Tumor-associated macrophages in lung cancer: Friend or foe? (Review)

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Received May 12, 2020; Accepted August 18, 2020

DOI: 10.3892/mmr.2020.11518

Abstract. Typically, tumor-associated macrophages (TAMs), an abundant population of leukocytes in lung cancer, are affected by tumor microenvironment (TME) and shift towards either a pro-tumor (M2-like) or an anti-tumor phenotype (M1-like). M2-polarized macrophages, are one of the primary tumor-infiltrating immune cells and were reported to be associated with the promotion of cancer cell growth, invasion, metastasis, and angiogenesis. TAMs are considered a potential target for adjuvant anticancer therapies, and recent therapeutic approaches targeting the M2 polarization of TAMs have shown encouraging results. The present review discusses recent developments in the role of TAMs in cancer, in particular TAMs functions, clinical implication and prospective therapeutic strategies in lung cancer.

Contents

1. Introduction

Lung cancer is one of the leading causes of cancer-associated mortalities worldwide, with a 5-year survival rate of <20% (1). Approximately 1.8 million new cases are diagnosed annually, of which 80% present with an advanced stage disease. Furthermore, ~50% of the patients are aged >65 years, while 30-40% are aged >70 years and are ineligible for surgery (2). In clinical practice, chemotherapy is the primary treatment modality for lung cancer. However, the majority of patients acquire chemoresistance and metastatic progression, which leads toward the failure of cancer-targeted therapies.

Several advances in tumor immunology in the past decade have aided the body's natural immune system in combating cancer. The tumor microenvironment (TME), characterized by the lack of nutrients, acidic and hypoxic environment, consists of cancerous and non-cancerous cells supporting tumor growth, invasion and metastasis (3). Furthermore, immune cells lose their anti-tumorigenic ability and antagonize antitumour activity. The mutual conversion of tumor-associated macrophages (TAMs), an abundant population of leukocytes in lung cancer, are determined by the TME (4). The TAM phenotypes dynamically alter during tumor progression. The M1-like macrophages are initially activated, and they produce chemokines and cytokines to recruit the cytotoxic $CD8^+$ T and NK cells, which express high levels of IFN-γ and other cytokines to destroy the tumor cells (4). However, during tumor progression, the M2-like TAMs protect the cancer cells from anti-tumor immune responses, and promote their proliferation, angiogenesis, and metastasis. These M2-like TAMs secrete TGF-β to impede the cytotoxicity of NK cells, and express high levels of programmed cell death ligand 1 (PD-L1) to restrict the anti-tumor activity of T cells (5,6).

Clinical studies have suggested that increased TAM density correlates with a poor prognosis in solid tumors (5,7,8) Several animal model experiments have validated this observation by demonstrating that increased TAM density is associated with tumor progression and metastasis, and overexpression of macrophage growth factors or chemokines (9,10). The deletion or re-differentiation of TAMs enhances immune cell-mediated anti-tumor responses and benefits from chemotherapy (11-13). Therefore, targeting TAMs may be at the forefront of lung cancer research and a novel strategy for lung cancer therapy. The present review provides an overview of TAM biology and proposes a therapeutic strategy for targeting TAMs in lung cancer.

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Key words: tumor-associated macrophages, lung cancer, tumor microenvironment, targeted therapy

2. Macrophage plasticity in lung cancer development

Origin of TAMs in lung cancer. Accumulating evidence has suggested that TAMs originate from blood monocytes, and are recruited at tumor sites by tumor-derived chemotactic signals, including monocyte chemo-attractant protein-1 (MCP-1), which is also known as CCL2 (11-13). Furthermore, a small wave develops from *in situ* monocyte-macrophage proliferation and splenic monocytes. However, lung cancer exhibits a high proportion of tissue-resident macrophages, named alveolar macrophages (AMs), which are different to other solid tumors. The AMs are also derived from peripheral blood monocytes, but di-erentiated in response to interferon-γ (IFN-γ) and lipopolysaccharide (LPS) (14). The peripheral monocytes and resident mature monocytes significantly contribute toward the origin of TAMs in lung cancer. Furthermore, the functional diversity of TAMs is affected by local TME, and macrophage polarization occurs at any point in the tumorigenic process.

Opposite properties of M1 and M2 macrophages. Similarly to two polarized sets of T helper 1/2 (Th1/Th2) cells, the TAMs are divided by dichotomy as classically activated M1 macrophages and alternatively activated M2 macrophages. The classical or M1 macrophages are activated by microbial products or interferon-γ (IFN-γ), conferring pro-inflammatory and microbicidal functions, and the capacity to facilitate tumor cell destruction (15). The microbial products or IFN-γ activate signal transducer and activator of transcription 1 (STAT1), interferon regulatory factor (IRF) 3, IRF5, and NF-κB, enable M1 macrophages to generate additional pro-inflammatory mediators (16). These are characterized by high production of nitric oxide (NO) and reactive oxygen intermediates (ROI), secretion of pro-inflammatory cytokines, including TNF-α, IL-1, IL-12 and IL-23, and high levels of MHC molecules (15,17) (Fig. 1).

Additionally, Th2 cytokines, including IL-4 and IL-13, stimulate monocytes or macrophages to transform into the M2 phenotype (15). This macrophage subset triggers allergic reactions, promotes inflammation resolution and wound healing, and favors angiogenesis and tissue remodeling in cancer (Fig. 1). Apart from IL-4 and IL-13, other stimuli and signaling pathways, including IL-10, glucocorticoid hormones and IL-1R may also induce M2 macrophage polarization. There are central transcription regulators that activate the M2 phenotype, including STAT1, STAT3, STAT6, peroxisome proliferator-activated receptor (PPAR-γ), cAMP response element binding protein (CREB)-CCAAT/enhancer binding protein (C/EBP), hypoxia-inducible factor (HIF), IRF4 and PI3K/Akt (18-21).

Based on their functions, M2 macrophages are further classified into M2a, M2b, M2c and M2d (Fig. 2). M2a, induced by IL-4 or IL-13, as well as fungal and helminth infections, express high levels of mannose receptor (CD206), CD209, IL-4R and FcεR, and secrete large amounts of TGF-β and insulin-like growth factor, which contribute toward wound healing and tissue repair (22). M2b, stimulated in response to immune complexes, IL-1β and bacterial LPS, are high producers of IL-10, IL-1β, IL-6 and TNF-α, which exert anti-inflammatory effects (23). M2c, induced by IL-10, TGF-β and glucocorticoids, are considered to be involved in immunosuppression, tissue repair and matrix remodeling (24). These macrophages exhibit increased expression of RAGE, CD163 and CD206, and secrete large amounts of IL-10 and TGF-β (25). Finally, M2d, activated by leukocyte inhibitory factor, TLR ligands and adenosine, express low levels of CD206, but produce significant amounts of IL-10, TGF-β and VEGF to promote tumor progression by facilitating immunosuppression and angiogenesis (26).

TAMs display pro-tumor M2 type macrophages. Compared to M1 macrophages, TAMs produce fewer ROIs and inflammatory cytokines (IL-1β, TNF-α, IL-6, IL-12, CCL3 and CCL4) (27). While the NF-κB pathway is a key regulator of inflammation, TAMs display defective NF-κB activation, indicating low expression of NF-κB-dependent cytotoxic mediators and inflammatory cytokines (16). By contrast, typical M2 markers, including the scavenger receptor-A (SR-A), mannose receptor (MR), arginase-I (Arg-I), YM1 and FIZZ1, and MGL2 showed higher expression in TAMs (16). Previous studies have suggested that TAMs present M2-associated function by secreting pro-angiogenic and tumor-inducing chemokines, including epidermal growth factor (EGF), VEGF and TGF-β (28,29). Therefore, the notion that TAMs resemble M2 macrophages has been supported *in vitro* and *in vivo* (30).

The M2-type macrophages may be reversed to M1-type under certain conditions. Macrophages are highly plastic cells that may be differentiated into several phenotypes. Polarization is dynamic and affected by the TME. The dichotomy of M1 and M2 subtypes is over-generalized and only partially represents the continuity of polarization. For example, 5% of the AMs from lung cancer express M1 and M2 markers (31), and mixed polarization phenotypes (displaying M1 and M2 characteristics, HLA-DR, IL-1β, TNF-α, CD163 and IL10) have been described (32). Therefore, M1 and M2 markers may be used to distinguish macrophage populations to a certain extent.

3. Functional aspects of macrophages in lung cancer

TAMs in lung cancer initiation and progression. TAMs provide a suitable microenvironment to support growth, immunosuppression, invasion and therapeutic resistance in lung cancer, primarily by secreting TGF-β, IL-10, CCL18, matrix metalloproteases (MMPs), VEGF, COX2 and PDGF-B (Fig. 1).

IL-10. In vitro, the TAMs derived from THP-1 cells co-cultured with A549 and H1299 cells promoted epithelial-to-mesenchymal transition (EMT) and invasion in lung cancer cells (33,34). Furthermore, TAMs may activate and protect cancer stem cells (CSCs) to promote tumor progression by secreting IL-10 (35). When tumor cell proliferation is uncontrolled, oxygen and nutrition are limited, leading to hypoxia. Hypoxia skews macrophages to the M2-like phenotype with increased expression of IL-10, HIF1α and VEGF (36). Hypoxia then drives macrophage diversity to facilitate lung cancer cell metastasis, angiogenesis, and immune evasion *in vitro* and *in vivo* (36,37). Clinical data have demonstrated that increased gene expression of macrophage-derived IL-10 in tumor tissues was significantly correlated with stage, tumor size, lymph

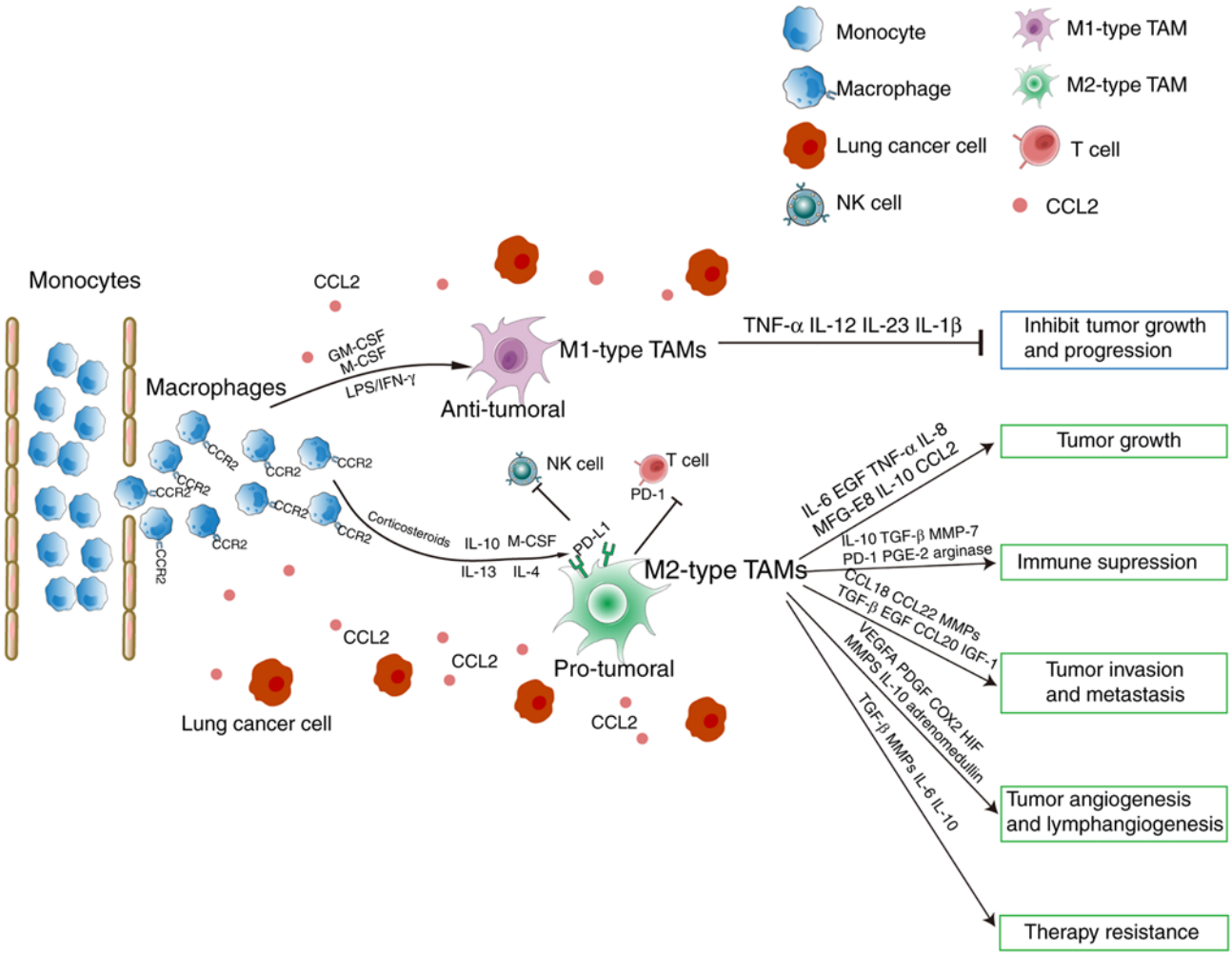

Figure 1. Macrophage polarization and function of TAMs in lung cancer. TAM, tumor-associated macrophage.

node metastasis, lymphovascular invasion, or histologically poor differentiation (38).

IL-6. The macrophages derived from THP-1 exhibit high expression of IL-6 when co-cultured with human non-small cell lung cancer (NSCLC) A549 or H1299 cells, and enhances the invasive ability of lung cancer cells by regulating EMT (34). Additionally, IL-6 may stimulate macrophages to express higher levels of IL-10, and together, IL-6 and IL-10 induce M2 macrophage differentiation in an IL-4-dependent manner via STAT3 activation (39); while, IL-6-induced macrophage infiltration proceeds via the CCL2/CCL5 pathway in NSCLC. Abrogation or suppression of IL-6 expression may inhibit TAM-induced invasion and angiogenesis in lung cancer cells (34,40).

TGF-β. TGF-β, together with its co-receptor endoglin, serves a vital role in tissue repair, and angiogenesis and lymphangiogenesis. A previous study reported an increase in the levels of endoglin during the process of monocyte transition to macrophages (41). Furthermore, macrophages and pro-inflammatory cytokines are significantly down-regulated in *Eng*$^{+/-}$ mice (42). The TGF-β, released by tumor cells and M2 type macrophages, may suppress M1 polarized macrophages, and stimulate mature macrophages to polarize to the pro-tumor M2 type. Maeda *et al* (43) reported that IL-10 expression in macrophages is positively associated with TGF-β expression, and that TGF-β enhances Mϕ to secrete IL-10, promoting tumor progression in tumor-bearing mice (43). A previous study has shown that TGF-β secreted by TAMs promotes EMT, and upregulates the expression of SOX9, which enhances tumor cell proliferation, migration and invasion (44). Furthermore, suppressing the expression of TGF-β may inhibit TGF-β1-induced EMT in A549 lung cancer cells (45).

MMPs. Furthermore, TAMs induce lung cancer cell invasion by producing MMPs, including MMP-9 and MMP-2, and degrading the extracellular matrix. MMP-9 expression is associated with lymph node metastases, tumor progression and prognosis (46). IL-10-induced macrophages enhance MMP-9 and MMP-2 expression and promote cancer cell invasion and migration (47). Therefore, inhibition of MMP production may reverse macrophage-mediated cancer cell invasion and migration activity (46-48).

Chemokines. Chemokines are a family of soluble and chemotactic cytokines that are secreted by and mediate the chemotaxis and migration of immune or tumor cells. Recent advances have indicated that chemokines originating from

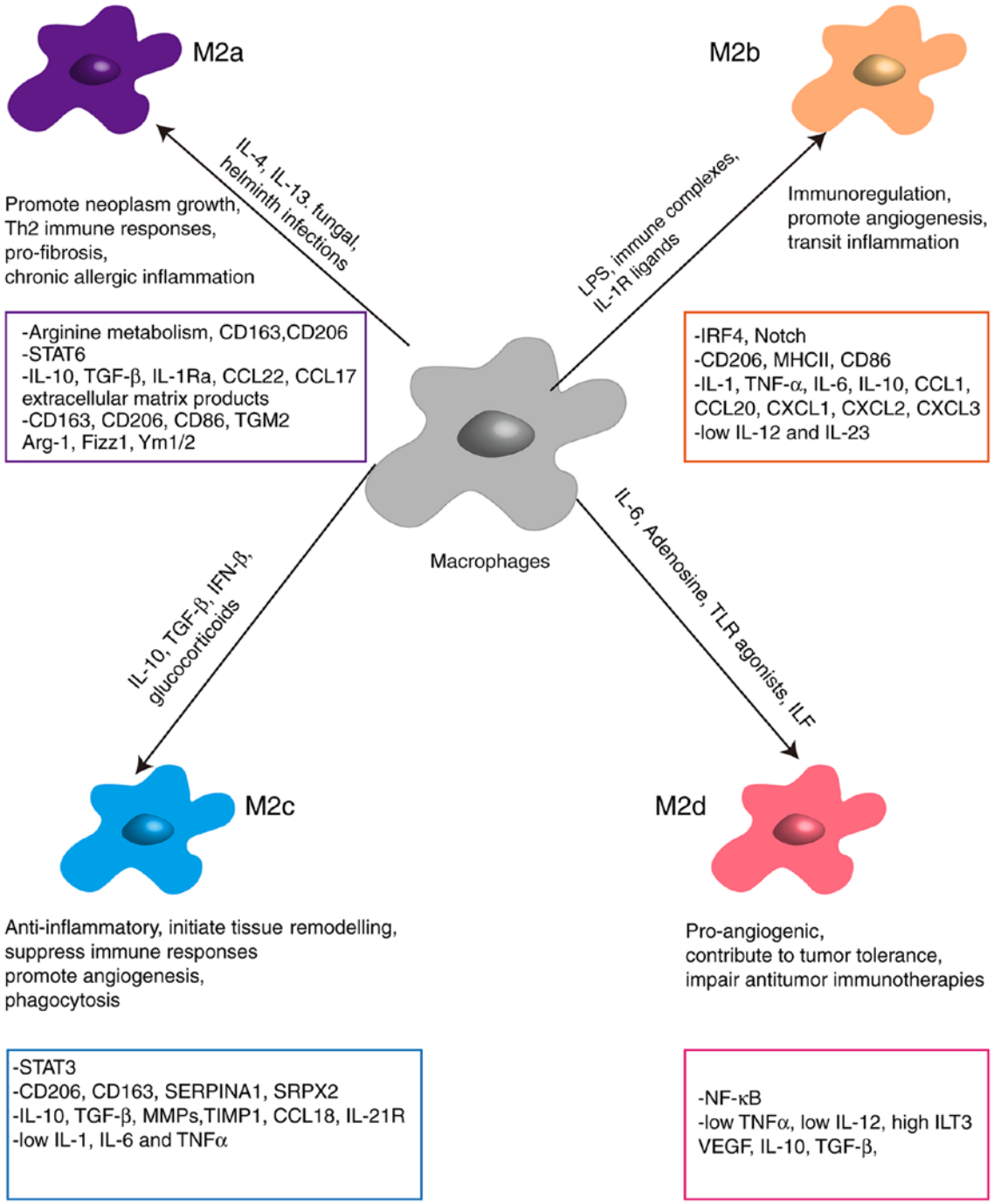

Figure 2. Different types of M2-like macrophages in lung cancer. Arg-1, arginase-1; CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; Fizz1, found in inflammatory zone 1; VEGF, vascular endothelial growth factor.

TAMs, including CCL18, MIP-3α, CCL5, CXCL8, and CCL22, serve critical roles in cancer progression by binding to their cognate receptors in carcinoma cells (49-51). Early evidence has suggested that CCL22 is highly expressed in lung cancer, and is a predictive marker for disease-free survival duration and tumor recurrence (49-52). CCL22 may promote the bone metastasis of lung cancer cells that express CCR4 (53). CXCL8, an M2-related chemokine secreted by TAMs, also serves a role in lung cancer. Previous studies have suggested that CXCL8 may induce EMT, and accelerate invasion and migration via the MAPK/NF-κB and JAK2/STAT3 signaling pathways (54,55). Therefore, therapies or drugs targeting CXCL8 may attenuate cell proliferation, invasion, and migration in lung cancer (55,56).

Angiogenesis. TAMs serve a key role in facilitating angiogenesis by producing pro-angiogenic factors, including IL-8, VEGF, urokinase plasminogen activator (uPA), and MMPs, (Fig. 1). TAM density is associated with intra-tumoral microvessel counts in NSCLC (57). Chen *et al* (58) reported that the THP-1-derived M2-type macrophages may promote angiogenesis in NSCLC, by producing proangiogenic factors, including IL-8, and supporting the generation of blood vessels (58). Hypoxia is a local attractant for TAMs in the

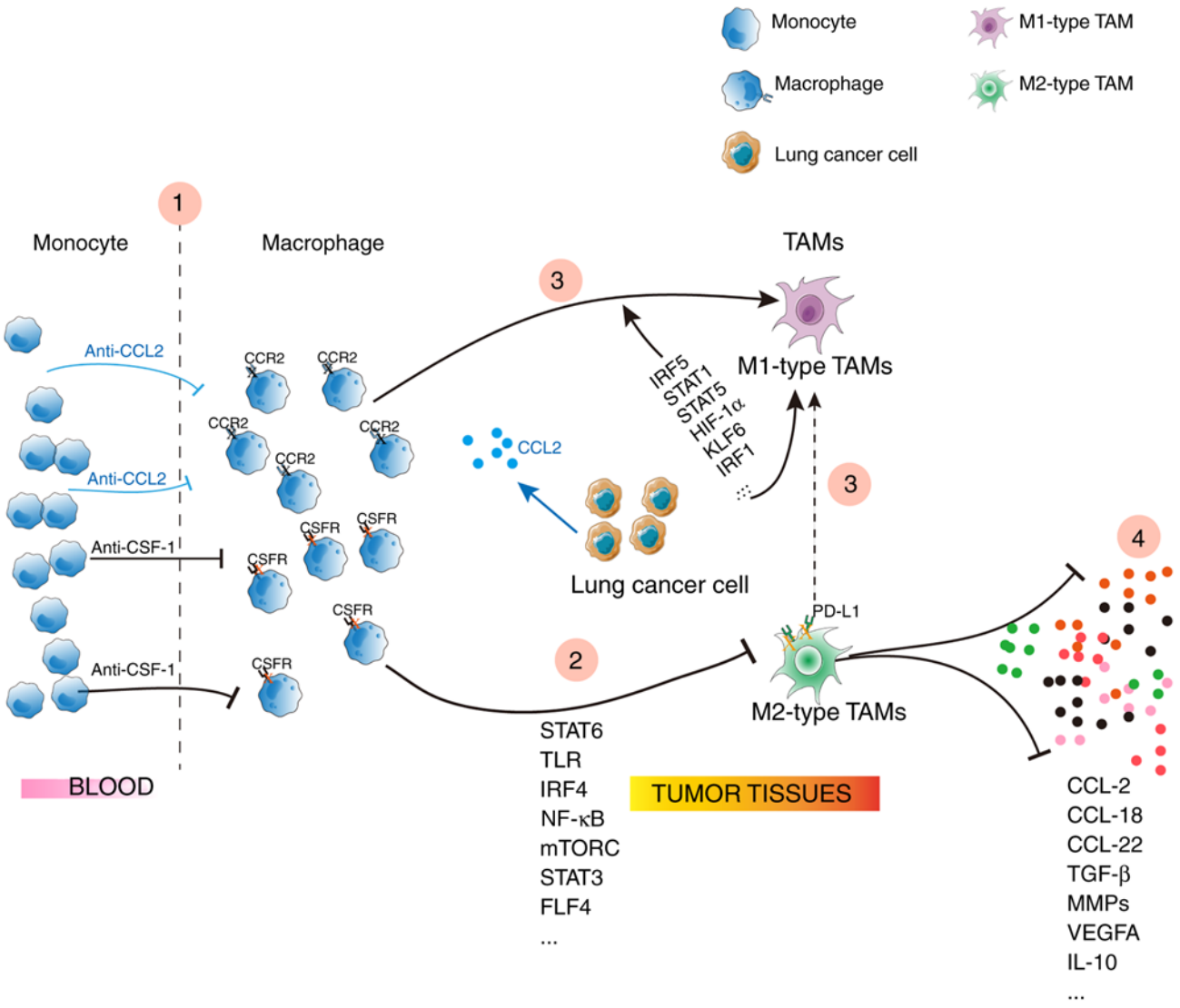

Figure 3. Anti-tumor therapies targeted TAMs in lung cancer. IL, interleukin; TGF-β, transforming growth factor-beta; MMPs, matrix metalloproteinases; VEGFA, vascular endothelial growth factor A; TAM, tumor-associated macrophage.

TME, which induces the expression of HIF-1 and HIF-2; and HIF-2 may upregulate VEGF expression (59,60). Additionally, VEGF is also a chemoattractant for TAMs, which forms a positive feedback loop to promote tumor angiogenesis (61).

Immunosuppression. In TME, macrophages not only lose their anti-cancer properties, but also impede the immunoregulatory functions of other immune cells. The TAMs upregulate the expression of PD-L1 to suppress T-cell toxicity and inhibit phagocytosis (5,62). The $CD8^+$ T cells are excluded by TAMs, and thus cannot act near the cancer cells (63). Furthermore, TAMs produce cytokines and other proteins to maintain immunosuppression, including CCL-22, CCL-17, TGF-β, arginase 1 and galectin-3 (28,29). The AMs stimulated by the Th2 cells produce immunosuppressive cytokines, including IL-10 and TGF-β in the lung TME to reduce the number of tumor-infiltrating lung dendritic cells (DCs) and block their maturation (64,65). Furthermore, IL-10 triggers the immunosuppression of T cells by upregulating PD-L1 expression in tumor macrophages (38,66). The blockade or deficiency of IL-10 may induce $CD8^+$ T cell cytotoxicity and promote tumor-resident $CD8^+$ T cell expansion (66). Additionally, the macrophage-derived CCL22 promotes an immunosuppressive tumor microenvironment by recruiting Tregs (67). Furthermore, Young *et al* (68) indicated that NK cell cytotoxicity is also suppressed and facilitates pulmonary metastases (68). Depletion of the AM or reversal of M2 polarization may relieve immunosuppression imposed by the macrophages, and strengthen local Th1 anticancer activity (64).

Chemotherapy resistance. Resistance to chemotherapy increases the difficulty of therapeutic efficacy, and drives tumor progression, recurrence, and distant, bone and lymph node metastasis. A strong correlation has been demonstrated between TAMs and chemotherapy resistance (13,69). A previous study reported that abundant $CD68^+$ and $CD163^+$ macrophages accumulate inside or adjacent to tumors following chemotherapy (69). In a mouse Lewis lung carcinoma model (LLC1s), treatment with chemotherapeutic agents induces neoplastic cells that release CXCL12, which enhances the infiltration of $CD206^+$ TAMs, inhibits tumor cell death, and assists in tumor relapse (13). Additionally, treatment with cisplatin or carboplatin induces tumor cells to secrete

IL-6 and/or prostaglandin E2 (PGE2), which mediates M2 macrophage polarization via activation of the STAT3, STAT1 and STAT6 signaling pathways, and resists cytotoxic chemotherapy (70,71). Furthermore, DeNardo *et al* (72) illustrated that paclitaxel treatment boosts the infiltration of macrophages, which limits the recruitment and efficacy of $CD8^+$ cytotoxic T cells, and inhibits the antitumor activity of paclitaxel (72). Recent large cohort clinical studies have reported a close correlation between the infiltration of M2-macrophages, poor response to chemotherapy, and poor clinical outcomes (73,74). The elimination of TAMs by anti-CSF-1 or anti-CCL2 antibodies, preventing M2-differentiation by COX inhibitors, and/or anti-IL-6R antibodies may enhance the cytotoxic effects of chemotherapeutic agents, including taxol, cisplatin, and doxorubicin (75,76). Therefore, concomitant therapy with an intervention strategy that reduces macrophage population or inhibits M2 polarization may amplify the antitumor activity of chemotherapeutic agents.

4. Clinical implications of TAMs in lung cancer

Clinical studies have suggested that the density of macrophages, particularly M2 type, is associated with a poor prognosis in almost all human cancer types (7,8). However, there are conflicting data with regards to lung cancer. CD68, a common monocyte/macrophage marker, when used to label TAMs, indicated it to act as an independent prognostic factor, and a higher percentage of tumor islets were found to be correlated with improved outcomes (77,78). However, other studies observed no association between $CD68^+$ macrophage densities and tumor islets or stroma with patients' survival duration (79,80). This is possibly due to involvement of the margin or central macrophages.

Usually, the $CD68^+CD163^+$ or $CD68^+CD206^+$ markers are used to identify M2 macrophages. Zhang *et al* (81) indicated that levels of M2-type ($CD68^+CD206^+$) were positively associated with peritumoral lymphatic microvessel density, but negatively associated with patients' prognoses (81). In line with this, emerging research has suggested that the accumulation of $CD163^+$ macrophages is closely correlated with a poor prognosis in lung cancer. Furthermore, an increased density of $CD68^+CD163^+$ macrophages in tumor nests and stroma was associated with lymph node metastases (81), but no such association was observed with recurrence-free survival (RFS), overall survival (OS), and TNM stages (80,82). However, Cao *et al* (7) found that levels of $CD68^+CD163^+$M2 were correlated with OS and DFS in NSCLC (7). Furthermore, increased infiltration of macrophages was observed in patients with lung squamous cell carcinoma (LUSC), wild-type *EGFR*, and smoking habits (7).

Additionally, M2-TAMs labeled with $CD204^+$ serve a role in prognosis. High infiltration of $CD204^+$TAMs in the stroma may be correlated with TNM stages, presence of vascular and pleural invasion, and OS and RFS in patients with stage II LUSC. However, no association was observed between the levels of $CD204^+$ macrophages and poor patient outcomes (83).

Taken together, the different data or contradictory results of previous studies may be explained by the tumor histological type and origin in patients, methodologies applied in counting TAMs, and definition of islet and stroma. Furthermore, a recent meta-analysis reported that M2-type TAMs or M1/M2 polarization in the lung cancer islets or stroma are associated with tumor progression. Therefore, targeting TAMs may be considered as a newer anti-tumor strategy in lung cancer.

5. TAM-targeted therapeutics

TAMs, the major component of leukocyte infiltration in tumors, serve an important role in tumor behavior, and thus therapies targeting TAMs are employed. To begin with, inhibition of macrophages infiltrating the tumor; CSF1-CSF1R and CCL2-CCR2 may induce macrophage recruitment, and blockade of CCL2-CCR2 or CSF1-CSF1R may decrease TAM infiltration, reversing the immunosuppressive status (84) (Fig. 3), but anti-CCL2 therapy may aggravate metastasis (85). A second strategy is that blockade of TAMs repolarize into the M2-type: Few signaling components regulate M2 macrophage polarization, including the Toll-like receptors (TLR), STAT6 and NK-κB. When these signals are intervened, TAMs lose their 'alternative' activated phenotype. A third strategy would involve reeducating TAMs to M1-type or switching M2 to M1: Several drugs, including BTH1677 (a yeast β-glucan immunomodulator), hydroxychloroquine, and celecoxib, switch M2-like TAMs to an antitumor phenotype, or M1-like TAMs (86-88). A final strategy is based on the fact that decreasing the levels of critical TAM-secreted cytokines involved in tumor biology: For example, CCL18, CCL22, and MIP-3α, mainly produced by the M2-type macrophages, confer malignant behaviors (9,10,49). Blockade of CCL18, CCL22, or MIP-3α weakens the TAM-mediated pro-tumor ability (9,10,89).

The aforementioned strategies provide enhanced and promising therapeutic effects, although there are a few major issues or side effects that require attention, including the efficiency of specific drug delivery and nontargeting TAMs. Evidence has indicated that nanoparticles or nanoparticle-based drug delivery are more reliable and effective in regulating the macrophage phenotype by ensuring that the drug reaches the cancer site without off-target activity. Several studies have demonstrated that nanodrugs offer superiority in mediating the polarization of macrophages with increased drug uptake. For instance, curcumin (Cur), baicalin (Bai), and ginseng-derived nanoparticles have been reported to alter TAM polarization without discernible toxicity (90-92). Compared to the drugs themselves, their nanoparticle derivatives showed improved pharmacokinetics and bioavailability in systemic circulation, and thus contributed toward excellent antitumor responses (90-92). Furthermore, few materials used in nanoparticle production, including TiO_2 and Ag, may preferentially polarize TAMs towards an M1 phenotype (93,94).

We hypothesize that every immune cell serves an equal role in the body, and macrophages have dual property; therefore, eliminating or decreasing macrophages is not a rational approach and has other disadvantages. By contrast, 'reeducating' the macrophages or targeting the tumorigenic cytokines or chemokines secreted by the macrophages should be studied as a preferred strategy for combating cancer.

6. Conclusions

Several experimental and clinical studies have demonstrated that TAMs serve a seminal role in the growth, angiogenesis, metastasis, and invasion in lung cancer. Furthermore, TAMs

confer chemotherapy resistance and immunosuppression. Therefore, TAMs are now considered a promising target in the treatment of lung cancer. However, no appropriate drugs have been administered in the patients, and newer treatment approaches may ascertain improved clinical outcomes.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Development Project of Shanghai Peak Disciplines-Integrative Medicine and Western Medicine (grant no. 20150407), National Natural Science Program of China (grant nos. 81673916 and 81403148) and the Development Plan of Shandong Medical and Health Technology (grant no. 2019WS581).

Availability of data and materials

Not applicable.

Authors' contributions

FX and YW wrote the manuscript; ZT made contributions to the figures; BL and JD contributed toward the literature review and revised the manuscript. All authors read and appvoed the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors have declared that they have no competing interests.

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