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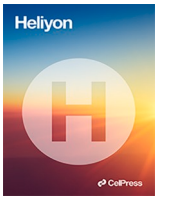

Review article

Traditional Chinese medicine in the treatment of lung pre-metastatic niche: Efficacies and mechanisms

YaNan Zhang [a,1], XiaoYan Wang [b,1], Yue Mou [a], YingZheng Wang [a], WeiDong Liu [a], WeiKe Feng [a], Rong Chen [a], MeiZhi Zhang [a,*], Jing Sun [a,**]

[a] College of Traditional Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan, Shandong Province, 250355, China
[b] College of Acupuncture and Tuina, Shandong University of Traditional Chinese Medicine, Jinan, Shandong Province, 250355, China

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ABSTRACT

Metastasis is the main cause of death in cancer patients, the lung is one of the most common metastatic organs of malignant solid tumors. Before tumor cells metastasize to the lungs, they interact with immunosuppressive cells, alveolar epithelial cells, and lung fibroblasts to form a pre-metastatic niche. The pre-metastatic niche is a key factor leading to tumor cell metastasis to the lungs. Research has found that traditional Chinese medicine and its components can inhibit the formation of pre-metastatic niche. Therefore, this article reviewed the research progress on the formation of lung pre-metastatic niche and the intervention of traditional Chinese medicine in pulmonary PMN, in order to provide new Chinese medicine prescriptions and research ideas for further clinical prevention and treatment of tumor metastasis to the lung.

1. Introduction

Malignant tumors have become one of the top disease affecting human life and health, and metastasis is the main cause of death in patients with malignant tumors that results in approximate 90 % deaths [1,2]. The lung is one of the most common metastatic organs of malignant solid tumors, multiple malignant tumors that occur in other parts of the body can spread to the lungs through hematogenous metastasis, lymphatic metastasis or direct spread [3–5]. Early stage of lung metastases is difficult to identify in clinical practice, and most cases are in advanced stage at the time of diagnosis. However, there is no effective treatment at present. Thus, studying related

Abbreviations: PMN, pre-metastatic niche; TCM, traditional Chinese medicine; ECM, extracellular matrix; AECs, alveolar epithelial cells; S100A8, S100 calcium-binding protein A8; CCL2, CC chemokine ligand 2; PTEN, phosphatase and tensin homolog deleted on chromosome ten; VEGF-A, vascular endothelial growth factor A; MMP9, matrix metalloproteinase 9; CSF-1, colony-stimulating factor 1; MDSCs, myeloid-derived suppressor cells; TLR3, Toll-like receptor 3; IRF3, Interferon regulatory factor 3; COX2, cyclooxygenase-2; IL1B, Interleukin-1 beta; IL6, Interleukin-6; TNFα, tumor necrosis factor α; NET, neutrophil extracellular trap; CAF, cancer-associated fibroblast; EVs, extracellular vesicles; TGF-β, transforming growth factor-β; α-SMA, alpha-smooth muscle actin; LLC, Lewis lung carcinoma; CCL12, CC chemokine ligand 12; CCR8, chemokine receptor 8; Tregs, regulatory T cells; ACACA, acetyl-CoA carboxylase; TDFs, tumor-derived factors; FAP, fibroblast activation protein; AMs, alveolar macrophages; IMs, interstitial macrophages; SAA3, Serum amyloid A-3 protein; VEGF, vascular endothelial growth factors; IFN-γ, interferon-γ; TANs, Tumor-associated neutrophils; EMCN, Endomucin; APS, Astragalus polysaccharides; LOX, lysyloxidase; VCAN, Versican; LPS, lipopolysaccharide.

* Corresponding author.
** Corresponding author.
E-mail addresses: meizhi2233@163.com (M. Zhang), sunsunjingjing@163.com (J. Sun).

[1] YaNan Zhang, XiaoYan Wang contributed equally to this work.

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molecular mechanisms underlying lung metastasis and exploring effective prevention and therapeutic drugs have great theoretical value and clinical significance.

Numerous studies had confirmed that tumor metastasis was heavily dependent on the formation of the associated pre-metastatic niche (PMN for short) [6,7]. The concept of PMN was first proposed by David Lyden et al. in 2005. It is believed that metastasis was a premeditated behavior of the primary tumor site, where some cytokines secreted by the tumor and bone marrow-derived cells reach the target organ before the disseminated tumor cells colonize, creating a microenvironment suitable for tumor cell growth, inducing floating primary tumor cells in circulation to colonize and proliferate here, ultimately forming a metastatic lesion [8]. Liu et al. [9] reported several characteristics of PMN in tumor progression, such as inducing immunosuppression and inflammatory response, facilitating angiogenesis, and increasing vascular wall permeability. Multiple related studies found that tumor cells could secrete significant amounts of cytokines to the target organ for metastasis, which were necessary components for the formation of PMN [10]. In this context, therapies against PMN might reduce the incidence of metastasis and thus greatly increase the survival rate of patients, which could provide a new idea for further clinical prevention and treatment of tumor metastasis.

The use of traditional Chinese medicine (TCM) for tumor prevention and treatment has a long history. As modern technology is moving forward, TCM preventing tumor metastasis has been investigated in greater depth. Modern TCM believed that the reason why tumors metastasize was due to the excess of evil *Qi* in cancer and the deficiency of positive *Qi* in the site of metastasis, that is, "where evil is related, its *Qi* must be deficient". The area with deficiency of positive *Qi* established a PMN [11]. As reported, TCM monomers and compound formulas could significantly inhibit the formation of PMN and then suppress tumor metastasis to the lung [12]. TCM intervention for PMN formation, therefore, holds promise as an effective approach preventing tumor metastasis to the lung. This review described the action and mechanism of TCM monomers and compound formulas in interfering with lung PMN, hoping to provide new TCM prescriptions and research ideas for further clinical prevention and treatment of tumor metastasis to the lung.

2. Lung PMN

In lung PMN, tumor cells interacted with the epithelial cells, fibroblasts, and macrophages that reside in the lung, which could induce the release of multiple types of cytokines and chemokines and in turn the abnormal activation of downstream signaling pathways, long-term chronic inflammatory reactions, immune tolerance, and extracellular matrix (ECM) deposition. All these changes facilitated the formation of PMN and then promoted the colonization and metastasis of tumor cells [13].

2.1. Alveolar epithelial cells

The alveolar epithelial cells(AECs), as normal cells at the pre-metastatic target organ site, could alter their original properties and promote the formation of PMN under the influence of cytokines secreted by tumor cells. Wang et al. [14] found that the Caveolin-1 in exosomes derived from breast cancer cells could promote ECM deposition via up-regulating the expression of PMN-related gene S100 calcium-binding protein A8(S100A8) in AECs and inducing Troponin C synthesis by fibroblasts. In the meantime, the PTEN/CCL2/VEGF-A signaling was inhibited, facilitating M1 macrophage polarization towards the M2 type, thereby promoting the formation of PMN and the metastasis of breast cancers to the lung.

Another study reported that alveolar epithelial type II cells (AECs II) could uptake the exosomal miR-200b-3p derived from breast cancer cells, inducing the high expression of CC chemokine ligand 2 (CCL2), S100A8/9, matrix metalloproteinase 9 (MMP9) and colony-stimulating factor 1 (CSF-1), facilitating the recruitment of myeloid-derived suppressor cells (MDSCs), and finally promoting the formation of inflammatory PMN [15].

In the study of Zeng et al. [16], the breast cancer 4T1 cells induced the expression of Hydroxyacid oxidase 1 in AECs through activating the TLR3-IRF3 signaling pathway, thereby leading to the accumulation of oxalate in lung tissue. In addition, the increased

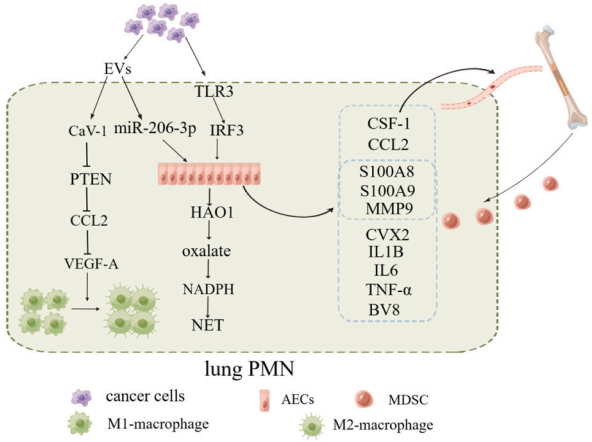

Fig. 1. The role and mechanism of alveolar epithelial cells in the formation of lung PMN.

oxalate level promoted the release of various cytokines (COX2, IL1B, IL6, TNFα, BV8, MMP9, S100A8, and S100A9) from lung tissues and activated NADPH oxidase to induce the appearance of neutrophil extracellular trap (NET), in turn facilitating the formation of PMN and ultimately promoting the colonization of breast cancer cells into the lung. Thus, a full understanding of the role of AECs in PMN formation may provide new insight into the immunosuppression in lung PMN as well as potential targets for prevention of lung metastasis(Its role and mechanism in the formation of lung PMN is shown in Fig. 1).

2.2. Fibroblasts

Lung fibroblasts are important components of the mesenchymal micro-environment that could induce extracellular matrix remodeling by expressing fibronectins and MMPs and then accelerate the formation of PMN(Its role and mechanism in the formation of lung PMN is shown in Fig. 2). The study of Kong et al. [17] revealed that the cancer-associated fibroblast (CAF) -derived extracellular vesicles (EVs) from salivary adenoid cystic carcinoma activated the TGF-β signaling in lung fibroblasts via integrinα2β1, which reshaped the lung microenvironment, inducing the formation of PMN and then promoting the colonization of tumor cells.

Vu et al. [18] confirmed that the stromal fibroblasts implanted in the lung could uptake the miR-125b in EVs from breast cancer cells and differentiate to CAF phenotype by enhancing the expression of marker protein alpha-smooth muscle actin (α-SMA), thereby promoting the formation of PMN. Wang et al. [19] found that exosomes derived from Lewis lung carcinoma (LLC) cells could facilitate the secretion of CCL1 by lung fibroblasts, and the CCL1 binding to receptor CCR8 induced the differentiation of regulatory T cells (Tregs), contributing to the formation of immune-tolerized PMN. Additionally, the authors noted that suppression of LLC-derived exosomes with GW4869 or blockade of the CCL1-CCR8 axis with AZ084 significantly decreased the differentiation of Tregs and metastasis of Lewis lung carcinomacells to the lung.

The study of Huang et al. [20] reported that the expression of acetyl-CoA carboxylase (ACACA) in lung fibroblasts of MMTV-PyVT mice with breast cancer decreased, which induced the acetylation of lysine residues within proteins and the synthesis of fatty acid, promoting the aging of lung fibroblasts and the transformation of inflammatory phenotype, and recruiting immunosuppressive myeloid-derived cells through the production of CXCL1. Gui et al. [21] found that tumor-derived factors (TDFs) secreted by melanoma cells could activate the p38 kinase in lung fibroblasts. Activated lung fibroblasts not only highly expressed fibroblast activation protein (FAP), but also secreted a large number of chemokines (CXCL1, CXCL3 and CXCL5) to recruit neutrophils. At the same time, activated lung fibroblasts also expressed fibronectin, which changed the extracellular matrix environment and promoted the formation of PMN in the lung.

2.3. Bone marrow-derived cell (BMDC)

Bone marrow-derived cells (BMDC) play a key role in PMN formation, BMDC were mobilized to different organs through the production of various factors by the primary tumor, forming a “niche” structure that promotes metastasis. BMDC includes myeloid-derived suppressor cells (MDSCs), macrophages, neutrophils, monocytes, etc. The high heterogeneity of BMDC has been elucidated, and different phenotypes of BMDC play different roles in the occurrence and development of tumors. During the formation of PMN, BMDC was shown to mediate the immunosuppressive response in PMN. Through secreting inflammatory cytokines, growth factors and pro-angiogenic factors, BMDC contributed to the remodeling of local microenvironment and in turn the proliferation and metastasis of

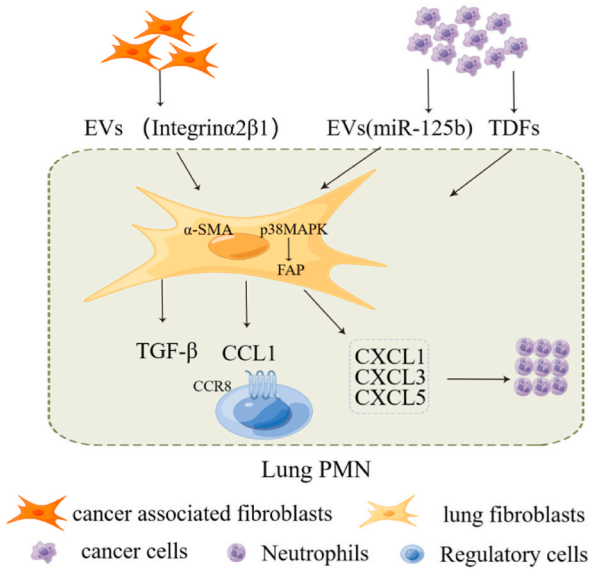

Fig. 2. The role and mechanism of fibroblasts in the formation of lung PMN.

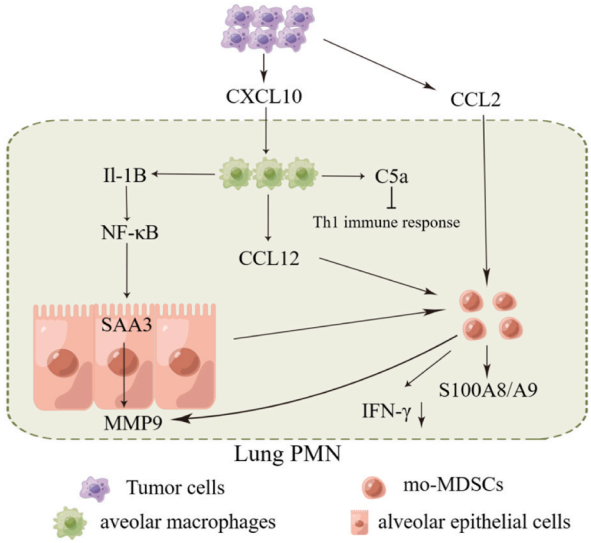

Fig. 3. The role and mechanism of macrophages in the formation of lung PMN.

tumor cells [22]. Li et al. [23] induced a lung PMN in mice models of breast cancer through injection of breast cancer 4T1 cells into the breast, and then they focused on BMDC and explored the molecular mechanism by which BMDC affect lung PMN formation. The results showed that the number of BMDC in the lungs of mouse models was significantly higher than that in control mice on the 7th and 14th day. In addition, significant increase was found in the serum levels of vascular endothelial growth factors (VEGF), granulocyte-macrophage colony-stimulating factors and IL-6 in model mice, suggesting the formation of lung PMN.

2.3.1. Myeloid-derived suppressor cells (MDSCs)

MDSCs, a heterogeneous group of cells composed of immature bone marrow cells and bone marrow progenitor cells with immunosuppressive properties, have the ability to suppress immune responses, and they play a key role in the formation of PMN [24,25]. In the study of Eisenblaetter et al. [26], a lung PMN was induced in a mouse model of breast cancer via injection of breast cancer 4T1 cells into the mammary fat pad. The analysis results reported that the CCL2 secreted by cancer cells stimulated the release of S100A8/A9 from MDSCs, which facilitated the formation of lung PMN and then promoted the metastasis of breast cancer to the lung. This finding suggested that CCL2 might be a potential effective target suppressing the formation of lung PMN.

Yan et al. [27] found an increase in the immature myeloid cells, Gr-1^{+}CD11b^{+}MDSCs, in the lungs of mice with breast cancer, which decreased the expression of interferon-γ (IFN-γ) and induced the secretion of large amounts of proinflammatory cytokines, eventually creating an inflammatory microenvironment suitable for tumor growth. Moreover, this study showed that the increase in the number of Gr-1^{+}CD11b^{+}MDSCs also mediated the substantial production of MMP9 and then promoted vascular remodeling. Collectively, MDSCs exhibited immunosuppressive properties after being activated by signaling molecules, and they promoted the formation of PMN by suppressing immune responses and secreting inflammatory factors.

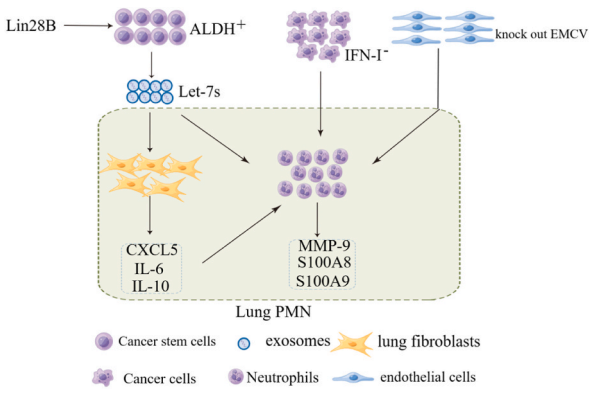

Fig. 4. The role and mechanism of neutrophils in the formation of lung PMN.

Table 1
TCM intervention for lung PMN.

Name	Composition	Model	Usage	Mechanism	Reference
Astragalus polysaccharides		by tail vein injection of 1 × 106 luciferase-labeled Lewis lung cancer cells	50, 100, 200 mg·kg-1 by gavage once a day for 4 weeks	downregulating the expression of MMP-9, lysyloxidase (LOX), fibronectin, and Versican (VCAN)	[44]
				downregulating the expression of HIF-1, S100A8, and S100A9,	[45]
polyphyllin VII		2LL-GFP/Luc cell (2 × 105) suspension injected into the right axilla	10 mg/(kg· d), inject intraperitoneally every 3 days until the 18th day	reducing the expression of S100A8 protein in lung tissue of tumor-bearing mice	[47]
Glycyrrhizic acid				decreased the proportion of M1-type macrophages and the production of CCL2 and TNF-α in the colon through inhibiting the LPS/HMGB1/NF-κB pathway, thereby suppressing Gr-1+ myeloid cell migration and S100A8/A9 expression	[48]
Ruyiping (RYP) Decoction	edible tulip, curcuma zedoary, nidus vespae, raw coix seed, Fructus Akebiae. Edible tulip and nidus vespae	breast cancer 4T1 cells were injected into the 4th mammary fat pad of BALB/c mice under aseptic condition	5. 13, 10. 26, 20. 52 g/kg RYP crude drugs per day by gastrogavage , once per day for 14 successive days	suppressed the expression of Angpt2, VEGF, IL-6 and IL-1β, help maintain the integrity of vasculature, and impede the formation of PMN, thereby inhibiting the occurrence of lung metastasis	[50]
		2 × 106 cell/mL breast cancer 4T1 cells were inoculated 0.1 mL per mouse on the fat pad of the fourth nipple on the right side of BALB/c mice in aseptic condition.	the dosage in low-dose group was 5.67 g/kg/day, and that of high-dose group was 22.68 g/kg/day	protected microvascular integrity, inhibited the release of S100A8/A9, reduced the extravasation of fibrinogen, and decreased the expression of IL-1, IL-6, CXCL2 and CXCL5.	[51]
Jianpi Bushen Formula	Radix Codonopsis, Fructus Lycii, Rhizoma Atractylodis Macrocephalae, Fructus Ligustri Lucidi, Cuscuta chinensis, and Psoralea corylifolia Linn	0.2 mLforestomach carcinoma MFC cells (5 × 106 cells/mL) were injected subcutaneously into each right axilla of mice to form tumors	mice were administered 20 g/kg JPBS in a volume of 0.4 mL through oral gavage, once daily for consecutive 7 days	suppressed the formation of lung PMN through decreasing the expression of Rac1, Cdc42, SDF-1 and fibronectin in the lung tissue of gastric cancer mice	[52]
Xiaoyao Powder	Glycyrrhizia, Chinese Angelica, Poria, Paeonia Lactiflora, and Bupleurum chinense	A mouse colon cancer model was established by seeding 2 × 105 cells per mouse into the axilla of the left forelimb	200 mg, 400 mg, and 800 mg Xiaoyao Powder concentrate were orally administered (calculated as raw medicine). Continuous gavage for 28 days	reduced the expression levels of MMP-9, S100A8, and fibronectin in mouse lung tissue, the recruitment of VEGFR1+myeloid cells in mouse lung tissue and VEGF expression	[53]
XIAOPI formula	epimedium brevicornum, Cistanche deserticola, leonurus heterophyllus, salvia miltiorrhiza, Curcuma aromatica, rhizoma curcumae, Ligustrum lucidum, radix polygoni multiflori preparata, Crassostrea gigas and carapax trionycis	luciferase gene-tagged 4T1 (4T1-Luc) were inoculated subcutaneously into the mammary fat pads of mice at a density of 2 × 106.	1 g/kg/day by gavage	prevented breast cancer PMN formation and lung metastasis via inhibiting TAMs/CXCL1 signaling.	[54]
Baoyuan Jiedu Decoction	astragalus, ginseng, aconite root, honeysuckle, angelica, licorice	4T1-luciferase cells (1 × 106) were injected to the right mammary fat pad of Balb/c mice.	high-, medium-, and low-dose (equivalent to about 5.2 g crude drug/mL, 2.6 g crude drug/mL, 1.3 g crude drug/mL), 1 mL/10 g body weight, gavaged once a day	inhibited the recruitment of MDCSs to the lung via regulating the TGF-β/CCL9 signaling pathway, thereby interfering with the formation of PMN in the lung.	[55]
Shuangshen Granule	American Ginseng, Cordyceps sinensis, and Panax notoginseng	Co-culture technique to construct an in vitro model of the PMN: in the upper chamber of transwell, 3 × 105 (1 μ g/mL Lewis cells of sew2871 activated s1pr1 receptor) were added to the lower chamber, and a	Shuangshen Granule and SEW2871 were co-cultured for 96 h	reduced the content of MDSCs in lung PMN and down-regulate the expression of PMN markers fibronectin, LOX and MMP9, thereby inhibiting PMN formation and subsequent tumor lung metastasis	[56]

(*continued on next page*)

Table 1 (*continued*)

Name	Composition	Model	Usage	Mechanism	Reference
		mixture of lung single cell suspension and MDSCs (1:0, 1:0. 3, 1:0. 6, 1:1, 0:1) was added to make the total number of cells in the lower chamber 3 × 105			
Sijunzi Decoction	Ginseng, White Atractylodes Rhizome, Poria and Liquorice Root	1 × 106 luciferase-labeled LLC cells were injected subcutaneously in the shaved right flank of mice	25.74 g· kg-1 gavaged once daily for 45 consecutive days.	suppressed the effect of Gefitinib on the expression of CXCR1, CCR2 and c-Kit on the surface of neutrophils and monocytes in peripheral blood and lung tissue of mice, as well as the expression of inflammatory factor IL-1α and IL-6 in plasma expression	[58]

2.3.2. Macrophages

The macrophages in the mouse lung tissues include alveolar macrophages (AMs, $CD45^+F4/80^+CD11b^-CD11C^+$) and interstitial macrophages (IMs, $CD45^+F4/80^+CD11b^+CD11C^-$) [28]. The study of Shang et al. [29] showed that malignant melanoma cell-derived CXCL10 induced the expression of CCL12 in AMs and then promoted the recruitment of monocytic MDSCs to the lung, eventually inducing PMN formation and facilitating the metastasis of malignant melanoma cells to the lungs.

Sharma et al. [30] found that AMs inhibited the Th1 immune response in the lung via the complement C5a receptor (C5aR)/C5a axis, thereby promoting the formation of PMN. Zhang et al. [31] noted that the miR-6750 from nasopharyngeal carcinoma derived exosomes potentiated macrophage polarization to M1 type and then suppressed the formation of PMN. In the study of Zhang et al. [32], it was found that AMs-derived IL-1β stimulated the expression of Serum amyloid A-3(SAA3) in AECs in a NF-κB-dependent manner, and it increased MMP9 expression through autocrine. In addition, the increased SAA3 facilitated the formation of PMN by attracting $MMP9^+$ myeloid cells(The role and mechanism of macrophages in the formation of lung PMN is shown in Fig. 3).

2.3.3. Neutrophils

Neutrophils have two phonotypes: N1 and N2. N1-type tumor-associated neutrophils (TANs) exert antitumor activity through direct or indirect cytotoxic effects; while N2-type TANs contribute to immunosuppression, tumor growth, angiogenesis and metastasis via DNA instability or release of cytokines and chemokines [33]. It has been established that TANs played a role in PMN formation [34] (Its role and mechanism in the formation of lung PMN is shown in Fig. 4). Wu et al. [35] constructed a PMN model in mice by subcutaneous injection of breast cancer 4T1 cells, and they found that the loss of IFN-I induced robust infiltration of neutrophils in the lung tissues and promoted the expression of MMP9, S100A8 and S100A9, accelerating the formation of PMN and then facilitating tumor cell metastasis. The study of Qi et al. [36] reported that the presence of Lin28B expression increased the proportion of $ALDH^+$ stem cells in breast cancer. The exosomes secreted by $ALDH^+$ stem cells contained low levels of let-7s family members, leading to more CXCLs, IL-6 and IL-10 released from the lung fibroblasts, neutrophils and macrophages that resided in the pre-metastatic tissues. As a result, it caused neutrophils recruitment and transformation into N2 type neutrophils. It has been confirmed that the N2-type neutrophils in PMN could suppress T cell function to induce immunosuppression, thereby facilitating the formation of PMN and breast cancer metastasis to the lung. Endomucin (EMCN) is a type of transmembrane O-sialylated protein expressed on the surface of endothelial cells. It was reported that EMCN could induce the epithelial tubular morphogenesis in endothelial cells in vitro and the adhesion of blood leukocytes to the endothelium [37,38]. The study of Zhang et al. [39] built a syngeneic mouse model where specific knockdown of EMCN was done in endothelial cells, which upregulated the expression of MMP9, S100A8/A9 and TGF-β by recruiting $Ly6G^+$neutrophils, leading to the formation of pulmonary PMN.

Taken together, a series of complex interactions occurred between tumor cells and the parenchymal and nonparenchymal cells in the lungs, the recruited immune cells and inflammatory cells. These cells and their secreted cytokines, and the non-cellular components including ECM form a unique PMN in the lung. Thus, a deep understanding of the interactions betweem the above cells might provide a new idea for blocking tumor metastasis to the lung.

3. Understanding of lung PMN from the TCM perspective

TCM highlighted the idea of “treating disease before its onset”, which coincided with the treatment principle for PMN. In modern TCM, tumor metastasis was regarded as a result of excess of pathogenic *Qi(*TCM believes that the *Qi* of the human body is a highly dynamic and delicate substance that constantly moves. It spreads throughout the body, from the internal organs to the internal organs and external muscles, bones, and fur, exerting its physiological functions and promoting and stimulating various physiological activities of the human body*)* and deficiency of vital energy. Excess of pathogenic *Qi* in primary tumor site led to PMN formation in the pre-metastatic organ with faint healthy *Qi* [40].

Carcinomatous toxin reached specific organs through congenital main and collateral channels to cause disturbance in ascending and descending. Subsequently, vital-*Qi* failed to distribute, and thus the organ becomed the ‘most void place’. The disturbed

metabolism of "blood" and "water" resulted in blood stasis and phlegm coagulation, and also induces imbalance of the *Yin and Yang*, *Qi* and blood. As a consequence, poison and blood stasis intertwined, facilitating tumor cell colonization to the target organ and in turn tumor metastasis [41].

Thus, the formation of PMN was closely related to imbalance of the *Yin* and *Yang*, *Qi* and blood resulted from vital-*Qi* deficiency, phlegm coagulation, and blood stasis, etc. Accordingly, tonifying *Qi* and blood and regulating *Yin-Yang* balance to modify the PMN suitable for tumor cell survival are conducive to preventing tumor infiltration and metastasis, making the body stay in a state where *Yin* is at peace and *Yang* is compact.

4. TCM intervention for lung PMN

4.1. Intervention effect of TCM active ingredients on lung PMN

Currently, TCM active ingredients that had intervention effect on lung PMN included astragalus polysaccharide, polyphyllin VII, Glycyrrhizic acid(Table 1). Astragalus polysaccharides are the main active ingredients extracted from the traditional Chinese medicine Astragalus membranaceus, which have pharmacological effects such as regulating the body's immunity, enhancing macrophage activity, anti-tumor, and anti-inflammatory [42,43]. Ming et al. [44] constructed a PMN model by injecting Luc luciferase labeled Lewis lung cancer cells into the tail vein of mice. They found that Astragalus polysaccharides could effect PMN formation by downregulating the expression of MMP-9, lysyloxidase (LOX), fibronectin, and Versican(VCAN), thereby inhibiting tumor growth and metastasis. In addition, Liu et al. [45] found that Astragalus polysaccharides could inhibit the formation of the PMN in the lungs by downregulating the expression of HIF-1, S100A8, and S100A9, thereby reducing the metastasis of tumor cells to distant target organs.

Polyphyllin VII is the main active ingredient of polyphyllin with established tumor suppressive effect [46]. Luo et al. [47] found that polyphyllin VII could reduce the expression of S100A8 protein in lung tissue of tumor-bearing mice, indicating that polyphyllin VII might played an anti-tumor role through inhibiting lung PMN formation. Additionally, the authors noted that polyphyllin VII might affect lung PMN by interfering with MDSCs, while the specific mechanism requires further in-depth exploration.

Glycyrrhizic acid is a TCM material extracted from liquorice roots. The study of Qiu et al. [48] reported that glycyrrhizic acid inhibited MDSCs recruitment and S100A8/A9 expression in both 4T1 breast cancer and B16F10 melanoma mouse models and then suppressed the formation of PMN. Further investigation revealed that glycyrrhizic acid decreased the proportion of M1-type macrophages and the production of CCL2 and TNF-α in the colon through inhibiting the LPS/HMGB1/NF-κB pathway, thereby suppressing Gr-1^{+} myeloid cell migration and S100A8/A9 expression. These results showed that glycyrrhizic acid regulated colonic macrophages via targeting the gut microbiota, which might be a new strategy for prevention of PMN formation.

4.2. Intervention effect of TCM compound formulas on lung PMN

In comparison with single Chinese herbs and monomers, TCM compound have advantages such as better clinical efficacy, wider applicability, and fewer adverse reactions. Thus, they could improve the pathophysiological status of the body more comprehensively when applied for prevention of tumor metastasis [49]. Current studies have found TCM compound which were able to interfere with lung PMN included Ruyiping Decoction, Jianpi Bushen Formula, Xiaoyao Powder, XIAOPI formula, Baoyuan Jiedu Decoction, Shuangshen Granule, Sijunzi Decoction(Table 1).

Ruyiping Decoction is prepared by *Edible tulip*, *Curcuma zedoary*, *Nidus vespae*, *Raw coix seed*, *Fructus Akebiae. Edible tulip* and *Nidus vespae* are both monarch medicines that have a strong ability to protect against cancer and dissipate mass, and both are used based on the principle of "use of poisons as antidotes". In addition, *Nidus vespae* also has the function of warming kidney. *Curcuma zedoary* serves as a ministerial drug with the function of breaking blood stasis, which assists in dispersing tumour and dissipating mass. With the use of *Raw coix seed* and *Fructus Akebiae* as auxiliary agents, it could dissipate phlegm and regulate *Qi*, strengthen the spleen and clear the liver. Adding these two herbs, the whole formula could not only dissipate accumulation and transform ruffians, but also dispel evil without harming healthy *Qi*, better exerting the power of dispersing nodules and detoxifying. Ye et al. [50] found that the growth of breast tumor and PMN formation could be well regulated by the Ruyiping Decoction. From the perspective of mechanism of action, the Ruyiping decoction could suppress the expression of Angpt2, VEGF, IL-6 and IL-1β, help maintain the integrity of vasculature, and impede the formation of PMN, thereby inhibiting the occurrence of lung metastasis. Presumably, the Ruyiping Decoction might inhibit the expression of PMN-related factors to suppress PMN formation. Moreover, Ye et al. [51] also used the Ruyiping Decoction in combination with balloonflower root to treat 4T1 tumor-bearing mice. The results showed that such treatment strategy protected microvascular integrity, inhibited the release of S100A8/A9, reduced the extravasation of fibrinogen, and decreased the expression of IL-1, IL-6, CXCL2 and CXCL5. Thus, the combined use of Ruyiping Decoction and balloonflower root could inhibit the extravasation of fibrinogen by protecting pulmonary vascular integrity and then block the communication with the primary tumor, thereby suppressing the formation of lung PMN.

Jianpi Bushen Formula consists of herbal medicines including *Radix Codonopsis, Fructus Lycii, Rhizoma Atractylodis Macrocephalae, Fructus Ligustri Lucidi, Cuscuta chinensis, and Psoralea corylifolia Linn.* Zhu et al. [52] found that the Jianpi Bushen Formula (invigorating spleen and replenishing kidney) could suppress the formation of lung PMN through decreasing the expression of Rac1, Cdc42, SDF-1 and fibronectin in the lung tissue of gastric cancer mice. This study not only highlighted the potential role of lung PMN in early-stage cancer, but also provided reference for the use of Jianpi Bushen Formula to prevent and inhibit tumor metastasis.

Xiaoyao Powder, a classical prescription for soothing liver and relieving depression, is made up of *Glycyrrhizia*, *Chinese Angelica*, *Poria*, *Paeonia Lactiflora*, *and Bupleurum chinense*, Which has functions of soothing the liver and invigorate the spleen, nourishing blood

and resolving depression. Tang et al. [53] established a xenograft tumor model in mice by injection of colon carcinoma cells CT26.WT, after the intervention of Xiaoyao Powder, the lung metastasis was significantly reduced, and the expression levels of MMP-9, S100A8, and fibronectin in mouse lung tissue were significantly reduced, the recruitment of VEGFR1^{+}myeloid cells in mouse lung tissue was significantly reduced, and levels of phosphorylated STAT3 was inhibited in tumor tissue, resulting in a significant decrease in VEGF expression. These results demonstrated that Xiaoyao Powder could effectively inhibit the formation of PMN in the lung, and this inhibitory effect may be achieved through phenotype transformation of tumor related macrophages and inhibition of STAT3 signal transduction.

XIAOPI Formula is composed of *Epimedium brevicornum, Cistanche deserticola, Leonurus heterophyllus, Salvia miltiorrhiza, Curcuma aromatica, Rhizoma curcumae, Ligustrum lucidum, Radix polygoni multiflori preparata, Crassostrea gigas and Carapax trionycis*. The study of Zheng et al. [54] revealed that the activated TAMs(tumor-associated macrophages)CXCL1 pathway could promote the recruitment of hematopoietic stem cells and then induced their differentiation to MDSCs in breast cancer-bearing mice. After intervention with XIAOPI Formula, the number of MDSCs in lung tissues was significantly decreased, suggesting that the XIAOPI Formula could inhibit the formation of lung PMN in breast cancer. These findings indicated that targeting TAMs/CXCL1 pathway might one of the mechanisms of action of XIAOPI Formula intervention for PMN in breast cancer.

Baoyuan Jiedu Decoction is composed of *Astragalus, Ginseng, Aconite root, Honeysuckle, Angelica, licorice*. This prescription mainly benefits *Qi* and warms *Yang*, supplemented by detoxification and promoting blood circulation, guarding the healthy *Qi*, regulating the *Qi, blood, Yin and Yang* of the organs, regulating the internal environment of the body, and having the effect of dispelling evil and nourishing the body. The study of Tian et al. [55] showed that activation of the TGF-β pathway in breast cancer increased MDSCs recruitment to the lung and stimulated the MDSCs to secret CCL9, which in turn affected the formation of lung PMN. Thus, Baoyuan Jiedu Decoction could inhibit the recruitment of MDCSs to the lung via regulating the TGF-β/CCL9 signaling pathway, thereby interfering with the formation of PMN in the lung.

Shuangshen Granule was composed of *American Ginseng, Cordyceps sinensis, and Panax notoginseng*. As reported, Shuangshen Granule could significantly reduce the content of MDSCs in lung PMN and down-regulate the expression of PMN markers fibronectin, LOX and MMP9, thereby inhibiting PMN formation and subsequent tumor lung metastasis [56]. Additionally, Shuangshen Granule could also suppress PMN formation via inhibiting the S1pr1-stat3 signaling pathway and decreasing the expression of tumor-derived cytokines [57].

Sijunzi Decoction, prepared by *Ginseng, White Atractylodes Rhizome, Poria and Liquorice Root*, has the functions of strengthening the body resistance and tonifying Qi, Strengthening spleen and Consolidating Constitution [58]. The study of Zhang et al. [59] revealed that Gefitinib could increase the expression of chemokines and inflammatory factors in PMN, in turn inducing inflammatory responses and aggravating immunosuppression in tumor microenvironment. In contrast, application of Sijunzi Decoction could suppresse the effect of Gefitinib on the expression of CXCR1, CCR2 and c-Kit on the surface of neutrophils and monocytes in peripheral blood and lung tissue of mice, as well as the expression of inflammatory factor IL-1α and IL-6 in plasma expression. It could be seen that Sijunzi Decoction could enhance the efficacy of Gefitinib and then inhibit tumor metastasis. Improving Gefitinib resistance and regulating PMN formation might be an important immunological mechanism of Sijunzi Decoction for prevention of tumor metastasis.

5. Conclusion and outlook

In summary, the above experimental studies indicated that improving lung PMN with TCM could become a new direction for preventing tumor lung metastasis, demonstrating broad application prospects. However, researches on TCM intervention in pulmonary PMN mainly focused on animal or cell experiments, resulting in unclear specific components and mechanisms. In addition, due to the lack of evidence to support the translation of research results into clinical practice and high-quality clinical evidence-based trials, there are still many challenges to achieve its clinical translation. Therefore, in future research, large-scale, long-term, multi center high-quality clinical trials should be conducted to verify the efficacy and safety of traditional Chinese medicine in improving pulmonary PMN. At the same time, standardization and quality control of TCM and herbal preparations should be strengthened to ensure the efficacy and reproducibility of TCM. We look forward to exploring more potential Chinese herbal monomers and compound preparations through more sophisticated molecular biology techniques and high-throughput screening methods, providing more choices for improving lung PMN and preventing tumor metastasis to the lungs.

Data availability statement

Data included in article/supplementary material is referenced in the article.

CRediT authorship contribution statement

YaNan Zhang: Writing – review & editing, Writing – original draft, Funding acquisition. **XiaoYan Wang:** Writing – original draft, Supervision. **Yue Mou:** Resources. **YingZheng Wang:** Validation. **WeiDong Liu:** Resources. **WeiKe Feng:** Resources. **Rong Chen:** Resources. **MeiZhi Zhang:** Writing – review & editing, Supervision. **Jing Sun:** Writing – review & editing, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

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