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.

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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.
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, enabling 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)-CCAT/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 IL-10 (35). When tumor cell proliferation is uncontrolled, oxygen and nutrition are limited, leading to hypoxia. Hypoxia skewed 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
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
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

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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.
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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-ICL2 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 (77) 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 EGF, 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-ICL2 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 TiO₂ 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
confers 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 approved 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.

References

1. Brennan JE and Temple BR: Opinion: Alternative views of AMP-activated protein kinase. Cell Biochem Biophys 47: 321-331, 2007.
2. Gridelli C, Perrone F and Monfardini S: Lung cancer in the elderly. Eur J Cancer 33: 2313-2314, 1997.
3. Goswami KK, Ghosh T, Ghosh S, Sarkar M, Bose A and Baral R: Tumor promoting role of anti-tumor macrophages in tumor microenvironment. Cell Commun Signal 16: 1-10, 2017.
4. Mosser DM and Edwards JP: Exploring the full spectrum of macrophage activation. Nat Rev Immunol 8: 958-969, 2008.
5. Sumitomo R, Hirai T, Fujita M, Murakami H, Otake Y and Huang CL: M2 tumor-associated macrophages promote tumor progression in non-small-cell lung cancer. Exp Ther Med 18: 4900-4908, 2019.
6. Zhou Z, Peng Y, Wu X, Meng S, Yu W, Zhao J, Zhang H, Wang J and Li W: CL18 secreted from M2 macrophages promotes migration and invasion via the PI3K/Akt pathway in gallbladder cancer. Cell Oncol (Dordr) 42: 81-92, 2019.
7. Yeung OW, Lo CM, Ling CC, Qi X, Geng W, Li CX, Ng KT, Forbes SJ, Guan XY, Poom RC, et al: Alternately activated (M2) macrophages promote tumor growth and invasiveness in hepatocellular carcinoma. J Hepatol 62: 607-616, 2015.
8. Sarode P, Zheng X, Giotopoulou GA, Weigert A, Kuenne C, Günther S, Friedrich A, Gattenlöhner S, Stiewe T, Brüne B, et al: Reprogramming of tumor-associated macrophages by targeting β-catenin/FOSE2/ARID5A signaling: A potential treatment of lung cancer. Sci Adv 6: eaa6105, 2020.
9. Kimura Y, Sumiyoshi M and Baba K: Antitumor and antimetastatic activity of synthetic hydroxystilbenes through inhibition of lymphangiogenesis and M2 macrophage differentiation of tumor-associated macrophages. Anticancer Res 36: 137-148, 2016.
10. Hughes R, Qian BZ, Rowan C, Muthana M, Keklikoglou I, Olson OC, Tazzyman S, Danson S, Addison C, Clemons M, et al: Pervascular M2 macrophages stimulate tumor relapse after chemotherapy. Cancer Res 75: 3479-3491, 2015.
11. Flaherty DM, Monick MM and Hinde SL: Human alveolar macrophages are deficient in PTEN. The role of endogenous oxidants. J Biol Chem 281: 5058-5064, 2006.
12. Biswas SK and Mantovani A: Macrophage plasticity and interaction with lymphocyte subsets: Cancer as a paradigm. Nat Immunol 11: 889-896, 2010.
13. Flavell RB and Coussens LM: Macrophages and therapeutic resistance in cancer. Cell 130: 1261-1275, 2007.
14. Gridelli C, Perrone F and Monfardini S: Lung cancer in the elderly. Eur J Cancer 33: 2313-2314, 1997.
15. Biswas SK and Mantovani A: Macrophage plasticity and interaction with lymphocyte subsets: Cancer as a paradigm. Nat Immunol 11: 889-896, 2010.
16. Biswas SK, Angioli L, Paul S, Schioppa T, Saccani A, Sironi M, Bottazzi B, Doni A, Vincenzo B, Pasqualini F, et al: A distinct and unique transcriptional program expressed by tumor-associated macrophages (defective NF-kappaB and enhanced IRF-3/STAT1 activation). Blood 107: 2112-2122, 2006.
17. Klimp AH, Hollema H, Kempinga C, van der Zee AG, de Vries EG and Daemen T: Expression of cyclooxygenase-2 (COX-2) in human ovarian tumors and tumor-infiltrating macrophages. Anticancer Res 36: 137-148, 2016.
28. Schoppmann SF, Birner P, Stöckl J, Kalt R, Ullrich R, Caicic K, Kricheuer E, Nagy K, Alitako K and Kerjaschki D: Tumor-associated macrophages express lymphatic endothelial growth factors and are related to peritumoral lymphangiogenesis. Am J Pathol 158: 257-263, 2001.

29. Hotchkiss KA, Ashton AW, Klein RS, Lenzi ML, Zhu GH and Schwartz EL: Mechanisms by which tumor cells and monocytes expressing the angiogenic factor thymidine phosphorylase mediate human endothelial cell migration. Cancer Res 62: 557-563, 2002.

30. Mantovani A, Sozzani S, Locati M, Allavena P and Sica A: Macrophage polarization: Tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. Trends Immunol 23: 549-555, 2002.

31. Ohri C, Shikotra A, Green H, Waller d and Bradding P: Macrophages with the angiogenic factor thymidine phosphorylase correlated with late stage of lung cancer. J exp clin Cancer Res 30: 62, 2011.

32. Zhang J, Zhang S, Jing Z, Shang L, Jin S, Liu F, Shen J, Li Y, Hu J, Meng Q and Yu Y: Macrophages induce EMT to promote invasion of lung cancer cells through the IL-6-mediated COX-2/PGJ2/b-catenin signalling pathway. Mol Immunol 90: 197-210, 2017.

33. Helm O, Held-Feindt J, Grage-Griebenow E, Reiling N, Ungeferro H, Vogel I, Krüger U, Becker T, Ebsen M, Röcken C, et al: Tumor-associated macrophages exhibit pro- and anti-inflammatory properties by which they impact on pancreatic tumorigenesis. Int J Cancer 135: 843-861, 2014.

34. Che D, Bo P, Qiang T, Lihua F, Shi J, Jingyan C, Yan Y, Guangbin W and Zhenjun Y: Enhanced invasion of lung adenocarcinoma cells after co-culture with THP-1-derived macrophages via the induction of EMT by IL-6. Immunol Lett 160: 1-10, 2014.

35. Yang L, Dong Y, Li Y, Wang D, Gao Q, Ji S, Chen X, Lei Q, et al: IL-10 derived from M2 macrophage promotes cancer stemness via JAK1/STAT3/NF-kB/Notch pathway in non-small cell lung cancer. Int J Cancer 145: 1099-1110, 2019.

36. Zhang J, Cao J, Ma S, Dong R, Meng W, Ying M, Weng Q, Chen Z, Maj F, Fang Q, et al: Tumor hypoxia enhances Non-Small Cell Lung Cancer metastasis by selectively promoting macrophage M2 polarization through the activation of ERK signaling. Oncotarget 5: 9664-9677, 2014.

37. Laoui D, Van Overmeire E, Di Conza G, Aldeni C, Keirsse J, Morias Y, Movahedi K, Houbracken I, Schouppe E, Elkimry Y, et al: Tumor hypoxia does not drive differentiation of tumor-associated macrophages but rather fine-tunes the M2-like macrophage population. Immunity 90: 1196-1210, 2019.

38. Wang R, Zhang J, Wang S, Luo S, Liu S, Qin Y and Chen H: Increased IL-10 mRNA expression in tumor-associated macrophage correlated with late stage of lung cancer. J Exp Clin Cancer Res 30: 62, 2011.

39. Fu X, Duan W, Su C, Mao FY, Lv Y, Teng YS, Yu PW, Zhang Y and Xie X: Neutralization of ccl2 induces M2 macrophage differentiation through STAT3 activation that correlates with gastric cancer progression. Cancer Immunol Immunother 55: 1320-1329, 2006.

40. Cao H, Huang Y, Wang L, Wang H, Pang X, Li K, Dang W, Tang H, Wei L, Su M, et al: Lentinan promotes migration and invasion of breast cancer cells by stimulating IL-8 production in M2 macrophages. Oncotarget 7: 65441-65453, 2016.

41. Liu Q, Li A, Yu S, Qin S, Han N, Pestell RG, Han X and Wu K: DACH1 antagonizes CXCL18 to repress tumorigenesis of lung adenocarcinoma and improve prognosis. J Hematol Oncol 11: 53, 2018.

42. Tataroğlu C, Kargı A, Ozkalı S, Erşefoğlu N and Akköçu A: Association of macrophages, mast cells and eosinophil leukocytes with angiogenesis and tumor staging in non-small cell lung carcinomas (NSCLC). Lung Cancer 43: 47-54, 2004.

43. Chen J, Yao PL, Yuan A, Hong TM, Shun CT, Luo YL, Lee YC and Yang PC: Up-regulation of tumor interleukin-8 expression by infiltrating macrophages: Its correlation with tumor angiogenesis and patient survival in non-small cell lung cancer. Clin Cancer Res 9: 729-737, 2003.

44. Lewis JD, Landers JR, Underwood JC, Harris AL and Lewis CE: Expression of vascular endothelial growth factor by macrophages is up-regulated in poorly vascularized areas of breast cancer. J Pathol 192: 150-158, 2000.

45. Stein RJ and Fanger W: Tumor necrosis factor-α secreted by associated macrophages in breast cancer. J Mammary Gland Biol Neoplasia 7: 177-189, 2002.

46. Lewis JD, Landers JR, Underwood JC, Harris AL and Lewis CE: Expression of vascular endothelial growth factor by macrophages is up-regulated in poorly vascularized areas of breast cancer. J Pathol 192: 150-158, 2000.

47. Peranzoni E, Lemoine J, Feuillet V, Barrin S, Kantari-Mimoun C, Bercovici N, Guerin M, Biton J, Ouadhi H, et al: Macrophages impede CD8 T cells from reaching tumor cells and limit the efficacy of anti-PD-1 treatment. Proc Natl Acad Sci USA 115: E4041-E4050, 2018.
64. Sharma SK, Chintala NK, Vadrevu SK, Patel J, Karbowiczek M and Markiewski MM: Pulmonary alveolar macrophages contribute to the premetastatic niche by suppressing antitumor T cell responses in the lungs. J Immunol 194: 5529-5538, 2015.

65. Allavena P, Sica A, Vecchi A, Locati M, Sozzani S and Mantovani A: The chemokine receptor switch paradigm and dendritic cell migration: Its significance in cancer paradigm. Immuno Rev 177: 141-149, 2000.

66. Kao J, Liu Z, Dong C, Luan Y, Zhang A, Moore C, Fu K, Peng J, Wang Y, Ren Z, et al.: Targeting tumors with IL-10 prevents dendritic cell-mediated CD8+ T cell apoptosis. Cancer Cell 35: 901-915.e4, 2019.

67. Wang D, Yang L, Yue D, Cao L, Li L, Wang D, Ping Y, Shen Z, Zheng Y, Wang L and Zhang Y: Macrophage-derived CCL22 promotes an immunosuppressive tumor microenvironment via IL-8 in malignant pleural effusion. Cancer Lett 452: 244-253, 2019.

68. Young MR, Endicott RA, Duffie GP and Wepis HT: Suppressor alveolar macrophages in mice bearing metastatic Lewis lung carcinoma tumors. J Leukoc Biol 42: 682-688, 1987.

69. De Palma M and Lewis CE: Cancer: Macrophages limit chemotherapy. Nature 472: 303-304, 2011.

70. Dijkstra EM, Heusinkveld M, Tummers B, Vogelpoel LT, Mitchem JB, Brennan DJ, Knolhoff BL, Belt BA, Zhu Y, Sanford de, Paulus P, Stanley ER, Schäfer R, Abraham D and Abarinejad S: Targeting tumor-infiltrating macrophages decreases tumor-initiating cells, relieves immunosuppression, and improves chemotherapeutic responses. Cancer Res 73: 1128-1141, 2013.

71. DeNardo DG, Brennan DJ, Rexhepi E, Ruffell B, Shiao SL, Madden SF, Gallagher WM, Wadhwa N, Keil SD, Junaid SA, et al.: Leukocyte complexity predicts breast cancer survival and functionally regulates response to chemotherapy. Cancer Discov 1: 54-67, 2011.

72. Zhang C, Yu X, Gao L, Zhao Y, Lai J, Du D, Bao R, Jia B, Zhong L, Wang F and Liu Z: Noninvasive imaging of CD206-positive M2 macrophages as an early biomarker for post-chemotherapy tumor relapse and lymph node metastasis. Theranostics 7: 4276-4288, 2017.

73. Sugimura K, Miyata H, Tanaka K, Takiguchi S, Mori M and Doki Y: High infiltration of tumor-associated macrophages is associated with a poor response to chemotherapy and poor prognosis of patients undergoing neoadjuvant chemotherapy for esophageal cancer. J Surg Oncol 111: 752-759, 2015.

74. Paulus P, Stanley ER, Schäfer R, Abraham D and Aharinejad S: Colony-stimulating factor-1 antibody reverses chemoresistance in human MCF-7 breast cancer xenografts. Cancer Res 66: 4349-4356, 2006.

75. Salvagno C, Ciampricotti M, Tuit S, Hau CS, van Wervijk A, Coffelt SB, Kersten K, Vrijland K, Kos K, Ulas T, et al.: Therapeutic targeting of macrophages enhances chemotherapy efficacy by unleashing type I interferon response. Nat Cell Biol 21: 511-521, 2019.

76. Dai F, Liu L, Che G, Yu N, Pu Q, Zhang S, Ma J, Ma L and You Z: The number and microlocalization of tumor-associated immune cells are associated with patient's survival time in non-small cell lung cancer. BMC Cancer 10: 220, 2010.

77. Welsh TJ, Green RH, Richardson D, Waller DA, O'Bryne KJ and Bradley P: Macrophage and mast-cell invasion of tumor cells islets confers a marked survival advantage in non-small-cell lung cancer. J Clin Oncol 23: 8959-8967, 2005.

78. Pei BX, Sun BS, Zhang ZF, Wang AL and Ren P: Interstitial tumor-associated macrophages combined with tumor-derived colony-stimulating factor-1 and interleukin-6, a novel prognostic biomarker in non-small cell lung cancer. J Thorac Cardiovasc Surg 148: 1208-1216.e2, 2014.

80. Ma J, Liu L, Che G, Yu N, Dai F and You Z: The M1 form of tumor-associated macrophages in non-small cell lung cancer is positively associated with survival time. BMC Cancer 10: 112, 2010.

81. Zhang B, Yao G, Zhang Y, Gao J, Yang B, Rao Z and Gao J: M2-polarized tumor-associated macrophages are associated with poor prognoses resulting from accelerated lymphangiogenesis in lung adenocarcinoma. Clinics (Sao Paulo) 66: 1879-1886, 2011.

82. Jung KY, Cho SW, Kim YA, Kim D, Oh BC, Park DJ and Park YJ: Cancers with higher density of tumor-associated macrophages were associated with poorer survival rates. J Pathol Trans Med 49: 318-324, 2015.

83. Hirayama S, Ishii G, Nagai K, Ono S, Koijima M, Yamauchi C, Aokage K, Hishida T, Yoshida J, Suzuki K and Ochiai A: Prognostic impact of CD204-positive macrophages in lung squamous cell carcinoma: Possible contribution of CD204-positive macrophages to the tumor-promoting microenvironment. J Thorac Oncol 7: 1790-1797, 2012.

84. Li Y, Yao W, Yuan Y, Chen P, Li B, Li J, Chu R, Song H, Xie D, Jiang X and Wang H: Targeting of tumour-infiltrating macrophages via CCL2/CCR2 signalling as a therapeutic strategy against hepatocellular carcinoma. Gut 66: 157-167, 2017.

85. Keklikoglou I and De Palma M: Cancer: Metastasis risk after anti-macrophage therapy. Nature 515: 46-47, 2014.

86. Li Y, Cao F, Li M, Li P, Yu Y, Xiang L, Xu L, Lei J, Tai YY, Zhu J, et al.: Hydroxychloroquine induced lung cancer suppression by enhancing chemo-sensitization and promoting the transition of M2-TAMs to M1-like macrophages. J Exp Clin Cancer Res 37: 259, 2018.

87. Zhang Y, Sun Z, Pei J, Luo Q, Zeng X, Li Q, Yang Z and Quan J: Identification of α-mangostin as an agonist of human STING. Chemmedchem 13: 2057-2064, 2018.

88. Brandão RD, Veeck J, Van de Vijver KK, Lindsey P, de Vries B, van Elsken CH, Blok MJ, Keymeulen K, Ayoubi T, Smeets HJ, et al.: A randomised controlled phase II trial of pre-operative celecoxib treatment reveals anti-tumour transcriptional response in primary breast cancer. Breast Cancer Res 15: R29, 2013.

89. Zhu B, Zou L, Cheng X, Lin Z, Duan Y, Wu Y, Zhou F and Chen Z: Administration of MIP-3alpha gene to the tumor following radiation therapy boosts anti-tumor immunity in a murine model of lung carcinoma. Immunol Lett 103: 101-107, 2006.

90. Shiri S, Alizadeh AM, Baradaran B, Farhanghi B, Shanehbandi D, Khodayari S, Khodayari H and Tahvossi A: Dendrosomal curcumin suppresses metastatic breast cancer in mice by changing m1/m2 macrophage balance in the tumor microenvironment. Asian Pac J Cancer Prev 16: 3917-3922, 2015.

91. Han S, Wang W, Wang S, Ju R, Pan Z, Yang T, Zhang G, Wang H and Wang L: Multifunctional biomimetic nanoparticles loading baicalin for polarizing tumor-associated macrophages. Nanoscale 11: 20206-20220, 2019.

92. Cao M, Han H, Han X, Weng L, Wei Q, Sun X, Lu W, Wei Q, Ye J, Cai X, et al.: Ginseng-derived nanoparticles alter macrophage polarization to inhibit melanoma growth. J Immunother Cancer 7: 326, 2019.

93. Zhang J, Song W, Guo J, Zhang J, Sun Z, Li L, Ding F and Gao M: Cytotoxicity of different sized TiO2 nanoparticles in mouse macrophages. Toxicol Ind Health 29: 523-533, 2013.

94. Park J, Lim DH, Lim HJ, Kwon T, Choi JS, Jeong S, Choi H and Cheon J: Size dependent macrophage responses and toxicological effects of Ag nanoparticles. Chem Commun (Camb) 47: 4382-4384, 2011.