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REVIEW

Cellular and molecular characteristics of the premetastatic niches

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Abstract

The premetastatic niches (PMN) formed by primary tumor-derived molecules regulate distant organs and tissues to further favor tumor colonization. Targeted PMN therapy may prevent tumor metastasis in the early stages, which is becoming increasingly important. At present, there is a lack of in-depth understanding of the cellular and molecular characteristics of the PMN. Here, we summarize current research advances on the cellular and molecular characteristics of the PMN. We emphasize that PMN intervention is a potential therapeutic strategy for early prevention of tumor metastasis, which provides a promising basis for future research and clinical application.

KEYWORDS
extracellular vesicles, immunosuppression, premetastatic niches, tumor metastasis

1 | INTRODUCTION

Metastatic progression is the main factor of death in tumor patients, although the potential factors conducive to tumor metastasis remain unclear. Once established, metastasis is devastating. Before the colonization of the second organ, only a few proportion of the tumor cells that leave the primary tumor succeed in metastasis. Cancer cells are usually subjected to complex cascade processes, including shedding and intravasation of tumor cells, survival in the circulation, extravasation, settlement, and growth in the secondary organ. Clarifying potential mechanisms may help us identify strategies and therapeutic targets for the prevention of cancer metastasis that would benefit patients.

The "seed-and-soil" hypothesis contributes to our understanding of tumor metastasis. Metastatic tumor cells ("seeds") arrive at specific organ sites ("soil") where the niche is conducive to metastasis. An increasing number of studies suggest that primary tumors can facilitate colonization by inducing the formation of a supportive niche (called premetastatic niches [PMN]) at secondary organ sites. In recent years, the role and significance of PMN have gained increasing attention.[1]

It has been found that to make distant organs suitable for the colonization of tumor cells, PMN establishes complex mechanisms within the metastasis site. The progress of these studies provides good knowledge for clarifying the mechanism of early tumor metastasis and designing more favorable diagnostic and therapeutic methods. Accordingly, this article aims to summarize the cellular and molecular characteristics of PMN formation, which helps explain the mechanism of early metastasis.

All authors contributed equally to this work.

2 | MOLECULAR COMPONENTS

2.1 | Soluble factor and tissue factor

The identification of tumor-derived secretory factors will be discussed. These secretory factors demonstrate the ability to produce the PMN in different organs, as well as the cellular and molecular changes in different organs through their actions.

2.1.1 | Chemokine

Chemokines play an irreplaceable function in regulating the PMN. Tumor-associated macrophages (TAMs) and regulatory T cells (Treg) are recruited by chemokine C–C motif ligand 2 (CCL2) from primary tumor cells to form PMNs in the lung.[2] Th2 cytokines induce complement 3 in lung mesenchymal stromal cells, and their expression promotes the recruitment of neutrophils to stimulate PMN formation.[3] Vascular endothelial growth factor (VEGF) secreted by colorectal cancer cells stimulates TAMs to generate chemokine (C–X–C motif) ligand 1 (CXCL1), which accumulates myeloid-derived suppressor cells (MDSCs)into the liver tissue. MDSCs promote PMN formation and liver metastasis.[4] In conclusion, targeting chemokine signal transduction in the PMN is a potential therapeutic strategy to prevent tumor metastasis.

2.1.2 | Exosomes (protein and noncoding RNA) or extracellular vesicles

Exosomes are extracellular vesicles (EVs) with a size of 30–150 nm,[5] which contain a large number of proteins and nucleic acids from cells.[6] Exosomes from different cells and tissues have an "innate" secretion tendency of distributing to premetastatic sites, such as the lung, the liver, bone marrow, and the brain, which reflects the organotropism of releasing cells.[7] Chemotherapy-elicited EVs are enriched in annexin A6 (ANXA6), which promotes the activation of nuclear factor (NF)–κB-dependent endothelial cells and the polarization of $Ly6C^+CCR2^+$ monocytes in the pulmonary PMN.[8] EVs rich in miR-181a-5p secreted by colorectal cancer cells continuously activate hepatic stellate cells (HSCs) by targeting suppressors-of-cytokine-signaling 3 and activating interleukin-6 (IL-6)/STAT3 signaling pathways. The chemokine C–C motif ligand 20 (CCL20) derived from activated HSCs further activates the CCL20/CCR6/ERK (extracellular regulated protein kinases)1/2/ELK (transcription factor involved in ERK-induced cellular proliferation)-1/miR-181a-5p positive feedback loop, leading to the formation of PMN.[9] MiR-21, secreted by the in situ implantation of SCP28 breast tumor cells, promotes osteoclast formation and osteopenia by regulating PDCD4 protein, thus accelerating bone damage to reconstruct the microenvironment for bone Metastasis, which contributes to the formation of the PMN.[10] Collectively, targeting the exosome to prevent the formation of the PMN may become a therapeutic method to prevent progression of the tumor in the future.

2.1.3 | Extracellular matrix components

The extracellular matrix (ECM) forms a scaffold that supports the attachment of tumor cells and the reactivation of survival signals. The structure of the intrinsic ECM of an organ is usually not conducive to supporting the attachment and movement of tumor cells. Therefore, the reconstruction of ECM is an important step in PMN formation.[11,12] Among ECM components, fibrinogen deposition plays an indispensable role in the formation of the PMN. The EVs of melanoma cells with a low expression of IGF2 mRNA binding protein 1 inhibit the deposition of fibronectin and the aggregation of $CD45^+$ cells in the lung, thus blocking PMN formation.[13] Matrix metalloproteinases (MMPs) can target the ECM protein, which is one of the characteristics of PMN formation.[14] Lysine oxidase-like protein 2 (LOXL2) from liver cancer enhanced the recruitment of $CD11b^+/CD45^+$ BMDCs (bone marrow-derived cells) in the lung and significantly increased MMP9 and fibronectin in lung fibroblasts. LOXL2-induced matrix stiffening synergistically regulated the formation of pulmonary PMN.[15] Similarly, under hypoxic conditions, exosomes secreted by prostate cancer cells increased the levels of MMP2, MMP9, fibronectin, and collagen and upregulated the number of $CD11b^+$ cells at the PMN, promoting distant metastasis.[14] Periosteal protein (POSTN) is one of the components of the ECM, which interacts with fibronectin, tendinosin-c, and collagen I, IV, and V to exert function.[16] POSTN promotes the accumulation of pulmonary MDSCs in early breast cancer. POSTN detected in MDSCs showed that the activation of ERK, AKT, and STAT3 decreased the number of neutrophils and monocytes in the bone marrow of mice and inhibited the recruitment of MDSCs to the PMN.[17] However, more systematic research is needed to reveal these complex and confusing mechanisms.

3 | THE FORMATION AND CHARACTERISTICS OF PMN

Tumor cells need favorable environments with nutrients, immune cells, and the ECM to successfully colonize distant organs. They are separated from the primary tumor and enter the circulation, but due to factors such as immune system attacks, only a few of the tumor cells finally enter the distant host organs to form metastasis.[18,19] Therefore, metastatic organs need to construct an immunosuppressive niche to favor the survival of circulating tumor cells (CTCs) and prevent the attack of natural killer (NK) cells, $CD4^+$ and $CD8^+$ T cells. Protumor immune cells are important components of the PMN, such as MDSCs, Treg, TAMs, and tumor-associated neutrophils, which are recruited into host organs to form an immunosuppressive

niche.[20,21] The PMN is initiated by the primary tumor through the secretion of factors, which facilitates the successful colonization of metastatic tumor cells. The PMN has the following five characteristics. These characteristics are related to whether tumor cells can survive or remain dormant after reaching the metastatic site.

3.1 | Vascular alteration

Vascular alteration is a salient characteristic of PMN formation. It has been shown that many factors promote angiogenesis and permeability of tumor microenvironment (TME) to increase metastasis.[22] Epidermal proteins in EVs can promote angiogenesis by upregulating the expression of VEGF and VEGFR1 in pulmonary vascular endothelial cells.[23] Similarly, Zeng et al.[24] demonstrated that tumor-derived exosomes miR-25-3p favor the formation of the PMN and support colorectal cancer metastasis by inducing angiogenesis and permeability.[24] Peinado et al.[25] further demonstrated that the EVs derived from B16–F10 (mouse skin melanoma cell line) increase pulmonary vascular permeability and initiate PMN formation, which improves the capability of spontaneous lung and bone metastasis. Using proteomics, the EVs from breast cancer were identified as rich in nucleoside diphosphate kinase (NDPK), and the mice treated with EVs showed pulmonary vascular leakage, indicating that NDPK regulates the host microenvironment to facilitate the formation of the PMN and NDPK inhibitors attenuate metastasis.[26] The vasculature is crucial for multistage metastasis, including the entry of cancer cells to the metastatic organs and providing nutritional support for cancer cells.[27] Importantly, more research is needed to understand the function of the vasculature in PMN formation.

3.2 | Immunosuppression

The surveillance of immune system not only plays a key role in the tumor progression but also the immune status has a significant impact on PMN formation. Tumor cells survive through the established immunosuppressive niche to protect themselves from apoptosis. Immunosuppression in the PMN involves the regulation of immune cells by regulatory factors contained in tumor-secreted EVs. EVs secreted by pancreatic cancer cells contain immunosuppressive factors that inhibit NK-cell function, which is conducive to the formation of the PMN.[28] IL-6/STAT3 signaling is aberrantly activated for orchestrating PMN formation and immunosuppression in lung metastasis.[29] EVs secreted by melanoma shuttled tumor antigens to lymphatic endothelial cells for cross-presentation on major histocompatibility complex-I, leading to the induction of antigen-specific $CD8^+$ T-cell apoptosis.[30] EVs derived from Lewis lung cancer cells promote the secretion of chemokine (C–C motif) ligand 1 (CCL1) by pulmonary fibroblasts, activating specific receptor (C–C motif) receptor 8 (CCR8), and induce Treg differentiation, which ultimately contributes to the establishment of immunosuppressive PMN.[31] Together, the EVs released by primary tumor cells are crucial to the immune regulation of the PMN, and the immunosuppression of the PMN ultimately promotes tumor metastasis.

3.3 | Inflammation

Increasing evidence supports the involvement of inflammation in different steps of cancer development, including cancer initiation and progression.[32] Rodrigues et al.[33] found that the exosomes secreted by tumors contained CEMIP (cell migration-inducing and hyaluronan-binding protein) protein, which regulated brain endothelial cells and microglia. CEMIP induces endothelial cells and inflammation in perivascular niches and promotes tumor brain metastasis by upregulating pro-inflammatory cytokine tumor necrosis factor (TNF), prostaglandin–endoperoxide synthase 2 (PTGS2), and CCL/CXCL.[33] Sphingosine-1-phosphate (S1P) generated by tumor-induced sphingosine kinase 1 (SphK1) in the lung PMN increases the recruitment of macrophages into the lung and induces IL-6 and important signal pathways for lung metastasis and colonization. Obesity-related inflammation increases the expression of S1P, acts on S1PR1, promotes macrophage infiltration and tumor progression, and confirms the role of circulating S1P produced by tumor and SphK1/S1P/S1PR1 axis in inflammation and tumor metastasis.[34] Chronic inflammation is an important driving factor for tumor progression. Improper activation of toll-like receptor 4 (TLR4) and other sensory receptors in immune cells can lead to unresolved inflammation, contributing to tumor progression.[35] Leukotriene secreted by neutrophils can also contribute to tumor metastasis by accumulating in the PMN.[36] Neutrophil inflammation driven by TLR4 and myeloid differentiation factor 88 increases the metastasis of melanoma cells to the lung and lymph nodes.[37] In conclusion, further exploration is needed to investigate the role of inflammation-related factors in the formation of the tumor PMN.

3.4 | Organotropism

The organotropism characteristics of tumor metastasis are related to the PMN, because some types of cancer are easy to metastasize to specific organs with selective niches. Cancers disseminate to lymph nodes, the lung, bone, and the liver with different frequencies. Tumor cells release exosomes to establish a niche conducive to metastasis in organs. Tumor-derived exosomes remain in the organs with cancer cell metastasis, promoting the formation of the PMN.[38]

Lung metastasis is one of the most common metastatic sites in patients, and most of our research on PMN biology is based on the study of lung metastasis.[39] In lung PMN, the exosomes enrich the accumulation of integrin in the lung microenvironment to enhance the expression of S100A4 in fibroblasts to establish pro-inflammatory PMN.[38] Nicotinamide phosphoribosyltransferase secreted by the primary tumor activates neutrophils accumulated in the lung to

form neutrophil extracellular traps (NETs) through SIRT1, which facilitates PMN formation and lung metastasis of breast cancer.[40] In brain metastasis of lung cancer, nicotine exposure recruits STAT3-activated N2 neutrophils in the brain PMN, leading to the secretion of miR-4466, which promotes brain tumor stem cells through the SKI/SOX2/CPT1A axis, thereby promoting metastasis.[41]

Bone is a common metastatic site in many solid tumors.[42] Primary tumors and their derived circulating factors promote PMN formation and metastasis cell colonization by regulating the target cells resident in bone.[43] RANK/RANKL signal can induce osteolytic and immunosuppressive microenvironment in bone by inducing osteoclast generation and Treg amplification, thus prompting the formation of the PMN.[44,45] Subsequently, several studies further proved that miR-19a and miR-20a-5p favor osteoclast proliferation and differentiation, cause bone damage and tissue remodeling, and regulate the generation of the PMN.[46,47] However, the more detailed mechanism needs further research and discussion.

The formation of the liver PMN occurs at the initial stage of visceral metastasis. In 2015, Costa-Silva et al. conducted animal experiments to show that Kupffer cells receiving exosomes from pancreatic ductal adenocarcinoma (PDAC) caused TGF-β secretion and fibronectin expression of HSCs were upregulated, thus inducing the formation of niches before liver metastasis. Among them, macrophage migration inhibitory factor in exosomes plays a major role, which may be a prognostic marker for the development of PDAC liver metastasis.[48] Recently, the same study has found that in KPC (mouse model of pancreatic ductal adenocarcinoma) mice, the EVs of PDAC promote the enrichment of macrophages in the liver niches. It has been proved that the overexpression of Rab27a is related to the poor prognosis of cancer and may be related to the extensive remodeling caused by the release of systemic EVs, which contributes to the biogenesis of EVs.[49] The Rab27a GTPase is overexpressed in advanced cancer. However, these EVs could not prevent the decrease of myeloid cell infiltration in the liver of mice transplanted with Rab27a-deficient KPC cells, which indicated that Rab27a had other mechanisms in PMN formation besides the one mediated by EVs.[50] In short, the PMN in different metastatic target organs exhibits complex molecular and cellular components, and its detailed molecular mechanism needs to be further clarified.

3.5 | Metabolic reprogramming

Metabolic reprogramming has been shown to be involved in the formation of the PMN, including glucose metabolism, lipid metabolism, and oxalate metabolism. Fong et al.[51] found that tumor cells can inhibit pyruvate kinase and glucose uptake by secreting vesicles carrying high levels of miR-122 in the PMN. Glucose metabolism is also associated with macrophage-acquired immunosuppressive phenotype. Morrissey et al.[52] demonstrated that tumor-derived exosomes increase PD-L1 expression through NF-κB-dependent glycolytic reprogramming and promote macrophages to polarize toward immunosuppressive phenotype.

Lipid metabolism can also promote the formation of PMN. Zhang et al.[53] proved that HSPC111 is a major upregulated gene in HSCs incubated with exosomes derived from CRC (colorectal cancer) cells. HSPC111 changes the lipid metabolism of fibroblasts by phosphorylating ATP citrate lyase, upregulates the level of acetyl CoA, increases the acetylation of H3K27 in cancer-associated fibroblasts (CAFs), promotes the expression and secretion of C–X–C motif chemokine 5 (CXCL5), and affects the formation of the PMN and liver metastasis of colorectal cancer.[53]

Zeng et al.[54] proved that oxalate can induce the formation of NET by activating NADPH oxidase in the lung and promoting the PMN formation of breast cancer. Pharmacological inhibition of hydroxyacid oxidase 1 can effectively inhibit the accumulation of oxalic acid in the lung caused by a primary tumor.[54] These results indicate that systemic metabolism can be reprogrammed to promote disease progression by changing the utilization of glucose, lipid, and oxidase involved in PMN.

4 | COMPONENTS INVOLVED IN THE PMN

The PMN is established through complex cellular and molecular changes, which ultimately create a favorable microenvironment, and the transferred cells can be colonized and survive at an appropriate time.[55] Figure 1 summarizes the components and mechanisms related to PMN formation.

4.1 | Cellular components

4.1.1 | Myeloid-derived suppressor cells

Tumor-derived components are considered crucial factors in the initiation of the PMN, which involves crosstalks between tumor-derived factors and tumor-mobilized BMDCs.[20] MDSCs are a group of heterogeneous immature immune cells derived from BMDCs, which play a key role in the development of cancer by suppressing immune effector cell functions and contributing to the formation of PMN.[20,56,57] Antagonists of the S100A8-mediated TLR4/MD-2 complex can inhibit the recruitment of MDSCs in premetastatic lung.[58] Bone marrow–derived Gr-1$^+$ myeloid cells express thrombospondin-1 to inhibit metastasis.[59] In another study, Gr1$^+$ CD11b$^+$ immature myeloid cells decrease interferon-γ (IFN-γ) and elevate Th2 cytokine production in premetastatic lungs.[60] Granulocyte MDSCs increase vascular permeability by secreting MMP-9 and IL-10 in the PMN.[61] Primary tumor hypoxia provides cytokines and growth factors to build a PMN through the accumulation of MDSCs and inhibit the cytotoxic effect function of the NK-cell population.[62] In conclusion, multiple factors can promote the transfer of MDSCs to organs by mobilizing them to specific second organs and establishing a favorable microenvironment for transfer.

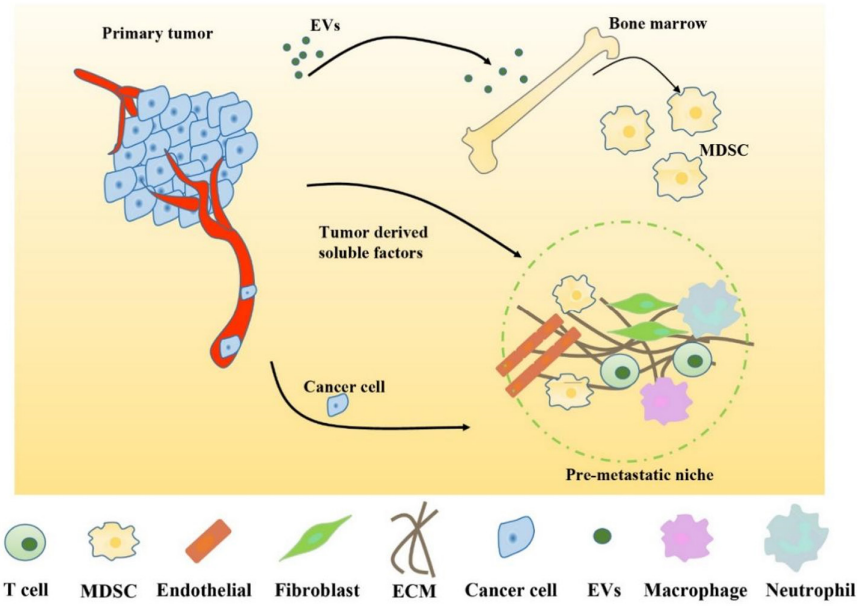

FIGURE 1 The main components and mechanisms of the PMN. EVs secreted by the tumor enter the circulation and bone marrow, mobilizing immune cells to reach distant organs, regulate the accumulation of immune cells, and form an inhibitory immune niche. The PMN mainly includes immune cells, cytokines, chemokines, and the ECM. ECM, extracellular matrix; EVs, extracellular vesicles; MDSC, myeloid-derived suppressor cell; PMN, premetastatic niche.

4.1.2 | Fibroblasts

Fibroblasts found in primary and metastatic tumors are called cancer associated fibroblasts (CAFs), which play a key role in PMN formation. The tumor cell educates fibroblasts to construct tumor-supported host matrix through STAT3 signal and c-Jun N-terminal kinase signal pathway, promotes ECM degradation and reconstruction, and stimulates PMN formation.[63,64] LncSNHG5-ZNF281-CCL2/CCL5 signal axis promotes angiogenesis and vascular permeability in CAFs and plays a key role in PMN formation in breast cancer.[65] The colonization of specific metastatic organs enables metastasis-related fibroblasts to have an inflammatory phenotype. For example, EVs derived from cancer cells activate fibroblasts to form the PMN by secreting TNF, IL-6, IL-8, IL-1α, and IL-1β.[64,66–68] Research on the formation of the CAF in the PMN and its tumor-promoting function has found many mechanisms, thus proposing a variety of potential therapeutic targets. These findings target CAF or related signaling pathways for drug development.

4.1.3 | Macrophages

The M1/M2 macrophage paradigm plays different functions in tumor progression. It mainly codisplays M1-like antitumor phenotype and M2-like tumor-promoting phenotype commonly considered as TAMs, and their importance in metastasis has been confirmed.[69] Colorectal cancer-derived exosome miRNA-934 promotes macrophage polarization into M2 macrophages and the formation of the PMN in colorectal cancer.[70] Exo-miR-519a-3p activates the mitogen-activated protein kinase/ERK pathway by targeting dual specificity phosphatase 2, which leads to M1 polarization to M2-like macrophages and accelerates liver metastasis of gastric cancer by inducing angiogenesis and promoting the formation of the PMN in the liver.[71]

4.1.4 | Neutrophils

Neutrophils account for about 80% of all white blood cells, which is essential to control infection. Circulating neutrophilism is associated with poor prognosis in patients with different cancers.[72] Numerous studies found that neutrophils are irreplaceable contributors to the formation of the PMN.[54,73] In IFN knockout mice, a higher metastatic load was shown, accompanied by a large number of neutrophils accumulating in the lungs. MMP9, S100A8/A9 and increasing expression of neutrophils in lung infiltration, help promote the formation of PMN and more effectively support tumor cell survival and proliferation in metastatic organs.[74] Ovarian tumor–derived inflammatory factors stimulate neutrophils to extrude chromatin reticulum called neutrophils extracellular traps (NET), and NET deposition promotes tumor cell proliferation and immunosuppression.[75,76] In addition, the accumulation of neutrophils within the PMN provides an immunosuppressive niche characteristic of decreased infiltrating $CD8^+$ T cells and upregulated PD-L1.[77–79] However, the signal of its influence on the mechanism of PMN immunosuppression needs further study.

4.1.5 | Endothelial cells

Intravasation and extravasation are necessary to the progress of the metastatic cascade.[80] Therefore, an endothelial barrier is very important in preventing tumor dissemination. It is proposed that altered endothelial cells directly influence inflammation and tumor metastasis.[81] Endothelial cells induce tumor cell growth by forming blood vessels, guide tumor cells to spread in blood or lymph, and play a major role in promoting the formation of metastasis. Tumor-resident bacteria *Escherichia coli* disrupt the gut endothelial barrier; upon endothelial barrier impairment, bacteria disseminate to the liver and improve the formation of a PMN.[82] EMCN (Endomucin) is a transmembrane

O-sialylated protein expressed on the surface of endothelial cells. Zhang et al.[83] proved that the lack of endothelial EMCN will not significantly affect the growth of the primary tumor but strongly promote spontaneous metastasis. The mechanism of EMCN deficiency is mainly through the recruitment of $Ly6G^+$ neutrophils and upregulation of MMP9, S100A8/A9, and TGF-β expression, leading to the formation of the PMN. Further investigation is needed to determine whether endothelial cells also play a crucial role in a different PMN organ.

4.1.6 | Cancer stem cells

A small number of pluripotent and mostly quiescent tumor cells, called cancer stem cells (CSCs), have been proved to be critical to the occurrence and development of tumors. Lin28B promotes primary tumors to produce more $ALDH^+$ CSCs and secrete exosomes enriched in let-7s, which can promote Lin28B recruitment of granulocytes and the transformation of N2 neutrophils. Then N2 neutrophils can form an immunosuppressive niche before lung metastasis through PD-L2 upregulation and promote lung metastasis of breast cancer.[78] Tumor stem cells in NSCLC (non-small cell lung cancer) are stimulating factors of bone metastasis. Research shows that CSCs in NSCLC can promote bone metastasis by promoting adenosine production and osteoclast activity, producing an immunosuppressive PMN.[84] TNF-α in breast cancer stem cells induces vascular cell adhesion molecule 1 (VCAM-1) to promote angiogenesis, and the formation of PMN which is induced by breast-liver organ crosstalk.[85] In conclusion, the role of CSC in PMN formation needs to be further clarified (Table 1).

5 | SIGNIFICANCE OF THE PMN FOR TUMOR METASTASIS INTERVENTION

5.1 | Prevention of PMN formation

Blocking the formation of the PMN will be a promising strategy for taking early action on tumor metastasis. Methods to block the formation of the PMN include using loaded micellar nanoparticles,[86] therapeutic treatment using miRNA-enriched liposomes,[87,88] and reducing vascular permeability and ECM deposition.[89,90] Drugs loaded with micellar nanoparticles of tumor-targeting peptides can inhibit metastasis. For example, hydrophilic low-molecular-weight heparin inhibits the recruitment of MDSCs by competitive binding with P-selectin on the surface of endothelial cells, whereas hydrophobic all-trans-retinoic-acid promotes exhaustion by inducing the differentiation of MDSCs. By regulating MDSCs, micellar nanoparticles can significantly ameliorate the inflammatory and immunosuppressive niche of lung and tumor sites and inhibit the formation of the PMN.[86] Apart from exosomes, therapeutic miRNA-enriched liposomes can be used for disease treatment by targeting pathological recipient cells.[87] MiR-29 shows effective antifibrosis activity by negatively regulating collagen expression. By designing a lung-targeting liposomal nanovesicle delivery system to carry miR-29a-3p, this system significantly reduced the collagen I secretion of lung fibroblasts in vivo, thereby reducing the establishment of the PMN of tumor cells and inhibiting lung metastasis.[88] FR17 administration interrupts the activation of fibroblasts and inhibits vascular leakage and angiogenesis induced by tumor-derived factors in the PMN.[89] The fusion compound of cytokine LIGHT and vascular-targeting peptide (LIGHT-VTP) can normalize tumor blood vessels; furthermore, LIGHT–VTP efficiently targets pathological blood vessels in the PMN, reducing vascular permeability and ECM deposition, thus blocking metastatic lung colonization.[90] Unfortunately, most of these therapies are in the basic research stage and have not yet entered the preclinical or clinical trials.

5.2 | Early diagnosis and prediction of cancer

The biological interaction between TME and PMN is increasingly important in tumor progression. Providing an animal model for the PMN is crucial for research and prediction.[91,92] Using liquid biopsy technology to detect the factors in PMN, exosomes, and CTCs as markers for early diagnosis and prediction of cancer is of great significance. Some studies have confirmed that the expression of Tenascin-C in regional lymph nodes may be a good predictor of bladder cancer metastasis, providing an important target for early metastasis intervention and treatment.[93] S100 protein is one of the most important chemokines in the PMN. Therefore, Eisenblaetter et al.[94] adopted S100A8/A9-specific single-photon emission computed tomography probe for the first time to predict the formation of the lung PMN in a syngeneic mouse breast cancer model.

6 | PERSPECTIVE

Although there are significant advances in the PMN research, other mechanisms of the PMN need to be further studied in the future. Research shows that different tumors can promote the formation of the PMN in metastatic organs by targeting different stromal cells. Better recognition of the role of PMN cells and molecules in different metastatic organs will help prevent early cancer metastasis. The potential research in this field in the future may focus on the following aspects: (1) Do all primary tumors produce the PMN? (2) When the primary tumor forms, does it start to form the PMN? (3) How does the PMN produced by primary tumors change dynamically, and what are the key factors? (4) There is no imaging method that can detect PMN, and it is difficult to obtain premetastatic tissue.

AUTHOR CONTRIBUTIONS

Hongfei Liu and Guoxin Zhang collected documents and prepared manuscripts. Ran Gao conceptualized, supervised and revised the manuscript. All authors read and approved the final manuscript.

TABLE 1 Summary of molecular and cellular components in PMN formation.

Donor cell	Molecular components	Tumor or stroma derived	Main functions and mechanisms	References
MDSCs	S100A8	Stroma	Changes the immune microenvironment and inhibits the recruitment of MDSCs	58
	Thrombospondin-1	Stroma	Inhibits the recruitment of Gr1 (+) myeloid cells	59
	IFN-γ	Stroma	Decreases IFN-γ and elevates Th2 cytokine production	60
	IL-10/MMP9	Stroma	Increases vascular permeability and immunosuppression	61
Fibroblasts	miR-122	Tumor	Inhibits the glucose uptake of fibroblasts in PMN and increases the nutrition of tumor cells	51
	HSPC111	Tumor	Promotes the secretion of CXCL5, and CXCL5–CXCR2 axis enhances HSPC111, thus promoting the formation of PMN	53
	IL-1α/IL-1β	Tumor	Induces fibroblasts to secrete CXCL9/10 and form fibroblast niches	64
	Nidogen 1	Tumor	Promotes PMN formation by enhancing angiogenesis and the permeability of lung endothelial cells	66
	ITGBL1	Tumor	CRC-derived Stimulates the TNFAIP3-mediated NF-κB signaling to activate fibroblast niches	67
Macrophages	miRNA-934	Tumor	Induces M1-like macrophages to form M2-like macrophages, promoting PMN formation	70
	miR-519a-3p	Tumor	Induces M2-like polarization of macrophages and promotes intrahepatic PMN	71
Endothelial cells	EMCN	Stroma	EMCN deficiency mainly affects the host microenvironment and leads to the lung PMN	83
Neutrophils	Interferon	Stroma	Lung infiltrating neutrophils facilitate an improved PMN formation	74
	PAD4	Stroma	Inhibits NETs and PMN formation	75
	Lin28B	Tumor	Enables the recruitment of neutrophils and N2 conversion, building an immune-suppressive PMN	78
CSCs	let-7s	Tumor	Forms an immunosuppressive PMN	78
	Adenosine	Tumor	Promotes immunosuppressive PMN	84
	TNFα	Tumor	TNFα treatment in breast cancer stem cells induces PMN formation	85
Other components				
Exosomes	Annexin A6	Tumor	Promotes the activation of endothelial cells, CCL2 induction, and $Ly6C^{+}CCR2^{+}$ monocyte expansion in the pulmonary PMN	8
	miR-181a-5p	Tumor	CCL20 activates the CCL20/CCR6/ERK1/2/Elk-1/miR-181a-5p positive feedback loop, leading to the formation of PMN	9
	miR-21	Tumor	miR-21 derived from SCP28 cells facilitates the formation of PMN	10
Chemokine	CCL2	Tumor	Recruits TAMs and Treg to form PMN	2
	Complement 3	Stroma	Promotes the formation of NETs to promote PMN	3
	VEGF	Stroma	Stimulates TAMs to produce chemokine CXCL1, thereby recruiting MDSCs to form PMN	4

Abbreviations: CCL2, C–C motif ligand 2; CRC, colorectal cancer; CXCL1, chemokine (C–X–C motif) ligand 1; CXCR2, chemokine receptor 2; ELK, transcription factor involved in ERK-induced cellular proliferation; EMCN, Endomucin; ERK, extracellular regulated protein kinases; IFN-γ, interferon-γ; IL, interleukin; MDSCs, myeloid-derived suppressor cells; NET, neutrophil extracellular traps; NF, nuclear factor; PMN, premetastatic niche; TAMs, tumor-associated macrophages; TNF, tumor necrosis factor; Treg, regulatory T cells; VEGF, vascular endothelial growth factor.

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ETHICS STATEMENT

None.

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