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The prognostic impact of traditional Chinese medicine monomers on tumor-associated macrophages in non-small cell lung cancer

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[ABSTRACT] Non-small cell lung cancer (NSCLC) accounts for 80%–85% of all lung malignancies and good diagnosis and prognosis of NSCLC are critical to the increase of its survival rate. Tumor-associated macrophages (TAM) abundantly present in numerous cancer types, and the role of TAMs in tumor biology and their prognostic value in cancer become major topics of interest. After various stimulations in the tumor microenvironment, TAMs develop into a M1 (tumor-inhibitory) phenotype or M2 (tumor-promoting) phenotype. Recent studies show that traditional Chinese medicine (TCM) monomers have markedly inhibitory actions for NSCLC through M1/M2 modulation. Due to the TCM monomers mainly covered five categories, i.e. terpenoids, flavonoids, polysaccharides, natural polyphenols, and alkaloids. Thus, we will discuss the regulation of TCM monomers on TAM involve in these five parts in this review. In addition, the potential role of TAMs as therapeutic targets will be discussed.

[KEY WORDS] Lung cancer; Tumor microenvironment; Tumor-associated macrophages; Traditional Chinese medicine (TCM) monomer; Immunotherapy

Introduction

Lung cancer is the leading cause of cancer death throughout the word; according to GLOBOCAN, 1.8 million new lung cancer cases occurred each year [1]. Non-small cell lung carcinoma (NSCLC) is considered as the main lung adenocarcinoma, accounted for around 85% of diagnosed lung cancer cases [2-4]. In last decades, drugs and treatments targeted on NSCLC have been developed [5-6]. However, unfortunately, at its early stage, the 5-year survival is 49% due to a poor prognosis of NSCLC [7].

Over the past several years various promising biomarkers have emerged during the detection, diagnosis and treatment in lung cancer [8-9]. However, some biological markers have a significant role in prognosis, and it also determined tumors aggressiveness and predict drug response [10-11]. After studying and identifying specific proteins and it could provide the potential benefits of prognosis and drug targeting, such as erlotinib and gefitinib, which have been approved for patients harboring specific EGFR mutations [10, 12-13]. At the same time, some of these certain proteins show a relationship with tumor microenvironment. Such oncogenic EV protein signature which was regulated tumor microenvironment and it will aid in the development of novel diagnostic strategies for prediction and assessment of gefitinib resistance in NSCLC [14]. The tumor microenvironment is composed of proliferating neoplastic cells, a vascular network of endothelial cells, and infiltrated immune cells [15]. Understanding the role of local tumor microenvironment in tumor promotion and progression might be helpful to establish new strategies against NSCLC.

Solid tumors, such as NSCLC, are organ-like structures composed by tumor cells and non-malignant stromal cells,

such as vascular endothelial cells, fibroblasts and infiltrated immune cells, and tumor-associated macrophages (TAM) are the most prominent cells of non-malignant stromal cells [15-17]. TAM can polarize into two different phenotypes (M1 or M2), induced complex functions in their interaction with neoplastic cells [18] and its mechanisms show in figure 1. Meanwhile, in NSCLC, TAM infiltration marked with peritumoral lymphangiogenesis and poor prognosis [19-20]. Interestingly, traditional Chinese medicine (TCM) can achieve anti-tumor effects and good prognosis by improving the tumor microenvironment.

TCM has played an important role in anticancer therapy as there are more than 500 compounds from terrestrial and marine plants or microorganisms, and its roles are involved in antioxidant, antiproliferative, or antiangiogenic properties [21-22] (Table 1). Recently, it has been gradually recognized that natural products have clinical effect in NSCLC, especially in enhancing the anti-tumor activity and drugs sensitivity. And its mechanism is closely related to the regulation of tumor immunity. On this basis, we systematically summarize anticancer mechanism of TCM on tumor-associated macrophages in non-small cell lung cancer.
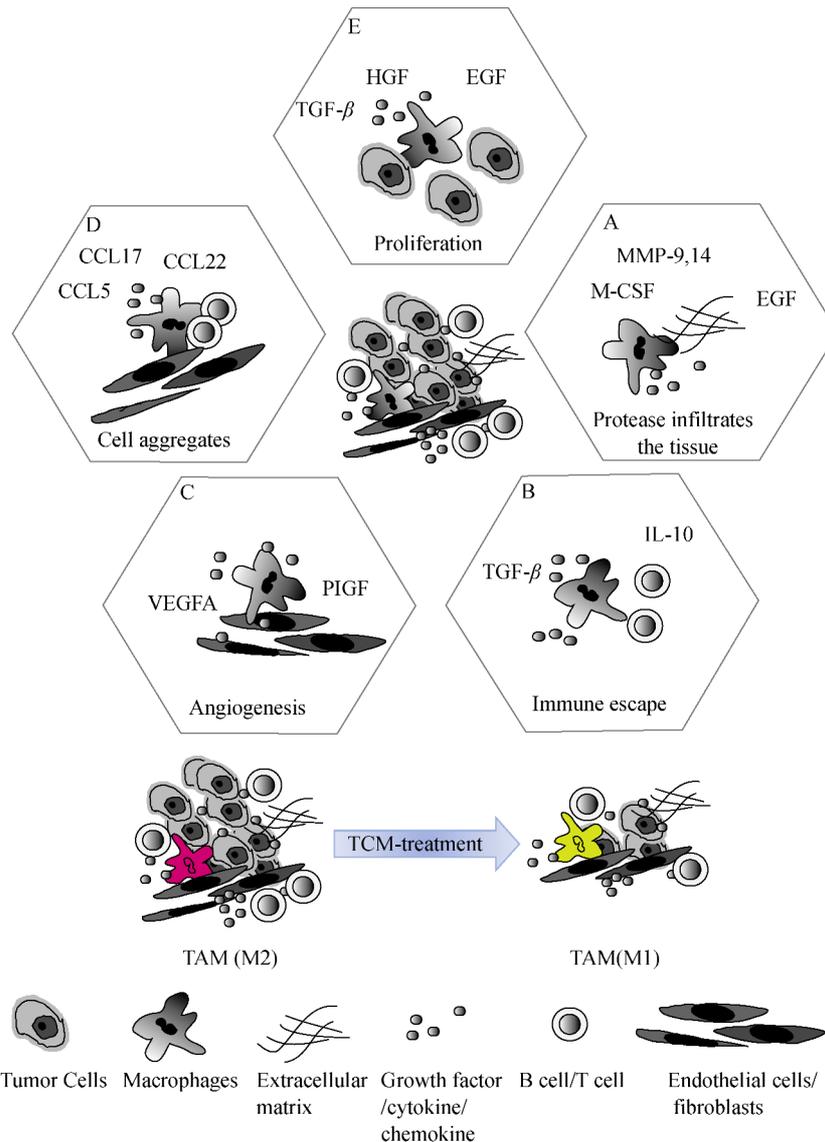

Fig. 1   Tumor-associated macrophages (TAMs) supports tumor growth. A. TAMs promotes tumor invasion by secreting multiple substrates and tumor aggregation factors such as EGF; B. Macrophages achieve immunosuppression by secreting immunosuppressive factors such as IL-10, TGF-*β* and depriving essential amino acids of T cells in environment; C. Angiogenesis is achieved by releasing of pro-angiogenic factors such as VEGF and PIGF; D. In order to providing a favorable environment for tumor progression, mesenchymal cells and immune cells with tumor-promoting effects need to aggregate, and macrophages complete this process by secreting a variety of different cytokines and chemokines; E. Macrophages promote the proliferation of tumor cells by secreting different growth factors such as EGF, PDGF, HGF and bFGF.

Table 1   Part of traditional Chinese medicine (TCM) category for tumors treatment

Category	For example
Effective parts of TCM	Terpenoids, Flavonoids, Polyphenols, Polysaccharides, Alkaloids, Isoflavones, Ginsenosides, Other ingredients
A single TCM	*Astragalus*, Medlar, *Glycyrrhiza glabra*, *Ganoderma lucidum*, *Codonopsis*, *Scutellaria barbata*, *Curcuma longa*
TCM monomer	Triptolide, Oridonin, Luteolin, Tanshinone, Acteoside, Geniposide, Resveratrol

Tumor-associated macrophages and NSCLC

TAM could polarize into two different phenotypes (M1 or M2), and the M1 (or classically activated) phenotype of macrophages are thought to be responsible for a pro-inflammatory, such as TNF-α, interleukin (IL)-12, IL-1, and cytotoxic response against tumor cells [23]. On the other hand, M2 (also known as alternatively activated) macrophages are associated with tumor progression by secreting molecules like vascular endothelial growth factor (VEGF) and transforming growth factor (TFG-β), as well as known to be modulated by IL-4, IL-13 and IL-10 [24-28]. Furthermore, M2 macrophages are found to be the predominant phenotype of TAM in solid tumors [29], when a M1-to-M2 shift in macrophage phenotype, it will then secrete anti-inflammatory mediators, such as IL-10, prostaglandin E2 (PGE2), lactoferin and VEGF [30]. Some studies suggest that high TAM density is associated with clinical prognosis, which it often shows a controversial and inconclusive prognostic significance in tumors, for example it shows a worse overall survival in gastric, urogenital and head neck cancers, and colorectal cancer with a better overall survival in patients [31]. it also found to have an intrinsic relationship between TAM polarization and apoptotic index (AI) in influencing tumor progression and the overall survival of patients in NSCLC patients [11, 25, 32-34]. Meanwhile, higher numbers of macrophages in patients show a shorter relapse-free survival in early p-stage (I, II or IIIa) [35-36]. However, the prognostic value of TAM for patients with lung tumors remain controversial, and it is also imperative to address the role of the macrophages in local tissue microenvironment in the regulation of tumor proliferation and immune control [37].

Terpenoids and TAMs

Triptolide (TP), which belongs to a bioactive epoxy-diterpene lactones in *Tripterygium wilfordii* extracts, and has been evidenced strong anti-proliferative property to several types of cancers, such as lung cancer [38-41], liver cancer [42], osteosarcoma [43], so it would be a promising anti-cancer drug [38]. As we all known, the immune escape of tumor cells which is associated with TAM is an important pathogenesis in tumor progression. Interestingly, TP has been reported to inhibit autoimmunity, allograft rejection, and graft-versus-host disease (GVHD) [44]. Chronic inflammation orchestrates a tumor-supporting microenvironment that is an indispensable participant in the neoplastic process, and macrophages are an important part of the inflammatory environment of tumors [45-46]. Also it is shown that TP suppressed expression of proinflammatory downstream effectors induced specifically by different TLR agonists, and modulated tumor-associated macrophages in a tumor microenvironment in cancer therapy [47-48]. At the same time, it has been demonstrated that TP exhibited both anti-IR lung fibrosis and anti-lung cancer activities, and its mechanism was related to its inhibition on the axis of alveolar macrophages-NOXes-ROS-myofibroblasts [49].

TCM achieved anti-tumor effects by inhibiting angiogenesis, and its antitumor mechanism was associated with macrophage. For examples, oridonin belongs to a diterpenoid compound and can be extracted from TCM, it elicited antitumor effects on many cancer types, including lung cancer [39, 50-55], and the mechanism was associated with including macrophage immunosuppressive activity [56-57]. The monomer weakened the metastasis and invasiveness of tumor cells mainly through secreting a variety of matrix degradation enzymes to reduce the adhesion between cells, and these anti-tumor mechanisms through TAM are shown in Fig. 1A.

Ginsenoside is a promising anti-tumor agent in lung cancer cells. And it had been found that ginsenoside can modulate the differentiation of TAMs and its interaction with tumor microenvironment, which showed that ginsenoside had a preference to reduce M2 macrophage marker CD206 and decrease the expression levels of VEGF, MMP2, and MMP9 in co-cultured lung cancer cells [58]. ginsenoside exerted antitumor activities *via* indirect immunomodulatory actions, without causing adverse effects as seen in doxorubicin [59-60]. Rhizoma Paridis saponins are extracted from paridis plants, and have been found to show inhibition of pulmonary adenoma [61-62], and they can inhibit the promotion of M2 macrophages to cancer cells migration *in vitro* [63].

TAM promoted tumor cells proliferation by secreting different growth factors such as EGF, PDGF, etc. In this regard, Icariin inhibited the growth of human lung adenocarcinoma A549 cell xenografts by increasing the expression of ERS-related molecules (p-PERK and CHOP), up-regulating PUMA, and down-regulating Bcl2 and EGF [64].

Flavonoids and TAMs

TAM achieved immunosuppression through secreting immunosuppressive molecules such as IL-10, TGF-β (Fig. 1B). Luteolin has been evidenced that it exerted remarkable tumor suppressive activity on several cancers, including NSCLC [65-67]. Luteolin suppressed the productions of pro-inflammatory cytokines interlukin-6 (IL-6), interlukin-12 (IL-12) and TNF-α in macrophages [68]. Interestingly, the antitumor mechanism of luteolin in NSCLC was mediated by downregulation of TAM receptor tyrosine kinases, and it was found to decrease the protein levels of all three TAM RTKs in the A549 and A549/CisR cells in a dose-dependent manner [69].

TAM promoted tumor growth through angiogenesis by secreting angiogenic factors, such as VEGF, PIGF. Isoflavone is one kind of compounds that occur naturally in a variety of plants, and with relatively high levels in soybean. It significantly inhibited tumor angiogenesis and NSCLC tumor growth through VEGFR2 signaling pathways [70]. Interestingly, isoflavone intake was associated with a decreased risk of lung cancer in never smokers, in a large-scale, population-based, prospective study in Japan [71]. Tanshinone IIA showed a significant anti-tumor activity in lung cancer tissues, its mechanism is involved in down-regulating Bcl-2 expression and up-regulating Bax expression, and enhancing the immunological function [72].

Polysaccharides and TAMs

Lycium barbarum polysaccharides were found to own multiple pharmacological activities in treating tumors such as lung cancer, colon cancer, breast cancer [73-75]. Meanwhile, *Lycium barbarum* polysaccharides have a highly significant effect on tumor growth and improve the immune system and reduce the immunotoxicity, such as increasing expression of NK and LAK cells and macrophage phagocytosis, whose functionis inhibiting tumors growth [75-77]. In addition, several polysaccharides inhibited tumors growth through suppressing production of pro-inflammatory cytokines in TAM. For examples, *Codonopsis* has shown wide applications in clinical therapy, and its extract has cytotoxic activity against all tested cancer cell lines, such as lung, colon, breast, and melanoma [78]. it had found that exposure to 14-DS-1 (DSPS), extractes from the traditional medicinal plant *Codonopsis pilosula* induced macrophage activation and polarization by promoting the production of TNF-alpha and nitric oxide, when exposed to DSPS as well as promoted macrophage infiltration, whereas cancer cell migration was suppressed [79]. Additionally, *Astragalus* polysaccharides extracted from traditional plant *Astragalus* have been shown to be capable of restoring the impaired T cell functions in cancer patients. Meanwhile, when murine macrophage pretreated with *Astragalus* polysaccharides had increased *in vitro* and *in vivo* cytostatic activities towards MBL-2 tumor, and it could also act as a priming agent for tumor necrosis factor production in tumor-bearing mice [80], and its anti-tumor mechanism may be associated with modulating immune function, such as macrophage, to further mediate anti-cancer activity [81-83]. *Scutellaria barbata* polysaccharides which were extracted from Barbed Skullcap Herb have been used in TCM for treating liver, lung and rectal tumors [73, 84-86]. *Scutellaria barbata* are capable of enhancing macrophage function *in vitro* and inhibiting tumor growth *in vivo*, which suggested that the immunomodulatory function of *Scutellaria barbata* had a potential therapeutic effect in lung cancer [87-88]. Thus, they are less toxic and more selective, and have a certain therapeutic potential.

Natural polyphenols and TAMs

Resveratrol (RES) is a polyphenol compound and it has been widely used for its various health benefits, among of these, it has cytotoxic activity against cancers, including lung cancer and prostate cancer [89-90]. it is found that resveratrol inhibited lung cancer growth by suppressing M2-like polarization of tumor associated macrophages, and in a mouse lung cancer xenograft model, RES significantly inhibited the tumor growth, which was associated with inhibition of cell proliferation and decreased expression of p-STAT3 in tumor tissues [89-91]. Tea is a popular beverage, and the consumption of green tea is associated with a lower risk of several types of cancer, including stomach, esophagus, and lung. the mechanism of its anti-tumor was associated with down-regulating lipopolysaccharide-induced activity of the transcription factor NF-kappa B in macrophages [92-94]. Curcumin, which is the main active ingredient of extract from *Curcuma longa*, is a polyphenol compound and has been widely used to anti-tumor, anti-inflammation and neuroprotective effects [95-98]. the anti-tumor activity was associated with the mechanism of immunosuppression and potent anti-inflammatory, i.e. inhibiting NF-kappaB signaling in macrophages, and subsequent production of cytokines/chemokines responding to IAV infection, by enhancing IkappaBalpha and AMPK [98], or inhibiting of the JNK signaling pathway and underscores the utility of curcumin as an anti-inflammatory agent in macrophages and changing M1/M2 macrophage balance in tumor microenvironment [99-100], mechanism of curcumin to immune modulation could be related to its ability to enhance IL-10-mediated effects [101].

Alkaloids and TAMs

In clinic, vinblastine has been administrated for the treatment with several tumors, such as leukemia, lung cancer, and breast cancer [102-106]. it has been reported that vinblastine-treated neutropenic rats had significantly reduced lung injury based on total lung volume at 4 h [107]. cellular uptake of paclitaxel was significantly reduced in macrophages and significantly increased in human cancer cells, and therefore, it showed strong growth inhibitory effects on human cancer cells [108]. The medicinal action of the DDMC/PTX complex, a supramolecular DEAE-dextran-MMA copolymer (DDMC)/ paclitaxel (PTX) complex, inhibit tumor-associated action of M2 macrophages and inhibit metastasis of cancer cells [109].

Discussions

Macrophage is a population of diverse innate immune cells with a major role in the host tissue homeostasis and immunity to pathogens, and it originates from both embryonic precursors and hematopoietic stem cell-derived monocytes [110-111]. during an inflammatory condition such as bacterial infection, monocytes become the major source of influx expanding the macrophage pool [112]. Meanwhile, macrophages are found in the majority of tissues, including the intestine [113], dermis [114], and mammary gland [115]. So it comes as no surprise that these pleiotropic cells contribute to a wide variety of organ-specific and systemic disease pathologies, including cancer. it has

been found that there is a positive correlation between macrophage density and tumor growth. Thus, macrophages are now recognized as important therapeutic targets in the treatment of cancer.

TAMs are the major tumor-promoting immune cells in the tumor microenvironment, and they have promoted tumor progression through different mechanism. Macrophages can be divided into two subgroups: M1 and M2. M1-type macrophages, which are classically activated, play important roles in the innate response against invading pathogens. M2-type macrophages, which are alternatively activated, play important roles in tissue repair and tumor progression [116]. Thus, the balance of these two-type macrophages determines the anti- or pro-tumor effects of the macrophage population [111]. the

characterization of TAM subtypes and the understanding of their varying interaction with tumor cells have proven to be challenging.

TCM is an important complementary strategy for treating cancer in China [117] (Table 2). it has been accepted in China that TCM can reduce the toxicity and enhance the anti-tumor effect of chemotherapy and radiotherapy, alleviate tumor-induced clinical symptoms, and prolong the survival time of postoperational and advanced stage cancer patients [118]. TCM monomer influenced not only tumor cells, but immune cells and cytokines as well as signal pathways. So with the rapid development of immunology, TCM effect on regulating TAM will play a more important role in tumor complementary and alternative therapies.

Table 2   Part of TCM monomers and its effects

TCM monomers and compounds	Effects	Mechanisms of action
Triptolide, Oridonin, Geniposide	Lung, colon, breast and liver cancer, osteosarcoma,	Inhibited autoimmunity and modulated tumor-associated macrophages; have a inhibition on the axis of alveolar macrophages-NOXes-ROS-myo-fibroblasts, reduced M2 TAM and decreased the expression levels of VEGF, MMP2, and MMP9
Luteolin, Isoflavone, Tanshinone	Lung, colon, renal, prostate, ovarian, gastric and breast cancer	Suppressed productions of pro-inflammatory cytokines in macrophages; inhibited VEGFR2 signaling pathways and enhanced immunological function associated with macrophages;
Lycium barbarum polysaccharides, *Astragalus* polysaccharides, *Scutellaria barbata* polysaccharides	Melanoma, lung, colon, breast and liver cancer	Improved immune system and reduced immunotoxicity, Restoring impaired T cell functions;
Natural polyphenols, Resveratrol	Stomach, esophagus, prostate and lung cancer	Suppressed M2 TAM, Immunosuppression and potent anti-inflammatory, Inhibit NF-kappaB or JNK signaling in macrophages, Immune modulation
Vinblastine	Leukemia, lung and breast cancer,	Suppress tumor-associated action of M2 macrophages

With the development of research on anti-cancer activity of TAM, many studies have been conducted. Natural active compounds play a role in the plasticity of NSCLC therapy, and have been increasingly identified. Above all, it is worth figuring out the functional relationship and biochemical mechanism between different catalogs of TCM monomer and TAM.

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