Sandri S et al (2014) Osteopontin shapes immunosuppression in the metastatic niche. Cancer Res 74:4706–4719
Sato Y, Shimizu K, Shinga J et al (2015) Characterization of the myeloid-derived suppressor cell subset regulated by NK cells in malignant lymphoma. Oncoimmunology 4:e995541
Sawant A, Deshane J, Jules J et al (2013) Myeloid-derived suppressor cells function as novel osteoclast progenitors enhancing bone loss in breast cancer. Cancer Res 73:672–682
Sceneay J, Chow MT, Chen A et al (2012) Primary tumor hypoxia recruits CD11b+/Ly6Cmed/Ly6G+ immune suppressor cells and compromises NK cell cytotoxicity in the premetastatic niche. Cancer Res 72:3906–3911
Seshadri M, Poduval TB, Sundaram K (1979) Studies on metastases. I. Role of sensitization and immunosuppression. J Natl Cancer Inst 63:1205–1210
Shaw AK, Pickup MW, Chytil A et al (2015) TGFβ signaling in myeloid cells regulates mammary carcinoma cell invasion through fibroblast interactions. PLoS One 10:e0117908
Shen T, Zhou L, Shen H et al (2017) Prognostic value of programmed cell death protein 1 expression on CD8+ T lymphocytes in pancreatic cancer. Sci Rep 7:7848
Shen M, Wang J, Yu W et al (2018) A novel MDSC-induced PD-1(−) PD-L1(+) B-cell subset in breast tumor microenvironment possesses immuno-suppressive properties. Oncoimmunology 7:e1413520
Shi Y, Ou L, Han S et al (2014) Deficiency of Kruppel-like factor KLF4 in myeloid-derived suppressor cells inhibits tumor pulmonary metastasis in mice accompanied by decreased fibrocytes. Oncogenesis 3:e129
Shi H, Zhang J, Han X et al (2017) Recruited monocytic myeloid-derived suppressor cells promote the arrest of tumor cells in the premetastatic niche through an IL-1beta-mediated increase in E-selectin expression. Int J Cancer 140:1370–1383
Shiels MS, Copeland G, Goodman MT et al (2015) Cancer stage at diagnosis in patients infected with the human immunodeficiency virus and transplant recipients. Cancer 121:2063–2071
Shojaei F, Wu X, Zhong C et al (2007a) Bv8 regulates myeloid-cell-dependent tumour angiogenesis. Nature 450:825–831
Shojaei F, Wu X, Malik AK et al (2007b) Tumor refractoriness to anti-VEGF treatment is mediated by CD11b+ Gr1+ myeloid cells. Nat Biotechnol 25:911–920
Shojaei F, Wu X, Qu X et al (2009) G-CSF-initiated myeloid cell mobilization and angiogenesis mediate tumor refractoriness to anti-VEGF therapy in mouse models. Proc Natl Acad Sci USA 106:6742–6747
Sinha P, Clements VK, Bunt SK et al (2007) Cross-talk between myeloid-derived suppressor cells and macrophages subverts tumor immunity toward a type 2 response. J Immunol 179:977–983
Sinha P, Okoro C, Foell D et al (2008) Proinflammatory S100 proteins regulate the accumulation of myeloid-derived suppressor cells. J Immunol 181:4666–4675
Solito S, Pinton L, Mandruzzato S (2017) In brief: myeloid-derived suppressor cells in cancer. J Pathol 242:7–9
Song J, Lee J, Kim J et al (2016) Pancreatic adenocarcinoma up-regulated factor (PAUF) enhances the accumulation and functional activity of myeloid-derived suppressor cells (MDSCs) in pancreatic cancer. Oncotarget 7:51840–51853
Stacker SA, Achen MG, Jussila L et al (2002) Lymphangiogenesis and cancer metastasis. Nat Rev Cancer 2:573–583
Steeg PS (2016) Targeting metastasis. Nat Rev Cancer 16:201–218
Supuran CT, Winum JY (2015) Carbonic anhydrase IX inhibitors in cancer therapy: an update. Future Med Chem 7:1407–1414
Terai S, Fushida S, Tsukada T et al (2015) Bone marrow derived "fibrocytes" contribute to tumor proliferation and fibrosis in gastric cancer. Gastric Cancer 18:306–313
Thorn M, Point GR, Burga RA et al (2014) Liver metastases induce reversible hepatic B cell dysfunction mediated by Gr-1+ CD11b+ myeloid cells. J Leukoc Biol 96:883–894
Toh B, Wang X, Keeble J et al (2011) Mesenchymal transition and dissemination of cancer cells is driven by myeloid-derived suppressor cells infiltrating the primary tumor. PLoS Biol 9:e1001162
Topalian SL, Drake CG, Pardoll DM (2015) Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell 27:450–461
Ugel S, De Sanctis F, Mandruzzato S et al (2015) Tumor-induced myeloid deviation: when myeloid-derived suppressor cells meet tumor-associated macrophages. J Clin Invest 125:3365–3376
Umansky V, Blattner C, Gebhardt C et al (2016) The role of myeloid-derived suppressor cells (MDSC) in cancer progression. Vaccines 4:E36
Vadrevu SK, Chintala NK, Sharma SK et al (2014) Complement c5a receptor facilitates cancer metastasis by altering T-cell responses in the metastatic niche. Cancer Res 74:3454–3465
van Deventer HW, Palmieri DA, Wu QP et al (2013) Circulating fibrocytes prepare the lung for cancer metastasis by recruiting Ly-6C+ monocytes via CCL2. J Immunol 190:4861–4867
Vrakas CN, O'Sullivan RM, Evans SE et al (2015) The measure of DAMPs and a role for S100A8 in recruiting suppressor cells in breast cancer lung metastasis. Immunol Invest 44:174–188
Wang L, Chang EW, Wong SC et al (2013) Increased myeloid-derived suppressor cells in gastric cancer correlate with cancer stage

and plasma S100A8/A9 proinflammatory proteins. J Immunol 190:794–804
Wang Z, Xiong S, Mao Y et al (2016) Periostin promotes immunosuppressive premetastatic niche formation to facilitate breast tumour metastasis. J Pathol 239:484–495
Wang D, Sun H, Wei J et al (2017a) CXCL1 is critical for pre-metastatic niche formation and metastasis in colorectal cancer. Cancer Res 77:3655–3665
Wang Q, Liu F, Liu L (2017b) Prognostic significance of PD-L1 in solid tumor: an updated meta-analysis. Medicine (Baltimore) 96:e6369
Welcker M, Clurman BE (2008) FBW7 ubiquitin ligase: a tumour suppressor at the crossroads of cell division, growth and differentiation. Nat Rev Cancer 8:83–93
Wen SW, Sceneay J, Lima LG et al (2016) The biodistribution and immune suppressive effects of breast cancer-derived exosomes. Cancer Res 76:6816–6827
Wong CC, Gilkes DM, Zhang H et al (2011) Hypoxia-inducible factor 1 is a master regulator of breast cancer metastatic niche formation. Proc Natl Acad Sci USA 108:16369–16374
Wyczechowska D et al (2015) Isolation and characterization of human MDSC from peripheral blood of patients with various malignancies (TUM6P. 971). J Immunol 194(1 Supplement):141.119–141.119
Yamashita YM, Yuan H, Cheng J et al (2010) Polarity in stem cell division: asymmetric stem cell division in tissue homeostasis. Cold Spring Harb Perspect Biol 2:a001313
Yan J, Huang J (2014) Innate γδT17 cells convert cancer-elicited inflammation into immunosuppression through myeloid-derived suppressor cells. Oncoimmunology 3:e953423
Yan HH, Pickup M, Pang Y et al (2010) Gr-1+ CD11b+ myeloid cells tip the balance of immune protection to tumor promotion in the premetastatic lung. Cancer Res 70:6139–6149
Yan HH, Jiang J, Pang Y et al (2015) CCL9 induced by TGFbeta signaling in myeloid cells enhances tumor cell survival in the premetastatic organ. Cancer Res 75:5283–5298
Yang L, DeBusk LM, Fukuda K et al (2004) Expansion of myeloid immune suppressor Gr+ CD11b+ cells in tumor-bearing host directly promotes tumor angiogenesis. Cancer Cell 6:409–421
Yang L, Huang J, Ren X et al (2008) Abrogation of TGF beta signaling in mammary carcinomas recruits Gr-1+ CD11b+ myeloid cells that promote metastasis. Cancer Cell 13:23–35
Ye XZ, Yu SC, Bian XW (2010) Contribution of myeloid-derived suppressor cells to tumor-induced immune suppression, angiogenesis, invasion and metastasis. J Genet Genomics 37:423–430
Yumimoto K, Akiyoshi S, Ueo H et al (2015) F-box protein FBXW7 inhibits cancer metastasis in a non-cell-autonomous manner. J Clin Invest 125:621–635
Zhang B, Wang Z, Wu L et al (2013a) Circulating and tumor-infiltrating myeloid-derived suppressor cells in patients with colorectal carcinoma. PLoS One 8:e57114
Zhang H, Maric I, DiPrima MJ et al (2013b) Fibrocytes represent a novel MDSC subset circulating in patients with metastatic cancer. Blood 122:1105–1113
Zhang G, Huang H, Zhu Y et al (2015a) A novel subset of B7-H3+ CD14+ HLA-DR-/low myeloid-derived suppressor cells are associated with progression of human NSCLC. Oncoimmunology 4:e977164
Zhang X, Yuan X, Shi H et al (2015b) Exosomes in cancer: small particle, big player. J Hematol Oncol 8:83
Zhang Y, Velez-Delgado A, Mathew E et al (2017) Myeloid cells are required for PD-1/PD-L1 checkpoint activation and the establishment of an immunosuppressive environment in pancreatic cancer. Gut 66:124–136
Zhao T, Du H, Ding X et al (2015) Activation of mTOR pathway in myeloid-derived suppressor cells stimulates cancer cell proliferation and metastasis in lal(−/−) mice. Oncogene 34:1938–1948
Zhao T, Du H, Blum JS et al (2016a) Critical role of PPARgamma in myeloid-derived suppressor cell-stimulated cancer cell proliferation and metastasis. Oncotarget 7:1529–1543
Zhao T, Yan C, Du H (2016b) Lysosomal acid lipase in mesenchymal stem cell stimulation of tumor growth and metastasis. Oncotarget 7:61121–61135
Zheng R, Chen S, Chen S (2015) Correlation between myeloid-derived suppressor cells and S100A8/A9 in tumor and autoimmune diseases. Int Immunopharmacol 29:919–925