Journal of Inflammation Research

Dovepress
Taylor & Francis Group

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REVIEW

Tumor-Associated Macrophages in Lung Cancer: Origins, Functional Heterogeneity, and Therapeutic Implications

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Abstract: Tumor-associated macrophages (TAMs) are a heterogeneous population of immune cells that play a pivotal role in the tumor microenvironment (TME) of lung cancer. TAMs, which include both monocyte-derived macrophages (MDMs) and tissue-resident macrophages (TRMs), exhibit distinct functions that influence tumor progression, metastasis, and response to therapy. Recent studies have highlighted the spatiotemporal heterogeneity of TAMs, with MDMs primarily promoting tumor growth and immune suppression, while TRMs contribute to tissue homeostasis but can be reprogrammed to support tumor progression. Both subtypes contribute to the formation of an immunosuppressive TME, facilitate tumor metastasis through matrix remodeling, and contribute to therapeutic resistance by modulating the efficacy of chemotherapy, radiation therapy, and immunotherapy. Understanding the specific roles and heterogeneity of MDMs and TRMs as components of TAMs in lung cancer opens avenues for targeted therapies, such as inhibiting their recruitment, reprogramming their polarization, or blocking their pro-tumorigenic functions. This review synthesizes current knowledge on TAMs in lung cancer, highlighting their dual roles and the potential for developing novel therapeutic strategies that target these macrophages to improve patient outcomes.

Keywords: tumor microenvironment, macrophage polarization, immunotherapy, therapeutic resistance

Introduction

Lung cancer, one of the most common and deadliest malignant tumors globally, has become a major challenge to public health. According to data from the World Health Organization (WHO), lung cancer causes over 1.8 million deaths annually, accounting for nearly 25% of all cancer-related deaths.[1,2] Its high mortality rate and incidence make it one of the most serious diseases in the field of public health worldwide. Although smoking is the primary causative factor for lung cancer, the incidence of lung cancer among non-smokers has increased in recent years, especially among women and younger populations. This phenomenon is closely related to environmental pollution, genetic susceptibility, and changes in lifestyle. The high mortality rate of lung cancer is mainly due to its subtle early symptoms, with most patients being diagnosed at advanced stages, thus missing the optimal treatment window. Therefore, early diagnosis and treatment of lung cancer remain major challenges, and the limitations of existing therapeutic methods are evident.

The core challenges currently faced in the field of lung cancer treatment primarily lie in the efficacy bottleneck for advanced-stage patients, particularly those with small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). While traditional treatment methods, including surgery, radiotherapy, chemotherapy, and targeted therapy, have shown significant efficacy in some early-stage and locally advanced patients, substantial difficulties remain in treating advanced lung cancer. Surgical resection is only applicable to approximately 20% of early-stage patients.[3] Chemotherapy and

Received: 9 July 2025
Accepted: 17 October 2025
Published: 31 October 2025

radiotherapy, as standard treatment modalities, can slow tumor progression in the short term, but their associated side effects, low response rates, and high recurrence rates severely impact patients' quality of life.[4,5] For example, adjuvant chemotherapy following surgery in NSCLC only improves the five-year survival rate by 4–5%,[4] and approximately 40% of patients require dose reduction due to toxic reactions.[3,6] Furthermore, emerging immunotherapy approaches such as immune checkpoint inhibitors (ICIs) have provided survival benefits for some lung cancer patients, but immune resistance, tumor immune evasion mechanisms, and the complexity of the tumor microenvironment (TME) have greatly diminished the effectiveness of immunotherapy.[7] Therefore, overcoming these therapeutic bottlenecks and improving treatment outcomes have become urgent issues in the field of lung cancer therapy.

Recent research has found that the occurrence and development of tumors are not only closely related to the genetic mutations and proliferative capabilities of the tumor cells themselves, but also to the immune cells, stromal components, and their interactions within the TME. As the most abundant immune cell population in the TME, tumor-associated macrophages (TAMs) drive tumor malignancy through multifaceted mechanisms.[8] Within the TME, TAMs are considered important immune cells with significant immune regulatory functions. TAMs not only promote tumor growth and metastasis by influencing immune responses, promoting tumor angiogenesis, and remodeling the stroma but also weaken treatment efficacy through immune evasion mechanisms. The traditional view has been that TAMs primarily originate from the differentiation of hematopoietic precursors.[9,10] It is now widely accepted that TAMs can originate from long-lived yolk sac or fetal liver progenitors during organogenesis, or be recruited from bone marrow progenitor cells.[11,12] Based on their origin and functional characteristics, TAMs are mainly divided into two types: macrophages derived from blood monocytes (MDMs) and tissue-resident macrophages (TRMs).[13,14] These two types of macrophages play distinct roles in the lung cancer microenvironment, and their functions change as the tumor progresses and responds to treatment. MDMs promote tumor invasion, metastasis, and immune evasion by secreting various pro-tumor factors (eg, VEGF, MMPs) and immunosuppressive factors (eg, IL-10, TGF-β),[15,16] while TRMs initially exert anti-tumor effects in the early stages of lung cancer but, as the TME changes, their function shifts towards immune suppression, promoting tumor survival and metastasis.[17]

Therefore, understanding the mechanisms of TAMs in lung cancer, particularly their dynamic regulatory roles within the tumor immune microenvironment, is crucial for developing new treatment strategies. This article provides a comprehensive review of macrophage involvement in lung cancer, emphasizing their contribution to tumor initiation and focusing on the distinct functional characteristics of MDMs and TRMs and their roles in driving tumor progression within the tumor microenvironment (Figure 1). The relationship between TAMs, lung cancer immune evasion, and treatment resistance will be analyzed, and potential targeted therapeutic strategies against TAMs will be discussed. By comprehensively analyzing existing research findings, this article aims to provide theoretical foundations and practical guidance for the precise treatment of lung cancer and the development of novel therapeutic strategies.

Origin and Role of TAMs in Lung Cancer

TAMs play a critical role in the TME, and are primarily derived from two sources: MDMs and TRMs. Due to differences in their origin and function, these two types of TAMs exhibit distinct roles in regulating tumor progression and response to treatment in lung cancer (Figure 1). The following sections will detail the role and mechanisms of MDMs and TRMs in lung cancer.

Monocyte-Derived Macrophages (MDMs)

Recruitment and Polarization of MDMs

During the initiation and progression of lung cancer, monocytes in the bloodstream are recruited to the tumor site and differentiate into macrophages under the influence of chemokines in the tumor microenvironment. Key chemokines such as CCL2 and CSF-1 play pivotal roles in this process. CCL2 mediates the migration of monocytes from the bloodstream to tumor tissue by binding to its receptor CCR2, while CSF-1 promotes monocyte survival and differentiation into macrophages via binding to the CSF-1 receptor (CSF1R).[18–20] Additionally, hypoxia in the tumor microenvironment further enhances the expression of these chemokines by activating hypoxia-inducible factor-1α (HIF-1α), accelerating

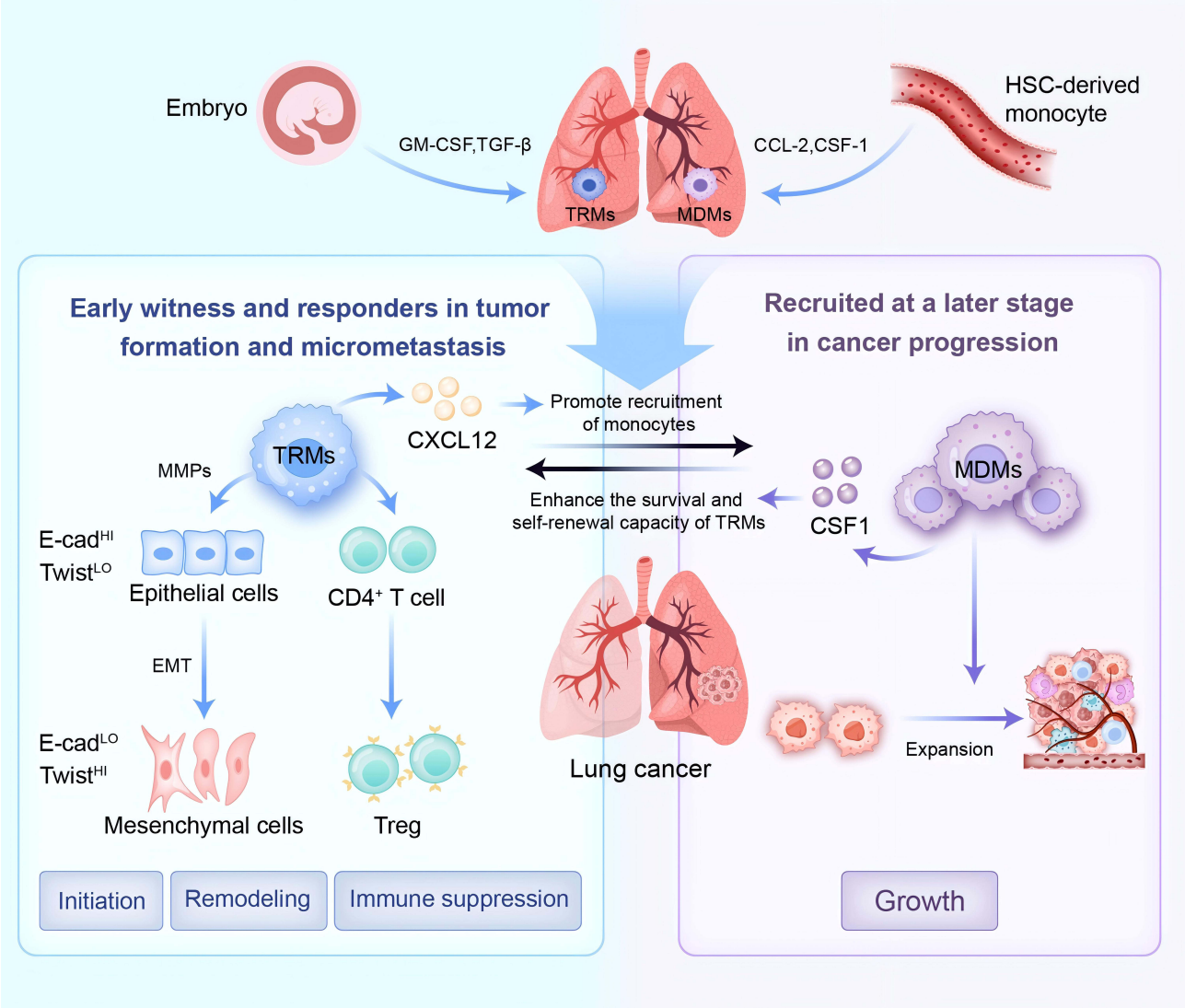

Figure 1 Origin and distinct functions of TRMs and MDMs in lung cancer initiation and progression: TRMs serve as early witnesses and responders in tumorigenesis and micrometastasis formation, sensing soluble cancer-associated products. In contrast, MDMs are recruited at later stages of cancer progression, contributing to tumor growth and metastasis.

monocyte recruitment.[21] Inflammatory factors such as TNF-α and IL-1β also play a role in promoting monocyte migration to the tumor site during the early stages of tumor development.[22]

Once recruited to the tumor microenvironment, MDMs polarize into different functional phenotypes according to local signals. In the early stages of lung cancer, MDMs predominantly polarize into M1-type macrophages. Upon stimulation by IFN-γ and LPS, M1 macrophages exhibit strong pro-inflammatory and anti-tumor activities by secreting high levels of TNF-α and IL-12, as well as generating reactive oxygen species (ROS) and reactive nitrogen species (RNS), which directly exert toxic effects on tumor cells to inhibit their proliferation. Furthermore, M1 macrophages enhance antigen presentation and promote immune responses to suppress tumor growth.[23,24] However, as the tumor progresses, anti-inflammatory cytokines such as IL-4, IL-10, and TGF-β gradually dominate, leading MDMs to polarize toward the M2-type macrophage phenotype. M2 macrophages suppress inflammation by secreting IL-10 and TGF-β, which promote tumor cell survival, proliferation, and immune evasion.[25,26]

https://doi.org/10.2147/JIR.S552449

The Role of MDMs in Lung Cancer Development

MDMs, particularly M2-type macrophages, play a multifaceted role in lung cancer progression, including promoting angiogenesis, tumor invasion, and immune evasion. M2 macrophages significantly enhance tumor angiogenesis by secreting vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs), such as MMP-9.[27] Angiogenesis provides tumors with sufficient nutrients and oxygen while facilitating invasion and metastasis. Research has shown that high expression of VEGF and MMP-9 is closely associated with rapid tumor growth and invasiveness in lung cancer.[28] Moreover, M2 macrophages promote extracellular matrix (ECM) degradation through the secretion of CCL18 and MMPs, aiding tumor cells in breaching tissue barriers and further invading and metastasizing to other organs.[29,30] This mechanism significantly increases the metastatic potential of lung cancer, adding complexity to treatment and worsening prognosis. Finally, M2 macrophages suppress anti-tumor immune responses by secreting immunosuppressive factors such as IL-10 and TGF-β, particularly by inhibiting T cell activity, which helps tumor cells evade immune system recognition and enhances their survival.[31,32]

In conclusion, MDMs, especially M2-type macrophages, play a crucial role in the development and progression of lung cancer. By promoting angiogenesis, ECM degradation, and immune suppression, they drive tumor expansion and worsening. Therefore, reprogramming or inhibiting the function of M2-type macrophages may offer new strategies and directions for lung cancer treatment.

Tissue-Resident Macrophages (TRMs)

In recent years, TRMs have been increasingly recognized for their important role in the pathogenesis and progression of various diseases, particularly cancer. Pulmonary tissue-resident macrophages, such as alveolar macrophages (AMs), serve as key representatives. These macrophages not only maintain lung tissue homeostasis but also respond to environmental changes, playing crucial roles in a variety of pathological processes, including lung cancer. TRMs are characterized by their unique origin, self-maintenance capacity, and dynamic adaptability, making them critical regulators in immune modulation and tissue homeostasis. The following sections will explore the characteristics of TRMs, their role in lung cancer progression, and their mechanisms in reshaping the lung cancer microenvironment.

Characteristics and Maintenance Mechanism of TRMs

The distinctiveness of TRMs lies primarily in their embryonic origin and their ability to self-maintain locally. Unlike MDMs, which are recruited from peripheral blood, TRMs originate from precursor cells in the yolk sac and fetal liver during early embryonic development. These precursor cells migrate to various organs, settle in tissues, and maintain long-term persistence through local proliferation.[33] For example, the long-term maintenance of alveolar macrophages relies on growth factors and signaling molecules in the local microenvironment, such as GM-CSF and TGF-β, which regulate key transcription factors, including PU.1 and PPAR-γ, to support the differentiation and function of TRMs.[34,35] In contrast, MDMs participate more in short-term emergency responses following inflammation or injury and rely on peripheral monocytes for replenishment, further highlighting TRMs' essential role in maintaining tissue homeostasis.

The Dual Pro-Inflammatory and Anti-Inflammatory Functions of TRMs

In homeostatic lung tissue, TRMs play a crucial role in maintaining immune balance by phagocytosing and clearing apoptotic cells, pathogens, and debris, thereby limiting the excessive expansion of inflammatory responses and preventing additional tissue damage.[36] Furthermore, TRMs secrete anti-inflammatory cytokines such as IL-10 and TGF-β, which help maintain lung immune tolerance by suppressing the activity of other immune cells. This function is particularly important for lung tissue exposed to the external environment. However, this homeostatic function undergoes significant alterations under pathological conditions. In the context of lung cancer and other tumor microenvironments, studies have shown that TRMs often exhibit anti-tumor activity in the early stages of the disease. By secreting pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-12, TRMs activate T cells and natural killer (NK) cells, thereby initiating an anti-tumor immune response.[37,38]

As the tumor progresses, however, the functions of TRMs are significantly influenced by the TME, with their phenotype gradually shifting from M1 polarization to M2 polarization. This transition from anti-tumor to pro-tumor

functionality is believed to be a key mechanism of tumor immune evasion.[20] M1-polarized TRMs typically exhibit strong pro-inflammatory characteristics and function primarily by secreting pro-inflammatory cytokines and producing ROS to directly kill tumor cells.[39] However, the presence of numerous immune-suppressive factors in the tumor microenvironment, such as TGF-β, IL-10, and tumor metabolites like lactate, activates signaling pathways through transcription factors such as STAT3 and HIF-1α, inducing a gradual shift of TRMs toward the M2 phenotype.[40] M2-polarized TRMs exhibit robust immune-suppressive functions by secreting immunosuppressive factors (eg, IL-10, TGF-β) and chemokines (eg, CCL2), inhibiting T cell and NK cell activity, while also recruiting regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) into the tumor microenvironment, further enhancing the tumor's immune escape capability.[30,41]

In conclusion, TRMs play a complex dual role in lung cancer development and progression. As guardians of tissue homeostasis, TRMs are crucial for maintaining immune balance and clearing foreign particles in normal lung tissue. However, within the tumor microenvironment, their function is altered by tumor-secreted metabolites and immune factors, transforming them into co-conspirators that promote tumor development. Research into the functional regulation and phenotypic reprogramming of TRMs holds promise for providing new directions and strategies for lung cancer treatment.

The Roles of TRMs in the Occurrence and Development of Lung Cancer

TRMs play a significant role in the TME, engaging in complex cell-to-cell interactions and diverse functions that impact tumor initiation, progression, invasion, metastasis, and the development of therapeutic resistance. TRMs not only modulate the TME by secreting chemokines and cytokines, but they also shape the TME through matrix remodeling and direct interactions with tumor cells (Table 1). This section systematically explores the mechanisms by which TRMs

Table 1 The Roles of TRMs in the Occurrence and Development of Lung Cancer

	Cytokines or Pathway	Function	References
Tumor Proliferation	EGFR	Drives downstream PI3K/AKT/mTOR signaling, enhancing tumor cell proliferation and survival.	[42, 43]
Induction of Angiogenesis	HIF-1α/VEGF-A	Induces endothelial cell proliferation and migration, promoting tumor angiogenesis.	[44, 45]
	MMPs	Degrades ECM (eg, collagen) to disrupt basement membrane structure, providing paths for endothelial cell migration.	[46–48]
	IL-6/JAK2/STAT3	Enhances endothelial cell response to VEGF signaling.	[49, 50]
ECM Remodeling and Tumor Metastasis	MMPs	Degrades ECM components (eg, collagen, fibronectin), disrupting basement membrane integrity, promoting tumor cell migration and invasion.	[51, 52]
	TGF-β	Collagen cross-linking and excessive ECM deposition, forming a dense fibrotic barrier.	[53]
	CCL2	Establishes "pre-metastatic niche."	[54, 55]
	Integrins	Enhances tumor cell adhesion and migration, increasing tumor cell invasiveness.	[56, 57]
Immune Suppressive Microenvironment and Immune Evasion	CCL2	Binds to CCR2 on monocytes, driving their migration toward tumor regions.	[32, 58]
	CCL5	Recruits immune suppressive cells (eg, MDSCs).	[59–61]
	CXCL12 (SDF-1)	Recruits immune suppressive cells (eg, MDSCs). [	[62, 63]
	IL-10	Inhibits dendritic cell antigen presentation, reducing T-cell activation, thus weakening adaptive immune response.	[64]
	TGF-β	Inhibits dendritic cell antigen presentation, reducing T-cell activation, thus weakening adaptive immune response.	[65, 66]
	PD-1/PD-L1	Leads to functional exhaustion and apoptosis of cytotoxic T cells (CTLs).	[67, 68]
	NKG2D	Inhibits NK cell cytotoxicity and cytokine secretion.	[69, 70]

influence the tumor microenvironment, including chemokine regulation, angiogenesis, matrix remodeling, direct contact, and the formation of therapeutic resistance, providing a theoretical foundation for targeted anti-tumor therapies aimed at TRMs (Figure 2).

TRMs Regulate Tumor Microenvironment Formation and Progression Through Chemokines

TRMs play a central role in shaping and regulating the TME. By secreting chemokines and immune-regulatory molecules, TRMs significantly promote tumor initiation, progression, and dissemination. CCL2 is a key chemokine secreted by TRMs that drives the migration of monocytes to the tumor site by binding to its receptor CCR2 on the

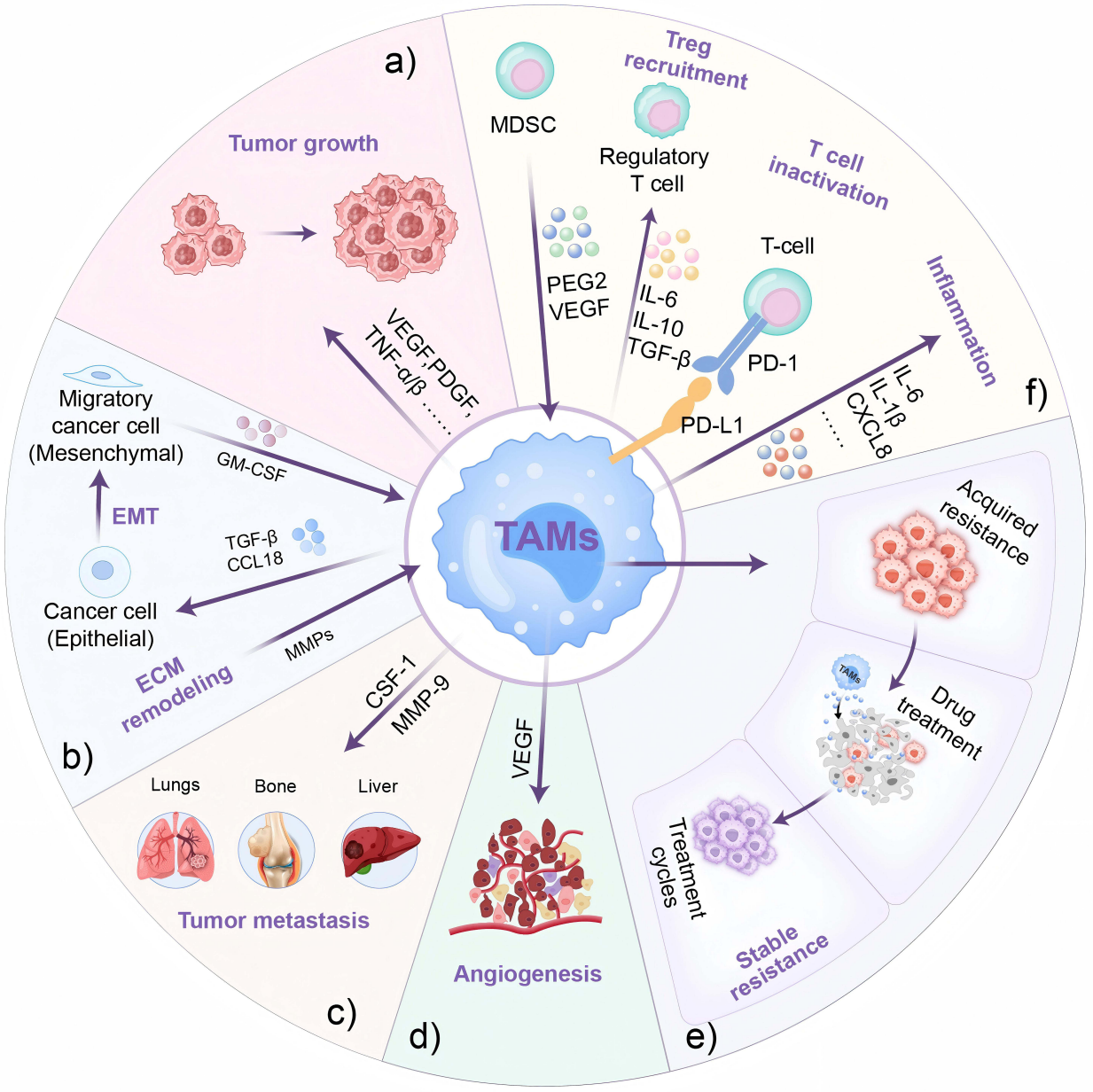

Figure 2 The multifaceted role of TAMs in lung cancer development. TAMs contribute to various stages of lung cancer progression, including: (**a**) enhancing tumor growth, (**b**) facilitating epithelial-mesenchymal transition (EMT) and extracellular matrix (ECM) remodeling, (**c**) promoting tumor metastasis, (**d**) supporting tumor angiogenesis, (**e**) contributing to resistance against anti-tumor therapies, (**f**) modulating immune responses, including recruitment of myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), T cell inactivation, and the promotion of inflammation.

monocyte surface.[30,58] Once monocytes migrate to the tumor microenvironment, they differentiate into TAMs, particularly MDMs, under the influence of local signals. Under the influence of immune suppressive factors such as TGF-β and IL-10, these MDMs further polarize into M2 macrophages. The polarized M2 macrophages secrete IL-10 and TGF-β, which significantly inhibit the activation of effector T cells and the cytotoxic activity of NK cells, thereby promoting tumor cell growth, invasion, and metastasis, establishing a malignant cycle of immune evasion.[28,71]

In addition to CCL2, TRMs also secrete various other chemokines and cytokines, such as CCL5 (RANTES) and CXCL12 (SDF-1), which play pivotal roles in the recruitment of immune-suppressive cells such as MDSCs.[59,62] The accumulation of immune-suppressive cells further strengthens the immunosuppressive effects, forming a positive feedback loop that stabilizes the TME. This chemokine network not only plays an important role in the formation of the early tumor microenvironment but also supports the maintenance of an immune-suppressive microenvironment during tumor progression, significantly enhancing the survival and adaptability of tumor cells.

In terms of regulating the immunosuppressive microenvironment, IL-10 and TGF-β secreted by TRMs have profound effects. IL-10 inhibits the antigen presentation capability of dendritic cells, lowering the activation level of T cells and thereby weakening adaptive immune responses. Meanwhile, TGF-β promotes the expansion of Tregs and inhibits the activity of cytotoxic T cells (CTLs), further diminishing the host's anti-tumor immune efficacy.[72] This multifaceted immunosuppressive mechanism not only weakens the host's immune surveillance of tumors but also significantly enhances tumor immune evasion, creating ideal conditions for its further spread and metastasis.

In summary, TRMs play a central role in shaping and sustaining the tumor microenvironment through the secretion of chemokines and immune-regulatory molecules. They drive the recruitment of monocytes and immune-suppressive cells, reinforcing the establishment and maintenance of an immune-suppressive microenvironment. Future research focusing on targeting the key molecules secreted by TRMs, such as CCL2, IL-10, and TGF-β, holds great potential for providing new therapeutic strategies for tumor treatment. Such precision therapeutic approaches may significantly enhance the efficacy of anti-tumor therapies by disrupting the dynamic regulation of the TME driven by TRMs.

Role of TRMs in Promoting Angiogenesis

TRMs play an essential role in tumor angiogenesis by secreting angiogenic factors. The local hypoxic conditions induced by rapid tumor cell proliferation serve as a major stimulus for angiogenesis. In this context, TRMs sense the hypoxic signals from tumor cells and the TME, activating the HIF-1α pathway to significantly upregulate the secretion of angiogenic factors such as VEGF-A.[44] VEGF-A binds to the VEGF receptor (VEGFR) on endothelial cells, inducing endothelial cell proliferation and migration, thereby promoting the formation of new blood vessels in the tumor. These newly formed blood vessels provide the tumor with oxygen and nutrients, while also offering a route for tumor cell diffusion and metastasis. For example, tumor cells can enter the bloodstream through newly formed vessels, facilitating the formation of metastatic lesions in distant tissues.[73,74]

Additionally, VEGF secreted by TRMs not only directly promotes angiogenesis but also indirectly promotes tumor progression by regulating the permeability and stability of blood vessels. Research has shown that VEGF enhances endothelial permeability, facilitating the migration of immunosuppressive cells, such as regulatory T cells and MDSCs, thus further suppressing the host's anti-tumor immune response.[73,75] This enhanced vascular permeability also provides favorable conditions for tumor cell invasion and metastasis.[76]

Beyond VEGF, TRMs also regulate tumor angiogenesis through the secretion of MMPs, such as MMP-9.[77] MMP-9 degrades collagen and other ECM components, providing the necessary material support for angiogenesis and tumor cell migration. The degradation of the ECM not only facilitates the migration of endothelial cells to form new blood vessels at the tumor site but also creates a more favorable migration path for tumor cells.[46] Studies have shown that MMP-9 also releases stored VEGF from the ECM, further amplifying the angiogenesis signal.[78]

The angiogenic role of TRMs is critical not only for tumor cell proliferation and invasion but also for tumor therapy resistance. For instance, studies have found that abnormalities in the structure of new blood vessels, such as high permeability and irregularity, may impede the effective distribution of chemotherapy drugs within the tumor, leading to reduced therapeutic efficacy.[79] Furthermore, the role of TRMs in tumor angiogenesis affects the efficacy of immune

checkpoint inhibitors, as their influence on the distribution and activity of immune cells can alter the tumor immune microenvironment.

Recent research has also highlighted that TRMs cooperate with molecules beyond angiogenic factors to further enhance tumor angiogenesis. For example, IL-6 secreted by TRMs enhances endothelial cell responses to VEGF signals by activating the STAT3 pathway.[49] Additionally, TRMs promote the activation of fibroblasts and ECM remodeling during angiogenesis through TGF-β secretion, providing more stable mechanical support for vascular expansion.[53,80]

In the future, targeting the angiogenic factors and related pathways secreted by TRMs may provide novel strategies for tumor treatment. For instance, developing VEGF inhibitors, MMP inhibitors, or drugs targeting HIF-1α could effectively block TRM-mediated angiogenesis, thereby limiting tumor growth and metastasis.[81–83] Moreover, combining anti-angiogenesis therapies with immunotherapy strategies is likely to further improve tumor treatment outcomes.

Remodeling of Tumor Stroma and Metastasis

The tumor stroma plays a crucial role in the TME, providing both physical support to tumor cells and significantly influencing tumor growth, migration, and metastasis through interactions with these cells. TRMs, as key immune regulatory cells in the TME, play an essential role in the remodeling of the tumor stroma and the metastatic process by secreting a variety of matrix-modulating factors.

Firstly, TRMs drive substantial ECM remodeling within the TME by secreting MMPs and lysosomal enzymes. As zinc-dependent endopeptidase family members, MMPs, particularly MMP-2 and MMP-9, specifically degrade core ECM components such as type IV collagen and fibronectin, disrupting the integrity of the basement membrane.[51,52] This proteolytic action exerts a dual effect: on one hand, it promotes tumor cell migration and invasion by clearing physical barriers,[84,85] and on the other hand, it releases growth factors stored in the ECM, such as VEGF and TGF-β, which activate pro-angiogenic and epithelial-mesenchymal transition (EMT) signaling pathways.[86] Notably, MMP-9 derived from TRMs has been shown to induce linear rearrangement of collagen fibers, forming ECM "tracks" that promote metastasis and guide tumor cell directional migration.[87] Moreover, this dynamic ECM remodeling process is accompanied by changes in mechanical signaling, such as increased matrix stiffness, which further enhances tumor cell invasion through the integrin-focal adhesion kinase (FAK) pathway.[88,89] This dynamic remodeling of the stroma provides essential conditions for tumor invasive growth and distant metastasis.

In addition to ECM remodeling, TRMs also drive fibrosis in the tumor stroma by secreting pro-fibrotic factors such as TGF-β. This process results in enhanced collagen cross-linking (mediated by lysyl oxidase) and excessive deposition of ECM, leading to the formation of dense fibrotic barriers.[53] Such structural changes not only provide mechanical support for the tumor to resist immune attacks but also limit the diffusion of chemotherapy drugs (eg, cisplatin, gemcitabine) and immune checkpoint inhibitors (eg, PD-1/PD-L1 antibodies) through physical obstruction, thus weakening therapeutic efficacy.[90] Studies have also shown that TGF-β activates fibroblasts, further intensifying the fibrotic process in the tumor stroma, which complicates the tumor microenvironment and makes targeted therapy more difficult.[53] In addition, during stromal remodeling, TRMs promote tumor cell metastasis by regulating intercellular interactions. Specifically, TRMs secrete IL-6 and CXCL12 (SDF-1), which activate STAT3/PI3K-AKT signaling pathways in tumor cells, promoting EMT and invasive migration. IL-6 cooperates with TGF-β through the JAK2/STAT3 pathway to enhance fibrosis,[91,92] while the CXCL12/CXCR4 axis upregulates MMP expression via PI3K-AKT, accelerating ECM degradation and tumor metastasis.[93]

The role of TRMs in stromal remodeling and metastasis extends beyond the local tumor environment, influencing the formation and adaptation of distal metastatic sites. TRMs secrete chemokines such as CCL2 to establish a "pre-metastatic niche", with the CCL2-CCR2 axis being the core pathway for monocyte recruitment. Research shows that CCL2 induces the directional migration of $CCR2^{+}$ monocytes from the bone marrow to metastatic sites (eg, liver, lungs), where they subsequently differentiate into pro-metastatic M2-type TAMs.[54,55] In a colorectal cancer liver metastasis model, the CCL2-CCR2 axis significantly promotes the formation of metastatic lesions by enhancing the M2 polarization of TAMs.[55,94] Furthermore, the construction of a fibrotic microenvironment and an immune-suppressive tumor microenvironment further supports the growth of metastatic lesions. Notably, TRMs exhibit marked heterogeneity across different organs. For instance, liver TRMs recruit M2-type TAMs through CCL25 to suppress osteosarcoma lung metastasis,[95]

while colorectal TRMs secrete CXCL2 to promote M2 macrophage infiltration and facilitate lung metastasis of tumor cells.[96] This organ-specificity underscores the "compass" role that TRMs play in guiding metastasis.

These findings highlight the multifaceted role of TRMs as "accomplices" in tumor metastasis: from early establishment of the pre-metastatic niche to assisting tumor cells in crossing the endothelium, and later supporting the growth of metastatic lesions. Therapeutic strategies targeting the CCL2-CCR2 axis, such as CCR2 inhibitors, are currently undergoing clinical exploration. However, attention must be paid to the physiological functions of TRMs in tissue homeostasis to avoid adverse effects from widespread inhibition. Future research should focus on the precise targeting of organ-specific TRM subpopulations.

Mechanisms of Direct Contact with Tumor Cells

In addition to modulating the TME through the secretion of paracrine factors, TRMs also regulate tumor cell behavior through direct contact. This direct interaction, mediated by the engagement of transmembrane receptors and ligands, not only influences tumor cell proliferation and migration but also exerts profound effects on the host's immune response. Studies have shown that integrins on the surface of TRMs play a pivotal role in this process. Integrins such as CD49a/CD49b expressed on TRMs can bind to ECM proteins, such as collagen, in the tumor microenvironment.[56] Moreover, the interaction between integrin αvβ3 and its ligands on tumor cells enhances their adhesion. This adhesion not only facilitates the migration of tumor cells within the matrix but also activates intracellular signaling pathways (eg, Rho/ROCK pathway) that further enhance tumor cell invasion.[57] Furthermore, both TRMs and tumor cells express the CD47 molecule.[97] The CD47 molecule on TRMs binds to the SIRPα receptor on tumor cells, inhibiting macrophage-mediated phagocytosis of tumor cells, thereby helping the tumor cells evade immune clearance.[98] Research has shown that IFN-γ in the tumor microenvironment upregulates CD47 expression, and this mechanism participates in immune evasion in various cancers, such as lung cancer[99] and melanoma.[100] Anti-CD47 therapy can remodel the tumor immune microenvironment and promote M1 polarization of macrophages.[101]

Direct contact also plays a significant role in TRMs' regulation of tumor cell proliferation and survival. For example, TRMs' contact with tumor cells activates the epidermal growth factor receptor (EGFR) signaling pathway, driving downstream PI3K/AKT/mTOR signaling cascades. This pathway promotes the expression of cell cycle proteins (eg, cyclin D1) and inhibits apoptosis, significantly enhancing tumor cell proliferation and survival.[42,43] Studies have shown that abnormal activation of the EGFR/PI3K/AKT/mTOR axis is directly associated with the malignant progression of various tumors, including prostate cancer and non-small cell lung cancer.[102,103] Additionally, TRMs directly transport metabolic substrates, such as lactate and cholesterol, to tumor cells, helping them cope with metabolic stress. Specifically, lactate plays a dual role in the TME: as an energy substrate through glycolysis (Warburg effect) to fuel tumor cells, and as a signaling molecule that induces microenvironmental acidification (lower pH) and histone lactylation modification, which significantly inhibits the proliferation and cytotoxic function of immune cells (eg, $CD8^+$ T cells, NK cells). This promotes the polarization of immunosuppressive cells (eg, TAMs), thus establishing an immune-evading microenvironment.[104,105] Lactate-mediated immunosuppression is closely linked to tumor malignancy progression, including angiogenesis, metastasis, and treatment resistance. This metabolic cooperation between cells not only enhances tumor cell survival but also further boosts their ability to grow and expand in unfavorable environments.

In terms of immune regulation, TRMs' contact with tumor cells can weaken the host's immune response via inhibitory signaling pathways. For example, TRMs can interact with PD-1 on effector T cells through PD-L1, triggering downstream inhibitory signaling cascades that lead to the functional exhaustion and apoptosis of CTLs.[67,68] At the same time, TRMs can regulate the interaction between NK cell activation receptors (eg, NKG2D) and their ligands (eg, MIC molecules), inhibiting NK cell cytotoxicity and cytokine secretion.[69,70] These mechanisms collectively form an essential pathway for tumor immune evasion, conveying negative regulatory signals via inhibitory receptors (eg, PD-1) and altering the expression patterns of immune checkpoint molecules, ultimately creating an immunosuppressive network in the tumor microenvironment that provides favorable survival conditions for tumor cells.

Notably, TRMs' direct contact may also indirectly promote tumor progression through collaboration with cancer-associated fibroblasts (CAFs). TRMs activate CAFs via cell-to-cell contact or paracrine signaling, inducing CAFs to secrete pro-fibrotic factors (eg, TGF-β), which accelerate the fibrosis process in the tumor stroma.[106] This fibrotic process

not only enhances mechanical support for tumor cells but also forms physical barriers that limit the penetration of anti-tumor drugs. Furthermore, the interaction between TRMs and CAFs can promote the formation of an immunosuppressive microenvironment through the TGF-β signaling pathway, further weakening anti-tumor immune responses.[107] This multicellular network cooperation reveals a broader regulatory dimension of TRMs in the TME. This collaborative effect suggests that TRMs' direct contact not only regulates tumor cells but also potentially extends its influence by impacting stromal cells and immune cells.

In clinical applications, targeting the mechanisms of direct contact between TRMs and tumor cells has become a key focus of research. For example, monoclonal antibodies blocking the CD47-SIRPα pathway can significantly enhance macrophage-mediated phagocytosis of tumor cells and synergize with PD-L1 inhibitors to produce anti-tumor effects.[108,109] Additionally, therapeutic strategies targeting TRM integrin molecules or PD-L1, in combination with immune checkpoint inhibitors, are considered to have significant potential. For example, bispecific antibodies that simultaneously target the CD47-SIRPα and PD-1/PD-L1 pathways not only enhance T cell-mediated anti-tumor functions[108] but also remodel myeloid cell immune functions in the TME.[110] In the future, further elucidating the molecular mechanisms of TRMs' direct contact with tumor cells will provide theoretical support for the development of more precise anti-tumor therapies.

Contribution to the Formation of Tumor Drug Resistance

TRMs significantly contribute to the development of resistance to various therapeutic strategies in the TME through complex mechanisms. Studies have shown that TRMs promote tumor resistance by regulating the structure and function of the TME, interfering with the distribution and metabolism of chemotherapy drugs, weakening the effects of immunotherapy, and even indirectly impacting targeted therapies, thus providing more favorable survival conditions for tumor cells.[111]

In chemotherapy, the role of TRMs is particularly prominent. TRMs within the TME secrete matrix metalloproteinases (eg, MMP-2/9) and fibrotic factors (eg, TGF-β), significantly altering the ECM structure, promoting fibrosis and collagen deposition in the tumor stroma. These fibrotic structures not only provide mechanical support for tumor cells but also create barriers that chemotherapy drugs struggle to penetrate.[112,113] Research has shown that CAFs synergize with TRMs to cause uneven drug distribution through collagen deposition.[114] This barrier effect results in a significant reduction in the concentration of chemotherapy drugs within the tumor, thereby weakening their cytotoxic effect. For example, in pancreatic cancer, TGF-β-driven ECM remodeling directly leads to gemcitabine resistance.[115] TGF-β not only activates fibroblasts to differentiate into myofibroblasts[116] but also upregulates collagen synthesis via the Smad-dependent pathway.[117,118] In models of chronic kidney disease and pulmonary fibrosis, the TGF-β/Smad pathway has been confirmed as a core driver of abnormal ECM deposition.[119,120] In tumors, this pathway promotes the formation of fibrotic microenvironments and, through cross-activation of STAT3 (eg, IL-6 secretion), indirectly enhances the expression of multidrug resistance proteins (eg, MDR1) in tumor cells, further boosting their ability to pump out chemotherapy drugs.[121,122] Furthermore, TRMs help tumor cells resist chemotherapy-induced oxidative stress by releasing antioxidant molecules, such as glutathione, with this metabolic protection further diminishing the effectiveness of chemotherapy. For example, in uric acid-induced cell injury models, antioxidant intervention significantly reduced MMP secretion and ECM deposition.[123] Similarly, in tumors, TRMs protect cancer cells from oxidative stress through metabolic reprogramming.[124]

TRMs' role in immune checkpoint therapy resistance is equally significant. Immunotherapy, particularly the application of immune checkpoint inhibitors (eg, PD-1/PD-L1), has been a major breakthrough in cancer treatment in recent years. However, TRMs interfere with the effectiveness of immune checkpoint inhibitors through various mechanisms. TRMs secrete cytokines such as IL-10 and TGF-β, which directly suppress the anti-tumor activity of $CD8^+$ T cells and NK cells. In lung cancer, after activation by the MAEL gene via the Nrf2/PTEN pathway, morphine upregulates the expression of PD-L1, TGF-β, and IL-10, leading to a reduction in $CD8^+$ T cell proportion and promoting tumor immune evasion.[125] In addition to directly inhibiting the activity of effector T cells, TGF-β and IL-10 are key factors in the differentiation and maintenance of Tregs. In vitro, TGF-β combined with IL-2 can induce the differentiation of naïve $CD4^+$ T cells into $Foxp3^+$ Tregs,[126] while IL-10 drives dendritic cell (DC) tolerance via the β-catenin/IL-10 axis,

indirectly enhancing the immunosuppressive function of Tregs.[127] In the TME, Tregs inhibit effector T cell function through the secretion of IL-10 and TGF-β, forming a positive feedback loop with TRMs. For example, in glioma, IL-10 and TGF-β secreted by TMZ-resistant tumors recruit Tregs and suppress T and NK cell functions, thereby forming an immunosuppressive microenvironment.[128] Similarly, in clear cell renal cell carcinoma (ccRCC), IL-10 and TGF-β secreted by tumor cells not only inhibit immune cell activation but also promote Treg differentiation, further weakening effector T cell function.[129] Additionally, TRMs may directly block T cell activation by upregulating PD-L1 and other immune checkpoint molecules, thereby reducing the efficacy of immune checkpoint inhibitors. For instance, PD-L1 expression on ccRCC cells, in collaboration with the immunosuppressive function of Tregs, limits the effectiveness of immune checkpoint blockade.[129] Meanwhile, TRMs can collaborate with other immunosuppressive cells. IL-10 and TGF-β can suppress effector immune cells and recruit Tregs and MDSCs, which, in cooperation with TRMs, further enhance the immunosuppressive effect.[130] Research has shown that in sarcoma models, reduced Tregs and MDSCs are associated with an increased proportion of $CD8^+$ T cells and tumor suppression. Therefore, this immunosuppressive network is a core mechanism of resistance to immunotherapy.

In anti-angiogenesis therapy, TRMs reverse the effects of anti-angiogenic drugs by secreting VEGF and other angiogenic factors. VEGF recruits TAMs, which further secrete pro-angiogenic factors (eg, PTN, CRYAB) while inhibiting anti-angiogenic factors (eg, PEDF, TSP-1), creating a positive feedback loop.[131] This immune modulation makes anti-VEGF monotherapy difficult to sustain.[132,133] Additionally, angiogenic factors such as VEGF-A and VEGF-C can bypass the inhibition of anti-VEGF drugs by activating the VEGFR2/Rho/YAP signaling pathway or inducing the release of other pro-angiogenic factors (eg, SPP1, PDGF-BB).[134] For example, although anti-angiogenic isoforms like VEGF165b can suppress some angiogenesis, pro-angiogenic factors secreted by TRMs may escape inhibition by upregulating STAT1/ERK signaling or activating alternative pathways like FGF.[135,136] Under anti-angiogenic pressure, TRMs may also use exosomes (eg, t-EVs) to transmit pro-angiogenic signals, leading to vascular abnormalities such as reduced pericyte coverage and overexpression of VEGFR2.[134] Thus, TRMs, through multiple factor networks (VEGF/non-VEGF pathways, exosomes, immune cell interactions), remodel the tumor blood supply, leading to resistance.

In future research and clinical practice, targeting TRMs' critical role in tumor drug resistance could become an effective strategy to overcome therapeutic resistance. For example, molecular drugs targeting MMPs or TGF-β may help reduce fibrosis in the tumor stroma and improve the permeability of chemotherapy drugs. Combining TRMs-regulating agents with immune checkpoint inhibitors may significantly enhance the efficacy of immunotherapy. Additionally, inhibitors targeting metabolic regulators secreted by TRMs (eg, IL-6 and glutathione) could help reduce tumor cells' metabolic adaptability, improving treatment outcomes. In-depth research into TRMs' functional mechanisms and their role in drug resistance will provide more precise and effective strategies for cancer treatment.

Role Heterogeneity of M2-Like TAMs

In the lung cancer TME, the majority of TAMs—encompassing both MDMs and TRMs—adopt an M2-like polarization state, which is strongly associated with tumor progression, metastasis, and adverse clinical outcomes.[20,137] This pro-tumorigenic phenotype, often termed "alternatively activated", arises from dynamic responses to TME cues such as cytokines, hypoxia, and tumor-derived metabolites, leading to immunosuppression, angiogenesis, and ECM remodeling.[138,139] However, M2-like TAMs are not monolithic; they exhibit substantial functional heterogeneity, subdivided into distinct subtypes—M2a, M2b, M2c, and M2d—based on inducing stimuli, secreted mediators, and downstream effects.[140–143] This subclassification, informed by recent single-cell RNA sequencing and functional studies, underscores the plasticity of TAMs and highlights opportunities for subtype-specific interventions to disrupt their tumor-promoting activities.[144]

The M2a subtype, induced primarily by Th2 cytokines such as IL-4 and IL-13, is characterized by high expression of ARG1 and CD206, promoting tissue fibrosis and VEGF secretion to facilitate angiogenesis.[20] In lung cancer, particularly NSCLC, M2a TAMs contribute to stromal desmoplasia and tumor vascularization, correlating with advanced disease stages and reduced overall survival.[138] M2b macrophages, activated by immune complexes, Toll-like receptor (TLR) ligands, or IL-1β, exhibit a hybrid profile with both pro- and anti-inflammatory features, secreting IL-10 and TNF-α to modulate immune responses and enhance metastasis.[141,143] These cells are implicated in lung cancer progression by

Table 2 Summary of M2-Like Macrophage Subtypes, Their Inducing Stimuli, Functions, Roles in Lung Cancer, and Therapeutic Implications

Subtype	Inducing Stimuli	Key Functions	Role in Lung Cancer	Therapeutic Implications	References
M2a	IL-4/IL-13	Tissue fibrosis, VEGF secretion	Promotes angiogenesis and tumor growth; associated with fibrosis in NSCLC	IL-4R antagonists or VEGF inhibitors for reprogramming	[20, 138–140]
M2b	IL-1β/TLR ligands	Tumor progression, IL-10/TNF-α production	Enhances immune regulation and metastasis; correlates with poor prognosis	TLR antagonists to induce M1 shift	[141–144]
M2c	IL-10/TGF-β/glucocorticoids	Tissue remodeling, immunosuppression	Facilitates ECM degradation and Treg recruitment; drives ICI resistance	IL-10/TGF-β inhibitors combined with ICIs	[138–140, 145]
M2d	Adenosine/A2R or TLR ligands	Angiogenesis, tumor growth	Releases VEGF/MMPs; promotes vascularization in hypoxic TME	A2R inhibitors to mitigate pro-angiogenic effects	[20, 140, 142, 143]

fostering an immunosuppressive milieu that supports EMT and distant seeding.[144] The M2c subtype, driven by IL-10, TGF-β, or glucocorticoids, excels in ECM remodeling and phagocytosis of apoptotic cells, while potently suppressing effector T cells through IL-10 and TGF-β release, thereby promoting Treg recruitment and ICI resistance in SCLC and NSCLC.[138–140] Finally, M2d (or tumor-associated macrophage-like) cells, induced by adenosine via A2 receptors or TLR agonists in hypoxic conditions, prioritize angiogenesis through VEGF and MMP production, exacerbating tumor growth in oxygen-deprived niches common in lung adenocarcinomas.[20,142]

Recent advances emphasize that these subtypes are not mutually exclusive but can coexist or transition within the TME, influenced by spatial gradients (eg, hypoxic cores favoring M2d) and temporal dynamics (eg, post-therapy shifts toward M2c-mediated resistance).[140,141,143] For instance, in advanced NSCLC, M2a and M2b subtypes predominate, driving resistance to EGFR tyrosine kinase inhibitors (TKIs) and ICIs by enhancing PD-L1 expression and Treg infiltration.[137,139] This heterogeneity necessitates refined therapeutic strategies, such as CSF1R inhibitors to deplete TAMs broadly or subtype-targeted agents like IL-4R antagonists for M2a reprogramming.[145] Emerging approaches, including CD40 agonists for M2-to-M1 repolarization and combination therapies (eg, TGF-β blockers with ICIs), have shown promising results in preclinical models and early-phase trials, potentially overcoming resistance and improving patient stratification.[139,144] Table 2 summarizes the key features of M2 subtypes, their roles in lung cancer, and therapeutic avenues.

TAMs in the Progression of Lung Cancer: An Integrated Role

As central regulators of the TME, TAMs contribute to lung cancer progression by orchestrating diverse mechanisms, notably facilitating metastatic dissemination and fostering therapeutic resistance. Recent studies have revealed that while MDMs and TRMs differ in their developmental origins and functional characteristics, they cooperate via a complex network of cellular interactions to shape an immunosuppressive TME, thus influencing the biological behavior of lung cancer and treatment responses.

Functional Synergy Between MDMs and TRMs: Formation of a Dynamic Regulatory Network

MDMs and TRMs exhibit significant functional complementarity in the progression of lung cancer. The recruitment of MDMs is primarily driven by tumor-derived chemokines (such as CCL2 and CSF1), and after differentiation into a pro-tumor phenotype within the TME, they promote immune evasion and extracellular matrix remodeling by secreting immunosuppressive factors like IL-10, TGF-β, and MMP-9.[9,146] Notably, VEGF derived from MDMs not only directly stimulates angiogenesis but also activates the endothelial Notch signaling pathway through paracrine effects, thereby forming pro-metastatic ecological niches.[147]

In contrast, as components of the lung's innate immune barrier, TRMs undergo epigenetic reprogramming during tumor transformation.[148] Studies have shown that GM-CSF secreted by lung cancer cells can induce the conversion of TRMs into an immunosuppressive phenotype via the STAT3/IRF5 signaling axis.[149–152] These reprogrammed TRMs, characterized by high expression of PD-L1 and indoleamine 2,3-dioxygenase (IDO), significantly impair $CD8^+$ T cell function and promote Treg infiltration, thus fostering an adaptive immune-tolerant microenvironment.[70,153]

It is worth noting that a positive feedback loop forms between MDMs and TRMs: CSF1 produced by MDMs enhances the survival and self-renewal capacity of TRMs,[154] while TRMs, through CXCL12, mediate continuous recruitment of monocytes.[155] This dynamic interaction network not only amplifies the immunosuppressive effects of the TME but also promotes tumor cell stemness maintenance through metabolic cooperation (such as lactate exchange), leading to chemotherapy resistance.[156,157]

Spatiotemporal Heterogeneity: The Biological Basis of Therapeutic Resistance

Single-cell multi-omics studies have revealed the spatiotemporal heterogeneity of TAMs.[17,158] In terms of spatial distribution, MDMs are primarily enriched at the tumor-stroma interface, where they express high levels of MMP2/9 involved in basement membrane degradation,[159] whereas TRMs are localized in the perivascular regions, mediating the anchoring of circulating tumor cells through secretion of SDF-1α.[160] This spatial specialization suggests that they play stage-specific roles in the metastatic cascade.

From a molecular perspective, MDMs exhibit typical inflammation-related gene modules (such as activation of NF-κB and TNF signaling pathways),[161] while TRMs upregulate tissue repair-related genes (such as TREM2 and FOLR2).[162,163] Under therapeutic pressure, both populations can undergo phenotypic plasticity and transform into a pro-fibrotic phenotype, promoting collagen deposition and impairing drug penetration. This dynamic adaptive mechanism explains why single-agent therapies targeting CSF1R can only transiently reduce MDMs, while TRMs, through the autocrine secretion of IL-34, maintain their survival, eventually leading to therapeutic resistance.

Targeted Intervention Strategies: From Single-Axis Blockade to Systemic Regulation

Therapeutic strategies targeting the heterogeneity of TAMs must consider both spatial distribution and functional state. Preclinical studies have shown that CCR2 antagonists can effectively block the recruitment of MDMs, but when combined with PI3Kγ inhibitors, they can simultaneously reverse the immunosuppressive function of TRMs. In terms of metabolic intervention, inhibiting the glutamine metabolism of TRMs disrupts their mitochondrial oxidative phosphorylation, thereby restoring anti-tumor immune function. Notably, personalized treatment strategies guided by TAMs profiling based on single-cell sequencing are emerging, such as using CD47 antibodies to selectively eliminate M2-like TRMs.

Extracellular Vesicles in TAM-Mediated Lung Cancer Progression: Intercellular Communication and Immune Modulation

Building on the intricate roles of TAMs in driving lung cancer progression through functional synergy, spatiotemporal heterogeneity, and therapeutic resistance, an emerging dimension of their influence lies in the realm of intercellular communication mediated by extracellular vesicles (EVs). EVs, particularly exosomes, have emerged as pivotal mediators in the interplay between TAMs and lung cancer cells, facilitating intercellular communication that drives tumor progression, immune evasion, and therapeutic resistance. TAM-derived exosomes, enriched with bioactive molecules such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), proteins, and lipids, are secreted by both MDMs and TRMs, exerting pro-tumorigenic effects through autocrine, paracrine, and endocrine mechanisms. For instance, M2-polarized TAMs release exosomes containing miR-21-3p and miR-29a-3p, which promote lung adenocarcinoma cell invasion, migration, and angiogenesis by targeting genes involved in EMT and VEGF signaling.[164] These exosomes also enhance tumor cell stemness and chemoresistance by transferring factors like HIF-1α, which stabilizes cancer stem cell phenotypes and induces metabolic reprogramming in recipient cells.[165] Additionally, TAM-derived exosomes contribute to cisplatin resistance in lung cancer by delivering miR-3679-5p, which inhibits NEDD4L transcription, stabilizes c-Myc, and promotes aerobic glycolysis, as demonstrated in both in vitro and in vivo models.[166] In the context of metastasis, TAM-derived exosomes create pre-metastatic niches by modulating the ECM and recruiting additional immune cells,

thereby facilitating distant organ colonization in lung cancer models; for example, exosomes carrying miR-942 from M2 macrophages promote LUAD progression by targeting FOXO1 and activating the Wnt/β-catenin pathway, enhancing cell migration, invasion, and angiogenesis.[166,167] Furthermore, in gefitinib-resistant lung adenocarcinoma, M2 macrophage-derived exosomes enriched with TIMP1 modulate the CD74-MIF axis, promoting proliferation, migration, and invasion while suppressing anti-tumor immune responses, as evidenced by colony formation, Transwell assays, and in vivo tumor models.[165]

Conversely, lung cancer cell-derived exosomes reciprocally influence TAM polarization and function, reinforcing an immunosuppressive TME. These tumor-derived exosomes carry cargos such as miR-103a and lncRNAs that polarize MDMs and TRMs toward an M2-like phenotype via activation of pathways like PI3K/AKT and STAT3, leading to increased secretion of immunosuppressive cytokines (eg, IL-10 and TGF-β) and reduced phagocytic activity.[168] Under hypoxic conditions, tumor-derived exosomes containing miR-155-3p promote M2 polarization by activating STAT3 signaling and enhancing autophagy in macrophages, further amplifying tumor progression.[169] This bidirectional exosomal crosstalk amplifies TME immunosuppression, as reprogrammed TAMs further secrete exosomes that inhibit CD8+ T cell activation and promote Treg expansion through PD-L1 upregulation and IDO expression.[169,170] Spatiotemporal dynamics add complexity: in early-stage lung cancer, TRM-derived exosomes predominate in local immune modulation, while MDM-derived exosomes become more prominent during metastatic progression, contributing to therapeutic resistance by transferring drug efflux pumps or resistance-conferring miRNAs (eg, miR-6836-5p via the MSTRG.292666.16/MAPK8IP3 axis in osimertinib resistance) to tumor cells.[167,171]

Therapeutically, targeting exosomal pathways offers promising avenues for disrupting TAM-lung cancer interactions. Inhibitors of exosome biogenesis (eg, GW4869) or specific cargo blockers (eg, anti-miR oligonucleotides targeting miR-3679-5p or miR-942) have shown efficacy in preclinical models by reversing M2 polarization, reducing drug resistance, and restoring anti-tumor immunity.[172] Integrating exosome profiling with single-cell analyses could enable personalized strategies, such as exosome-based biomarkers (eg, high integrin αVβ3 levels in TAM-derived exosomes for predicting metastasis) or engineered exosomes for targeted drug delivery in NSCLC patients.[166]

Role of TAMs from Different Origins in Lung Cancer Treatment

TAMs occupy a critical position in the TME, where they not only support tumor growth and metastasis through various mechanisms but also profoundly influence the efficacy of chemotherapy, radiotherapy, and immunotherapy. Based on their developmental origins, TAMs comprise MDMs and TRMs, which exhibit distinct roles and functions in shaping treatment responses. This section will focus on how these macrophage subsets affect the efficacy of lung cancer therapy and explore the potential of targeting TAMs to improve clinical outcomes.

Impact of TAMs on Traditional Therapies (Chemotherapy, Radiation Therapy)

Chemotherapy and radiation therapy are key components in the treatment of lung cancer, aimed at inhibiting tumor growth through direct cytotoxicity or inducing apoptosis in tumor cells. However, TAMs can negatively influence chemotherapy and radiation efficacy through various immunosuppressive and pro-tumor mechanisms. Studies have shown that TAMs promote tumor cell resistance to chemotherapy and radiation by secreting factors such as IL-10, TGF-β, and VEGF. Furthermore, TAMs can activate the STAT3 signaling pathway via IL-6, enhancing tumor cell survival and inhibiting apoptosis by upregulating anti-apoptotic molecules like Bcl-2, thus weakening the tumor cell-killing effects of radiation.[173,174]

Radiation therapy typically induces tumor cell necrosis and releases danger-associated molecular patterns (DAMPs) to activate the immune system, but TAMs can attenuate the anti-tumor immune response by expressing immune checkpoint molecules like PD-L1.[175] Similarly, during chemotherapy, TAMs enhance drug resistance by promoting stromal remodeling and tumor angiogenesis. For example, CXCL12 secreted by TAMs enhances tumor cell survival and migration by interacting with CXCR4 on tumor cells.[30] Moreover, TAMs from different origins exhibit differential roles in chemotherapy and radiation therapy. TRMs are primarily found around stable blood vessels in tumors and are more involved in vascular remodeling and stability, while MDMs tend to accumulate in areas of tumor necrosis or

hypoxia, secreting immunosuppressive factors such as IL-10 and TGF-β, which more significantly impair treatment efficacy.[176]

TAMs in Immunotherapy

In recent years, immune checkpoint inhibitors (ICIs) have brought significant breakthroughs in the treatment of non-small cell lung cancer (NSCLC). However, TAMs play a complex bidirectional regulatory role in their efficacy. On the one hand, M1 macrophages secrete pro-inflammatory factors (such as TNF-α and IL-12) that enhance T cell activity and can synergize with immunotherapy to produce anti-tumor effects. On the other hand, M2 macrophages secrete immunosuppressive factors like IL-10, TGF-β, and express PD-L1, which diminish T cell activity and reduce the effectiveness of ICIs.[177]

Furthermore, TAMs promote tumor vascular abnormalities, hindering T cell infiltration into the tumor microenvironment, thus further weakening the action of immune checkpoint inhibitors. Studies on lung cancer have found that enzymes expressed by TAMs, such as Arginase-1 and IDO, consume amino acids required by T cells, thereby suppressing the immune response. This metabolic pathway provides additional support for the immunosuppressive effects of TAMs.[178]

Targeting the functional regulation of TAMs has emerged as a key strategy to enhance the effectiveness of immunotherapy. Reprogramming M2-type TAMs into M1-type macrophages can significantly enhance their anti-tumor effects. For example, CSF-1R inhibitors and STAT6 inhibitors have shown promising anti-tumor effects in various tumor models.[179] Blocking TAM recruitment is also an important strategy; CCR2 inhibitors reduce the recruitment of bone marrow-derived TAMs to the tumor, thereby decreasing the immunosuppressive nature of the TME and enhancing anti-tumor efficacy.[180] Research targeting TAM metabolic pathways has also shown potential, such as IDO inhibitors and Arginase-1 inhibitors, which can restore T cell activity and weaken TAMs' immunosuppressive functions.[181] Additionally, TAM-clearing agents delivered via nanoparticles can effectively reduce TAM numbers in tumors and significantly restore sensitivity to immunotherapy.

The distinct roles of TAMs from different origins in lung cancer treatment further illustrate the complexity of the tumor microenvironment. Targeted therapeutic strategies that modulate TAM functions offer promising avenues to enhance treatment outcomes in lung cancer patients.

Targeted Therapy for TAMs

Targeting TAMs has emerged as a promising therapeutic approach in lung cancer. MDMs, which predominantly polarize toward the M2 phenotype within the TME, display strong pro-tumorigenic functions, whereas TRMs demonstrate context-dependent activities, exerting both pro- and anti-tumor effects at different stages. These functional differences necessitate tailored strategies for therapeutic intervention.

Targeted Strategies for MDMs

Targeted therapies against MDMs focus on inhibiting their recruitment, reprogramming their function, and weakening their pro-tumor characteristics. MDMs are recruited to the tumor microenvironment via the CCL2-CCR2 signaling pathway, and CCR2 antagonists (such as PF-04136309) have been shown to reduce MDM recruitment, inhibit tumor growth, and enhance the efficacy of chemotherapy in mouse models of lung cancer.[30] Additionally, CSF-1 and its receptor CSF-1R are crucial for MDM survival, differentiation, and recruitment to tumors. CSF-1R inhibitors (such as Pexidartinib) significantly reduce MDM numbers in tumors, decreasing their pro-tumor activity and demonstrating synergistic effects when used in combination with immune checkpoint inhibitors (such as PD-1/PD-L1 inhibitors).[179] Reprogramming MDMs' functions is also an important strategy. TLR agonists and CD40 agonists can induce a shift from M2-type to M1-type macrophages, enhancing their anti-tumor effects. For instance, TLR7/8 agonists activate the immune-stimulatory capacity of MDMs, enhancing tumor antigen presentation and T cell activation.[177] CD40 agonists have demonstrated strong anti-tumor potential in various tumor models, particularly when combined with immune checkpoint inhibitors.[182] Inhibiting the pro-angiogenic and immunosuppressive functions of MDMs is also crucial, with Bevacizumab (anti-VEGF therapy) weakening MDMs' promotion

of tumor angiogenesis,[183,184] while IL-10 and TGF-β neutralizing antibodies enhance anti-tumor immune responses by alleviating immunosuppression.[185]

Targeted Strategies for TRMs

In contrast, TRMs, due to their stable origin and diverse functions, are targeted more by regulating their activity rather than direct elimination. TRMs typically exhibit anti-tumor functions, especially when stimulated by pro-inflammatory signals such as IFN-γ, which induces polarization into M1 macrophages, enhancing tumor clearance. Therefore, local injection of IFN-γ or the use of TLR agonists can effectively activate the anti-tumor function of TRMs.[186] Furthermore, the metabolic state of TRMs determines their functional characteristics. For example, inhibiting fatty acid oxidation can promote the shift of TRMs from M2 to M1 macrophages, thereby enhancing their anti-tumor activity. Fatty acid synthase (FASN) inhibitors have demonstrated potential in preclinical studies by altering the metabolic state of TRMs and inhibiting their pro-tumor functions.[187,188] On the other hand, TRMs in the tumor microenvironment secrete chemokines (such as CCL18) and matrix remodeling enzymes (such as MMPs), which are critical for tumor invasion and metastasis. Inhibiting these molecules can block the pro-tumor effects of TRMs. Additionally, blocking immune suppressive molecules (such as PD-L1) expressed by TRMs can relieve the inhibition of T cells, thereby restoring the anti-tumor capacity of the immune system.[189,190]

Whether targeting MDMs or TRMs, combination therapy strategies show significant promise. For instance, combining CSF-1R inhibitors with PD-1/PD-L1 inhibitors can achieve dual effects by reducing TAMs and activating T cells.[180] Moreover, combining anti-VEGF therapy with TLR agonists can simultaneously inhibit angiogenesis and enhance macrophage anti-tumor polarization.[191] Precision modulation of TAMs based on their different origins and functions holds great potential for improving lung cancer treatment efficacy, overcoming the limitations of current therapies, and offering more treatment options for patients.

Clinical Applications and Future Research Directions

The Potential of TAMs as Therapeutic Targets in Lung Cancer

TAMs critically contribute to the progression, metastatic dissemination, and therapeutic resistance of lung cancer, thereby representing a promising target for novel therapeutic interventions. Recent studies have progressively revealed the complexity of TAMs in the lung cancer microenvironment, driving the development of TAM-targeted therapies. Based on the origin, polarization state, and mechanisms of action of TAMs within the tumor microenvironment, therapeutic strategies targeting TAMs can be categorized into several directions.

First, targeted strategies focusing on the functional polarization of TAMs have gained increasing attention. M2-type TAMs typically exhibit pro-tumor functions, such as immunosuppression, promoting angiogenesis, and facilitating cell migration. Therefore, inhibiting the immunosuppressive functions of TAMs, particularly by inducing the transition of M2 macrophages to the M1 phenotype, has become a promising treatment approach. For example, the use of CSF-1R inhibitors (such as Pexidartinib) can significantly reduce the number of TAMs and modulate their functional phenotype, thereby restoring anti-tumor immune responses.[19,192] Additionally, studies have shown that utilizing specific immune checkpoint inhibitors can alleviate the immune suppressive factors (such as PD-L1) expressed by TAMs, thus enhancing the efficacy of anti-tumor immunotherapy.[193]

Secondly, the spatiotemporal distribution characteristics of TAMs within the lung cancer microenvironment complicate their targeted treatment. The functions and mechanisms of action of TAMs may vary at different stages of tumor progression. For example, during the early stages of tumorigenesis, MDMs may primarily promote tumor immune evasion by secreting pro-inflammatory factors, whereas in metastatic and late-stage tumors, TRMs may play a key role in promoting angiogenesis and immune evasion. Thus, designing multi-target combination therapies based on the origin and spatiotemporal characteristics of TAMs can more effectively inhibit the progression of lung cancer.

Furthermore, the potential of TAM-targeted therapies in combination treatments should not be overlooked. Combining TAM-targeting with traditional chemotherapy or immune checkpoint inhibitors has shown synergistic effects. Some studies have demonstrated that the combination of CSF-1R inhibitors with chemotherapy significantly enhances

treatment efficacy and even overcomes tumor resistance to therapy.[194,195] This opens new avenues for lung cancer treatment and may improve clinical outcomes for patients.

Development of TAM-Related Biomarkers and Their Applications in Lung Cancer Diagnosis and Prognostic Assessment

With an improved understanding of the role of TAMs in lung cancer, the development of biomarkers targeting TAMs has become a research hotspot for early diagnosis, staging, and prognostic prediction of cancer. Detecting TAM-associated markers in blood, tissue, or liquid biopsy samples can provide reliable evidence for personalized treatment.

Surface markers of TAMs, such as CD68, CD163, and CD206, are classic markers of M2 macrophages and have been widely used in immunohistochemical analyses of tumor tissues. Additionally, cytokines and chemokines secreted by TAMs (such as CCL2, VEGF, IL-10, and TGF-β) can also serve as potential prognostic biomarkers for lung cancer. Studies have found that elevated levels of CCL2 and VEGF are closely related to tumor malignancy, metastasis, and poor prognosis.[196,197] Monitoring the levels of these biomarkers allows for more accurate assessment of lung cancer progression and prediction of treatment responses.

Additionally, the rise of liquid biopsy technologies provides a new platform for the clinical application of TAM-related biomarkers. By monitoring TAM-derived cytokines, exosomes, and circulating tumor DNA (ctDNA) in the blood, it is possible to detect early changes in the tumor microenvironment, aiding in early diagnosis and prognostic evaluation.[198–200] These advances enhance the potential of TAM-related biomarkers in precision medicine for lung cancer.

Future Research Direction

Despite significant progress in targeting TAMs for lung cancer treatment, many unanswered questions remain. Future research should focus on the following areas:

In-Depth Study of TAM Heterogeneity and Their Specific Roles in the Lung Cancer Microenvironment

The heterogeneity of TAMs is not yet fully understood. While studies have revealed the distinct roles of MDMs and TRMs in lung cancer, a comprehensive understanding of their different subgroups and phenotypic variations remains insufficient. Future research should utilize technologies such as single-cell transcriptomics and mass spectrometry to further dissect the functional subpopulations of TAMs and explore their dynamic changes across different stages of lung cancer. Detailed subtype analysis will help in developing precision-targeted therapies for specific TAM types.

Development of New Model Systems to Simulate the Diversity and Function of TAMs in Human Lung Cancer

While animal models have provided a foundation for understanding the role of TAMs in lung cancer, due to species differences, the functional representation of TAMs in the tumor microenvironment may differ from human lung cancer. Therefore, it is crucial to develop more human-relevant tumor microenvironment models. 3D cell culture models, organoid models, and humanized mouse models, for example, can more accurately reflect the functions and interactions of TAMs during tumor progression. These systems will provide a more accurate experimental platform for preclinical drug screening and the development of new therapies.

Exploring the Interactions Between TAMs and Other Immune Cells

The interactions between TAMs and other immune cells, such as T cells, B cells, and dendritic cells, are a key mechanism in tumor immune evasion. Future research should further investigate the synergistic interactions between TAMs and other immune cells, particularly in the context of immune checkpoint inhibitor therapy. By regulating these interactions, it may be possible to enhance anti-tumor immune responses and improve the effectiveness of immunotherapy.

Conclusion

TAMs, as a critical immune cell population within the lung cancer microenvironment, exert diverse functions in driving tumor progression and facilitating metastatic dissemination. Depending on their origin and functional state, TAMs can be classified into M1 and M2 macrophages, which play key roles in tumor immune evasion, angiogenesis, and immune

tolerance. The function and phenotype of TAMs are not only regulated by the tumor microenvironment but may also change across different stages of disease progression.

Importantly, TAMs arise from two major sources: MDMs and TRMs. MDMs are typically recruited from circulating monocytes and are often skewed toward a pro-tumorigenic phenotype, contributing to angiogenesis, matrix remodeling, and immune suppression. In contrast, TRMs originate during embryonic development and maintain lung homeostasis, but under tumor-driven reprogramming they acquire immunosuppressive and tumor-supportive functions. A comprehensive understanding of the complementary and sometimes divergent roles of MDMs and TRMs is therefore essential for designing effective TAM-targeted strategies.

As the mechanisms by which TAMs contribute to lung cancer are progressively revealed, TAM-targeted therapies are emerging as a novel direction in lung cancer treatment. By intervening in TAM recruitment, polarization, functional reprogramming, and immune evasion mechanisms, more personalized treatment options for lung cancer patients can be provided. At the same time, the development of TAM-related biomarkers offers powerful tools for early diagnosis and prognostic assessment.

However, the heterogeneity of TAMs and their complex interactions with other immune cells still require further exploration. Future research should focus on gaining a deeper understanding of the dynamic changes of TAMs in the lung cancer microenvironment, developing more precise model systems, and exploring new targeted intervention strategies, with the goal of providing more effective treatment options for lung cancer patients.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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