

Review

MDSCs: The Key Players in the Formation of Pre-Metastatic Niche

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Abstract

The distal metastasis of tumor cells is viewed as a series of concurrent processes rather than a linear cascade of events. Accompanied with the progression of the primary tumor, a favorable microenvironment, referred as pre-metastatic niche, has been created in pre-metastatic organs and sites by primary tumors for subsequent metastases. The proposal of “pre-metastatic niche” theory brings fresh insight into our understanding of cancer metastasis. Myeloid-derived suppressor cells (MDSCs) are indispensable for the formation of pre-metastatic niche, which empower the niche to favor tumor cell colonization and promote metastasis. In this review, we aim to provide a comprehensive understanding of the regulation of pre-metastatic niche formation by MDSCs and to conceptualize the framework for understanding the related factors involved in cancer metastasis.

Keywords: MDSCs; pre-metastatic niche; recruitment; function

1. Introduction

The distal metastasis of tumor cells remains the dominant cause of cancer-related mortality. Metastasis is a multiple stepwise cell-biological process, which involves: one or several tumor cells acquire the capacity to invade locally through surrounding extracellular matrix (ECM) and stromal cell layers; intravasate into the circulation and escape from immune surveillance; arrest at distant organ sites; extravasate into the parenchyma of distant tissues; form micro-metastases in these foreign microenvironments; reinitiate their proliferative programs at metastatic sites, thereby generating macro-metastasis [1–3]. Traditionally, previous studies were mainly focused on oncogenic transformation, epithelial-mesenchymal transition (EMT), cancer stem-like cells (CSCs), etc. These perspectives were appealing while limited. The famous “seed and soil” hypothesis was proposed by Stephen Paget in 1889, which is widely cited and accepted, proposing the importance of both pre-metastatic tumor cells and a supportive microenvironment. In recent years, based on the “seed and soil” hypothesis, a new concept of “pre-metastatic niche” brought fresh insight into our understanding of cancer metastasis.

The theory of pre-metastatic niche was first proposed by Kaplan *et al.* [4] in 2005, who demonstrated that the vascular endothelial growth factor receptor 1 (VEGFR1⁺) cells from the bone marrow homed to tumor-specific pre-metastatic sites before the arrival of metastatic tumor cells, providing a permissive microenvironment for incoming tumor cells. Since then, much attention was focused on the characteristics and significance of the pre-metastatic niche in metastasis. Apart from MDSC, the formation of pre-metastatic niches is a result of tumor-secreted factors,

tumor-derived exosomes, reprogramming of tissue-resident stromal cells, etc. Myeloid-derived suppressor cells (MDSCs) are one kind of bone marrow-derived myeloid cells (BMDs), which play a major role in the pre-metastatic niche. A decreased accumulation of MDSCs in the pre-metastatic lung is associated with increased disease-free survival and overall survival [5]. In this review, we aim to conceptualize the framework and highlight the dynamic interplay between MDSCs and pre-metastatic niche.

2. The Characteristic of MDSCs

MDSC is a heterogeneous population, which is consist of immature myeloid cells and myeloid progenitor cells. Now MDSC is widely studied in pathological fields, such as tumors, bacterial and parasitic infections, chronic inflammation, sepsis and autoimmunity, though they were first characterized in tumor patients and tumour-bearing mice (Table 1).

Undoubtedly, most of the MDSCs are derived from hematopoietic progenitor cells (HPC), which are markedly expanded in the bone marrow, and then enter the blood stream and get the immunosuppressive activity. MDSCs include two major subtypes: polymorphonuclear (PMN) and monocytic (M)-MDSC, which were termed based on their phenotypic and morphological features. In mice, the surface marker of MDSCs is CD11b⁺Gr1⁺. Depending on the two different epitopes of Gr1, M-MDSCs are characterized as CD11b⁺Ly6C^{hi}Ly6G⁺, and PMN-MDSCs are CD11b⁺Ly6C^{low}Ly6G⁺. In human, the standard phenotypical markers of M-MDSCs are CD14⁺CD15⁺HLA-DR^{low/-} and PMN-MDSCs are CD11b⁺CD14⁺CD15⁺/CD66b⁺. The LIN⁻ (including



Table 1. Surface markers to define MDSCs.

Name	Markers (mouse)	Markers (human)
Total MDSCs	CD11b ⁺ Gr1 ⁺	HLA-DR ⁺ CD11b ⁺ CD33 ⁺
M-MDSCs	CD11b ⁺ Ly6C ^{hi} Ly6G ⁻	CD14 ⁺ CD15 ⁻ HLA-DR ^{low/-}
PMN-MDSCs	CD11b ⁺ Ly6C ^{low} Ly6G ⁺	CD11b ⁺ CD14 ⁻ CD15 ⁺ /CD66b ⁺
eMDSCs	-	LIN ⁻ (CD3, CD14, CD15, CD19, CD56) HLA-DR ⁻ CD33 ⁺
F-MDSCs	-	CD33 ⁺ IL4Ra ⁺

Table 2. Factors associated with the accumulation of MDSCs in pre-metastatic niche.

Factor	Source	MDSC subset	Receptor	Model	Reference
CXCL1	tumor-associated macrophage in the primary tumor	CXCR2 ⁺ MDSCs	CXCR2	colorectal cancer	[10]
SDF-1	systemic TIMP-1 treated hepatocyte	PMN-MDSCs	CXCR4	colorectal cancer	[21]
CCL2	BMDCs	MDSCs	CCR2	breast cancer	[5,22,37]
CCL12	alveolar macrophages	M-MDSCs	-	melanoma	[23,38]
IL6	-	PMN-MDSCs	-	lung cancer, colorectal cancer	[24,25]
G-CSF	-	MDSC	-	melanoma, lung cancer, lymphoma, breast cancer	[26,27,39]
COX1	platelet	CX ₃ CR1 ⁺ M-MDSCs	-	melanoma	[28]
HIF1 α	breast tumor cells	PMN-MDSCs	-	breast cancer	[29]
LOX	breast tumor cells	CD11b ⁺ myeloid cells	-	breast cancer	[30,31]
periostin	-	MDSCs	-	breast cancer	[32]
PGE2	-	MDSCs	-	prostate cancer	[33]
S100A8/A9	MDSCs	MDSCs	TLR4	lung cancer, breast cancer	[34,35]
miR-494	MDSCs	CXCR4 ⁺ MDSCs	-	breast cancer	[36]

CD3, CD14, CD15, CD19, CD56) HLA-DR⁻CD33⁺ cells are now defined as “early-stage MDSCs” (eMDSCs), which contain mixed groups of MDSC comprising more immature progenitors. The eMDSC subset has only been identified in human (not in mouse). In addition, a novel fibrocytic MDSCs (F-MDSCs) was described in human, which share the characterization of MDSC-, DC-, and fibrocyte-associated markers [6–9]. However, the reports about F-MDSCs are limited, and a better understanding of association between F-MDSCs and typical MDSCs is needed.

In addition to be detected in the blood, MDSCs have also been found in the lung and liver, which were two organs for future distal metastasis. Different from blood, the PMN-MDSCs from livers of NSG (NOD/SCID/IL2rg^{-/-}) mice do not express Ly6C [10]. Furthermore, in most experimental tumor models, the number of PMN-MDSCs are more markedly elevated than M-MDSCs, especially in pre-metastatic liver [10–12]. Similar to PMN-MDSCs, M-MDSCs have also been detected outside of the circulation, including in primary tumor sites, pre-metastatic tissues, metastatic lesions, and lymph nodes [13]. Different from monocytes, the differentiation of M-MDSCs into conventional macrophages (M Φ) and dendritic cells (DCs) is inhibited in the pre-metastatic tissues. The types of pathologic microenvironment determine the pathway of M-MDSCs differentiation. The M-MDSCs subset has the potential to give rise to a subset of CD11b^{hi}Gr1^{low}Ly6G⁻F4/80^{hi}

macrophages with potent immunosuppressive property in response to hypoxia, VEGF and colony-stimulating factor 1 (CSF1), which was termed as TAMs (tumor associated macrophages) [14,15]. This subset can also differentiate into inflammatory DCs after migration to the tumor microenvironment [16,17]. The existence of immune suppressive regulatory DCs in tumor microenvironment was described in recent years, but whether these DCs are immunosuppressive needs a further illustration. Some reported that M-MDSCs can contribute to the accumulation of tumor associated DCs by differentiating to inflammatory DCs (inf-DCs), which have specific phenotype and are critical components of anti-tumor response [16]. Some revealed that cancers can subvert DC function, inducing DC tolerization in the tumor microenvironment [18,19]. Accordingly, the PMN-MDSCs, M-MDSCs, TAM and DCs together accumulate in the tumor microenvironment, as well as in the pre-metastatic tissues, providing a tolerogenic environment and favoring tumor progression [19,20].

3. Recruitment of MDSCs in the Pre-Metastatic Niche

Multiple factors induce the mobilization of MDSCs to the pre-metastatic niche, including chemokines, growth factors, interleukins, resided extracellular matrix components and so on (Table 2, Ref [5,10,21–39]).

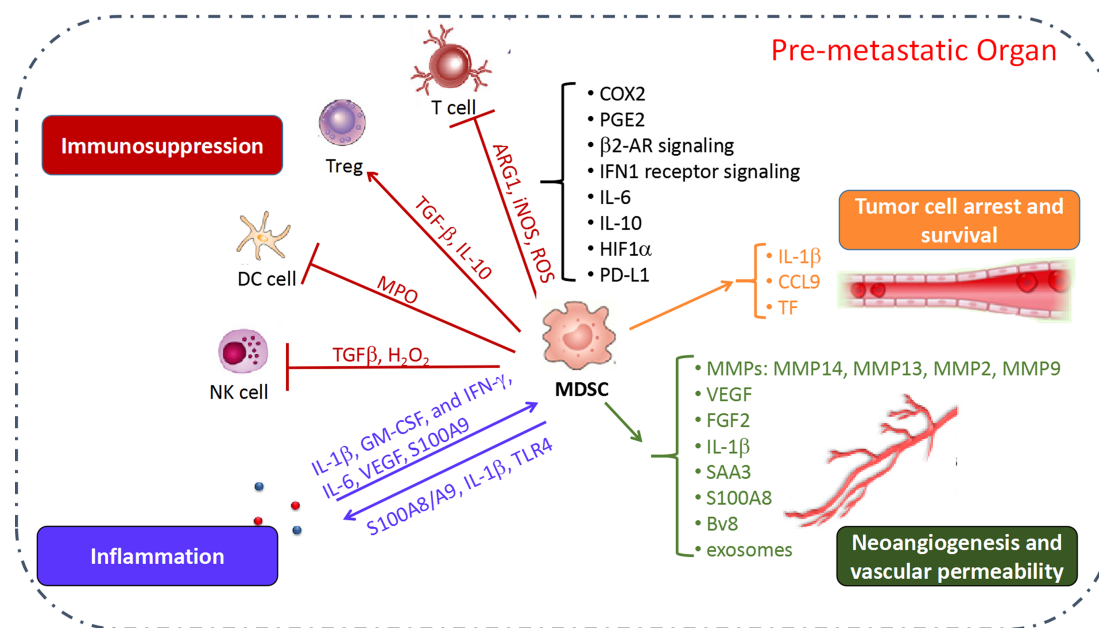


Fig. 1. Effects of MDSCs in the tumor pre-metastatic organs. MDSCs exert immunosuppression by regulating T cells, Treg, DCs and NK cells.

CXCL1 is one kind of chemokines which is originally known to recruit neutrophils during tissue damage [40]. In colorectal carcinoma, the tumor-associated macrophages produced CXCL1, which is induced by tumor cells secreted VEGFA, recruits CXCR2-positive MDSCs to form a pre-metastatic niche that ultimately promotes liver metastases [10]. The SDF-1/CXCR4-dependent Ly6G⁺ PMN-MDSCs recruitment in mice creates a pre-metastatic niche in the liver, a process which is initiated by elevated systemic levels of tissue inhibitor of metalloproteinases (TIMP-1) [21]. In breast cancer, the CCL2 induced Ly6C⁺CCR2⁺ M-MDSCs expansion in the pulmonary pre-metastatic niche facilitate lung metastasis, and the sole neutralization of CCL2 in hypoxic conditioned medium (HCM) results in decreased CD11b⁺Ly6C^{med}Ly6G⁺ myeloid cells in the pre-metastatic niche and reduced metastatic burden *in vivo* [22]. Our previous study shows that the knockdown of CCL12 in tumor-bearing mice significantly decreased M-MDSCs infiltration into the pre-metastatic lungs, resulting in reduced E-selectin expression and decreased tumor cell metastasis [23]. Interleukin 6 (IL-6) is a cytokine which is widely expressed in multiple immune cells and malignant tumors. The IL-6 accumulation has been reported to be associated with the enrichment of immunosuppressive MDSC in different cancer types, including malignant melanoma, hepatocellular carcinoma (HCC), squamous cell carcinoma (SCC), ovarian cancer and bladder cancer [41]. In lung cancer, IL-6 gene knockout in Gprc5a-ko/IL-6-ko mice completely reversed the G-MDSCs upregulation and M-MDSCs downregulation in Gprc5a-ko mice [24]. Increased S1PR1-STAT3 signaling in colorectal cancer cells induces a production of IL-6, leading to more MDSCs infiltration

that could prime distant pre-metastatic sites in the liver, and high level of circulating IL-6 associates with the percentage of CD14⁺HLA-DR^{-/low} MDSCs in the patients correlated with colorectal cancer liver metastasis (CRLM) [25]. Granulocyte colony-stimulating factor (G-CSF) is generally believed to induce the differentiation of myeloid progenitor and MDSC expansion. In the breast cancer model, G-CSF is detected to drive the mobilization of MDSC to the lung metastatic niche [26], and anti-G-CSF treatment dramatically decreased the number of circulating or tumor-associated CD11b⁺Gr1⁺ cells [27]. COX-1/TXA2 pathway in platelets participant in the aggregation of platelets on tumor cells, endothelial activation, and recruitment of metastasis-promoting CX₃CR1⁺ M-MDSCs, thus inhibition of this pathway in platelets diminishes the formation of a pre-metastatic niche [28].

MDSCs sustain tumor progression by establishing a pre-metastatic niche and dynamically remodeling the tumor microenvironment through the production of angiogenic factors and metalloproteases. Correspondingly, a class of matricellular proteins affect the recruitment and the immune-suppressive activity of MDSCs [42]. The upregulated fibronectin expressed by resident fibroblasts induced by tumor-specific growth factors, interact with VLA-4 expressed on VEGFR1⁺ BMDCs, supporting the adhesion of the BMDCs to form the pre-metastatic niche [4]. In breast cancer, primary tumor hypoxia not only provides hypoxia-inducible factor 1α (HIF-1α) but also increases secretion of lysyl oxidase (LOX) in plasma through the HIF-1α/LOX axis, which are both capable of recruiting CD11b⁺ myeloid cells, contributing to tumor progression by pre-metastatic niche formation [29–31]. Periostin (POSTN) is one kind of

nonstructural ECM proteins, which function as adaptor and modulator of interaction between cells and their extracellular microenvironment. In a mouse breast tumor model, POSTN is found to enhance the accumulation and immunosuppressive functions of MDSCs in the pre-metastatic lungs [32]. In addition, COX-2/mPGES-1/PGE2 modulates the accumulation of MDSCs to metastasized lungs in prostate cancer [33]. The upregulated S100A8/A9 in the pre-metastatic lung recruits MDSCs in an TLR4/MD-2 dependent manner [34,35].

Growing numbers of ncRNAs have been reported to have specific functions and underlying mechanisms in the formation of tumor microenvironment and pre-metastatic niches, ranging from microRNAs to long ncRNAs [43]. miR-494, which is dramatically induced by tumor-derived transforming growth factor β 1 (TGF- β 1), plays an essential role in regulating the accumulation and activity of MDSCs by targeting of phosphatase and tensin homolog (PTEN) and activation of the Akt pathway [36].

In addition to be mobilized by tumor-related factors, the circulating MDSCs in the blood can also protect the circulating tumors cells (CTCs) from being eliminated, shielding CTCs from immune surveillance [44]. In the microenvironment of blood, the CTCs and circulatory PMN-MDSCs form CTC/MDSC clusters and increase the metastatic properties of CTCs through ROS/Notch/Nodal signaling [45].

4. Functions of MDSCs in the Pre-Metastatic Niche

MDSCs are the major component for the formation of the pre-metastatic microenvironment before tumor distal metastasis or after surgical resection of primary tumors in mouse models of pulmonary metastases. Compared with chemotherapy, the adjuvant epigenetic treatment leads to longer periods of disease-free survival and overall survival, which can decrease the accumulation of MDSCs in the pre-metastatic lung [5]. Within the pre-metastatic niche, MDSCs are shown to suppress immune response, induce an inflammatory microenvironment, promote neoangiogenesis and vascular permeability, and promote the arrest and survival of tumor cells (Fig. 1). These evidences demonstrate that MDSCs might be the protagonist in the pre-metastatic niche, playing essential roles in the formation of pre-metastatic niche.

4.1 MDSCs Suppress Immune Response in Pre-Metastatic Niche

A main feature of MDSCs is immune suppression activity, which are important negative regulators of host innate immunity in tumor microenvironment. MDSCs utilize multiple suppressive mechanism to inhibit CD8⁺ T, DC, and natural killer cells (NK) through arginase 1 (ARG1), inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS) and so on.

One of the suppressive mechanisms attributed to MDSCs is the inhibition of T cell activation and proliferation. Different subsets of MDSCs might use different mechanisms by which to suppress T-cell. L-arginine (L-Arg) is a conditionally necessary amino acid which serves as a substrate for two enzymes: iNOS and ARG. Lack of L-Arg blocks T-cell proliferation and decreases expression of CD3 ζ chain and interferon γ (IFN γ) production [46–48]. Recent findings indicate that both MDSCs subsets express ARG1, which converted L-Arg into urea and L-ornithine. In addition, there are substantial differences of depriving L-Arg by MDSCs between mice and human. In murine MDSCs, an increased uptake and intracellular degradation of L-Arg is detected. In human MDSCs, enhanced ARG expression is found in the circulation [49]. Furthermore, multiple studies indicate that the PMN-MDSCs express higher level of ARG than M-MDSCs [50–52]. In addition, the expression of ARG1 is regulated by inflammatory cytokine and tumor cell-derived factors. In lung cancer, head and neck tumor, colon carcinoma and renal carcinoma, tumor cells derived cyclooxygenase-2 (COX2) induces and maintains ARG1 production, and PGE2 induces ARG1 expression in MDSCs by signaling through the E-prostanoid (EP) 4 receptor [53]. Increased stress-induced activation of β 2-AR signaling in MDSCs modulates the expression of ARG1, which is dependent upon STAT3 phosphorylation [54]. In hepatocellular carcinoma (HCC), wild-type hepatic stellate cells (HSCs)-induced MDSCs expressed increased level of iNOS and ARG1 compared with MDSCs induced by IL-6-deficient HSCs *in vitro* [55]. Additionally, IL-6/IL-8-ARG1 axis of CD45⁺CD33^{low}CD11b^{dim} MDSCs in human gastric cancer suppress CD8⁺ T cell activity [51].

Elevated iNOS expression is a hallmark of MDSCs in tumor-bearing condition. Only M-MDSCs express high level of iNOS, which metabolize L-Arg into NO. Both T-cell receptor and STAT1 are nitrated by MDSCs-produced NO, which results in T-cell activation inhibition and antitumor immune response reduction [56]. HIF-1 α is reported to be associated with increased activity of ARG1 and iNOS in MDSCs, leading to strong inhibition of T-cell functions in the tumor microenvironment [57]. In tumor-induced MDSCs, iNOS expression is enhanced by SETD1B, which regulates the trimethylation of histone H3 lysine 4 (H3K4Me3) at the nos2 promoter [56]. Moreover, in ovarian cancer patients, IL-6 and IL-10-driven STAT3 activation upregulates the expression of ARG1 and iNOS in induced M-MDSC [58]. CBP/EP300-BRD pathway maintain the immunosuppressive activity through STAT pathway-related genes and the expression of Arg1 and iNOS [59]. Clearly, the increased STAT3 and NADPH oxidase activity of PMN-MDSCs subset result in high release of ROS but low NO release. Nevertheless, the M-MDSCs subset expresses high levels of STAT1 and iNOS, and enhanced level of NO but low level of ROS are produced [60]. MDSCs-derived ROS and peroxynitrite, which are the product of the reaction

of ROS with NO, modify T cell receptor (TCR) and CD8 molecules. The modified TCR and CD8 molecules can not bind phosphorylated MHC, leading to the antigen-specific tolerance of CD8⁺ T cells [61].

MDSCs can also exert their immunosuppression by inducing regulatory T cells through cytokine [62]. For example, in tumor-bearing host, Gr-1⁺CD115⁺ MDSCs mediate the development of Treg cell through a combination of multiple pathways dependent on TGF- β , IL-10, and cell-cell contact [63]. miR-130a and miR-145 directly target TGF β receptor II (T β RII) and are down-regulated in the Gr-1⁺CD11b⁺ immature myeloid cells, leading to increased T β RII, and increased response to TGF β [64]. In CD33⁺ MDSCs, the indoleamine 2,3-dioxygenase (IDO) expression is positively related with Foxp3⁺Tregs, which were all correlated with advanced clinical stage prior to neoadjuvant chemotherapy in tumor tissues [65].

In addition to inhibiting T cells, MDSCs can also regulate the functions of other immune cells, including NK cells, macrophages, and DCs. NK cells play a crucial role in anti-tumor immunity because of their innate ability to distinguish malignant cells from normal cells. In head and neck cancer model, PMN-MDSCs suppress NK-cell function through TGF β and production of H₂O₂ [66]. *In vitro*, binding of PGE2 to EP2 and EP4 receptors on M-MDSCs activates the p38MAPK/ERK pathway and elevates the secretion of TGF β as a result. Therefore, PGE2-treated M-MDSCs potently suppress NK-cell activity through production of TGF β [67]. In syngeneic orthotopic mammary cancer model, the cytotoxicity of NK cells is significantly decreased in the presence of MDSCs in pre-metastatic niche, resulting in a reduced anti-tumor response and an increased successful metastasis in the secondary organs [29]. Furthermore, in addition to decrease cytotoxicity, MDSCs are reported to inhibit NKG2D expression and IFN- γ production of NK cells both *in vivo* and *in vitro* [68]. However, a study reports that intraperitoneal polyinosinic:polycytidylic acid (poly I:C) treatment in B16-bearing mice induces MDSC activation, driving CD69 expression and IFN- γ production in NK cells [69], implying that the effect of MDSCs to NK cells is dependent on stimulating factors. In addition, DCs are a critical component of immune responses in cancer which cross-present tumor-associated antigens, and PMN-MDSCs are reported to block the cross-presentation by DCs, which is dependent on myeloperoxidase (MPO) [70].

Last but not least, HIF-1 α can also enhance the suppressive activity of MDSCs by inducing expression of programmed death-ligand 1 (PD-L1), leading to reduced production of IL-2 and decreased proliferation of cytotoxic T cells [71,72].

Recent findings revealed that type I interferons (IFN1) receptor signaling can also restrict acquisition of suppressive activity through an universal mechanism. In G-MDSCs, the downregulation of IFN1 signaling activates the

PI3K-Akt/mTOR pathway through SOCS1 downregulation [73], and the downregulation of IFNAR1 dependent on tumor-derived factors-driven p38 kinase leads to an overwhelmed IFN1 pathway in myeloid cells during tumorigenesis, leading to the acquirement of immune-suppressive activities [74]. In addition, through type I IFN signaling, DNMT1 5-azacytidine (AZA) can reduce the percentage of MDSCs in the tumor microenvironment [75].

4.2 MDSCs and Inflammatory Microenvironment Interact with Each Other in Pre-Metastatic Niche

An inflammatory microenvironment is implicated as a contributory factor to tumor development and metastasis in many cases. MDSCs promote the inflammatory microenvironment formation in pre-metastatic niche. During inflammation, S100A8/A9 is actively released and plays an important role in regulating the inflammatory response [76]. In cancer, S100A8/A9 is reported as a “soil signal” to attract cancer cells that with TLR4, and a study showed that abundant production and release of S100A8/A9 in the M-MDSCs is detected in the pre-metastatic region [77]. Our work showed that the recruited M-MDSCs in pre-metastatic niche produce IL-1 β , which is a hallmark of inflammation, thereby increasing the expression of E-selectin and contributing to the arrest of tumor cell on endothelial cells [23]. Another study showed that accompanied with the recruitment of CD11b⁺Gr1⁺ MDSCs, the proinflammatory cytokines, such as IL-1 β , monocyte chemoattractant protein-1 (MCP1), stromal cell derived factor 1 (SDF-1), and macrophage-derived chemokine are also significantly elevated. Ex vivo coculture of lung single-cell suspension with CD11b⁺Gr-1⁺ MDSCs significantly upregulated the production of basic fibroblast growth factor (bFGF), insulin-like growth factor-I (IGFI), IL-5, macrophage-derived chemokine, SDF-1, MMP9 and VEGFR1. This work suggested that the CD11b⁺Gr-1⁺ MDSCs is likely induce an inflammatory microenvironment in the pre-metastatic lung [78].

Except for the recruited MDSCs induce the inflammatory responses in pre-metastatic niche, MDSCs development and activation are also influenced by inflammation. In murine melanoma model, upregulated inflammatory factors such as IL-1 β , GM-CSF, and IFN- γ are accompanied with MDSC recruitment and increased immunosuppressive activity, which correlated with tumor progression. Upon manipulation with the phosphodiesterase-5 inhibitor sildenafil, reduced levels of numerous inflammatory mediators (e.g., IL-1 β , IL-6, VEGF, S100A9) are detected, which are in association with decreased MDSC amounts and immunosuppressive function [79]. Besides tooth loss, periodontitis can also increase the patient's risk for multiple disease [80]. It is reported that periodontal inflammation promotes metastasis of breast cancer through MDSCs recruitment, which is partially dependent on pyroptosis-induced multiple inflammatory factors and chemokines generation, such

as IL-1 β , CCL2, CXCL5 and CCL5 in the early steps of metastasis [81]. The pro-inflammatory cytokines S100A8 and S100A9 as well as these two factors-induced SAA protein and recruited CD11b⁺ myeloid cells by SAA together contribute to the development of pre-metastatic niches in the lung [82].

4.3 MDSCs Induce Neoangiogenesis and Vascular Permeability in Pre-Metastatic Niche

Neoangiogenesis and high vascular permeability are effective methods for tumor metastasis. MDSCs are defined as one of major contributors to stimulate angiogenesis and induce high vascular permeability in pre-metastatic niche. Angiogenesis is considered as a hallmark of cancer and an imperative process for tumor growth and metastatic dissemination [83]. Multiple investigations have been reported to illuminate the contribution of MDSCs to angiogenesis. It is well known that proteolysis mediated by matrix metalloproteinases (MMPs) promotes angiogenesis and inflammation in the tumor microenvironment. MDSCs can produce high levels of MMPs, such as MMP14, MMP13, MMP2 and MMP9, to promote angiogenesis and accelerate tumor neovasculature [83,84]. In addition, CD11b⁺Gr1⁺ MDSCs can also acquire endothelial cell properties or being incorporated into the vessel wall directly to contribute to tumor angiogenesis in the tumor microenvironment [85]. The activated MDSCs induce the production of VEGF and FGF2 so as to promote tumor angiogenesis [86]. Bv8 protein, which is produced by G-CSF-mobilized Ly6G⁺Ly6C⁺ cells, is implicated in angiogenesis and mobilization of myeloid cells. Anti-Bv8 antibody significantly decreases lung metastasis [39]. In response to the melanoma-derived exosomes, the MDSCs are reprogrammed into a pro-vasculogenic phenotype that is positive for c-kit, the receptor tyrosine kinase Tie2 and Met [87]. In the models of breast carcinoma, the MDSCs recruited to the pre-metastatic lungs appear to be a angiogenic switching through secreting several proangiogenic factors in tumors, including IL-1 β and MMP-9 [88]. Most cancers will appear organ-specific metastasis, a process also considered as “organotropism”. This process is related with multiple factors, including the tumor-intrinsic properties and their interaction with unique features of host organs. Studies show that the organotropic metastasis of tumor cells is mediated by tumor-derived extracellular vesicles. In addition to the angiogenesis, the vascular hyperpermeability in pre-metastatic niche contributes to subsequent tumor cell homing in lung vessels. The CCR2-CCL2 system has been reported to induce the abundant secretion of SAA3 and S100A8 to increase the permeability of vessels [89], which are also secreted by recruited MDSCs in pre-metastatic niche [77]. The interaction of MDSCs with epithelial cells increase the permeability in blood vessel [90], although the exact mechanism remains to be elucidated.

4.4 MDSCs Promote the Arrest and Survival of Tumor Cells in Pre-Metastatic Niche

The recruitment and survival of disseminated circulating tumor cells in target organs are essential for successful metastasis. E-selectin mediates adhesion of circulating cells to the vessel surface via interaction with its ligand present on the circulating cells [91]. In the pre-metastatic lung, the recruited M-MDSCs ahead of tumor cells increase the expression of E-selectin through IL-1 β , and thereby promote the arrest of tumor cells on endothelial cells. Depletion of M-MDSCs in the pre-metastatic lungs results in reduced E-selectin expression [23].

The survival of tumor cells in the hostile distant organs rate-limited the successful metastasis in cancer. CCL9 was highly induced in Gr1⁺CD11b⁺ immature myeloid cells and in pre-metastatic lung in tumor-bearing mice. It promotes tumor cell survival by increasing phospho-AKT (P-AKT) and BLC-2, in addition to decreasing the expression of poly (ADP-ribose) polymerase (PARP) [92]. PMN-MDSCs isolated from pre-metastatic livers of NSG mice bearing HCT-116 cecal tumors or LS-174T cecal tumors inhibits HCT-116 cell apoptosis, and the PMN-MDSCs enhancement of tumor cell survival is ratio dependent [10]. Tissue factor (TF) recruited CD11b⁺ macrophages enhances the survival of tumor cells after arrest in the lung, and impairment of macrophage function decreases tumor cell survival [93].

Based on the crucial function of MDSCs in the formation of pre-metastatic microenvironment, targeting MDSCs could be an effective means to hamper the establishment of pre-metastatic microenvironment. Multiple strategies have been proposed to target MDSCs which is including but not limited in the pre-metastatic niche. Studies have been conducted to explore drugs that focused on inhibiting the immunosuppressive activity of MDSCs. Sunitinib is a small molecule synthetic dihydroindole receptor tyrosine kinase (RTK) inhibitor. In various types of cancer patients, Sunitinib treatment can weaken the immunosuppressive activity of M-MDSC by reducing Arg-1 and pSTAT3 [94]. Another drug targeting MDSC is 5 phosphodiesterase (PDE5) inhibitor, which has been proved to reduce IL-4R α , pSTAT6 and Arg-1, thereby effectively blocking the function of MDSC [95,96]. Drugs targeting corresponding chemokines and receptors have also been developed. SX-682, a small molecule inhibitor targeting CXCR1 and CXCR2, significantly reduces the invasion of CXCR2⁺PMN MDSCs to tumors [97]. Blocking the interaction of CCL2-CCR2 by using carlumab or CCR2 antagonist PF-04136309 has been proved to have potential anti-tumor effect in several pre-clinical cancer models [98,99]. Maraviroc, a CCR5 antagonist, effectively block the CCL5/CCR5 axis and exhibit a significant anti-tumor effect in a phase I clinical trial [100]. CSF-1R inhibitors, such as IMC-CS4, GW2580, PLX3397, AMG820, imatizumab, and pecidatinib, also show an anti-tumor effect by inhibiting the recruitment of M-MDSC

[101,102]. Another way targeting MDSCs is the elimination of MDSCs. The traditional chemotherapy drugs such as gemcitabine and 5-fluorouracil can induce the apoptosis of MDSCs and reduce the number of MDSCs in the tumor microenvironment [103,104]. In addition, an anti-Gr1 antibody (RB6-8C5) is used to clear MDSCs in mice [105].

5. Conclusions and Perspectives

The successful arrival and survival of cancer cells in distant metastatic sites depends on the microenvironment they encounter. Traditionally, immunosuppression, inflammation, angiogenesis/vascular permeability, lymphangiogenesis, organotropism, and reprogramming are summarized as the major characteristics of the pre-metastatic niche, and the reprogramming include metabolic reprogramming, stromal reprogramming, and epigenetic reprogramming [106]. Last but not the least, the primary tumor mobilized MDSCs remodel the pre-metastatic microenvironment to create a favorable niche for the dissemination of tumor cell, including induction of immunosuppression, inflammation, neoangiogenesis, vascular hyperpermeability, and increased arrest and survival of disseminated tumor cells, revealing the leading role in pre-metastatic niche. Much attention has been focused on the functions of MDSCs in the formation of pre-metastatic microenvironment. Multiple factors participate in the formation, including chemokines, cytokines, extracellular vesicles and so on. Although the individual factor secreted by MDSCs is not enough to develop the pre-metastatic niche, their combined functions may result in a significant increase in the sequential steps of pre-metastatic niche development. However, the exact mechanism remains to be further elucidated. MDSCs play a pivotal role in pre-metastatic niche formation and tumor metastasis, while the detection and elimination of MDSCs in pre-metastatic niche remain a huge challenge in human. Therefore, effective control of the expansion of MDSCs and inhibition of the recruitment and function of MDSCs in pre-metastatic niche might be beneficial for relieving tumor metastasis to some extent. Furthermore, there are limiting clinical research on the function of MDSCs in the formation of pre-metastatic niche, and more attention is needed in clinic.

Author Contributions

This work was conceptualized by WC and HS; Preparation of the original draft was completed by WC, ZW, JL, YQ and HS; Editing and proofreading were completed by all authors. All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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