Pulmonary fibrosis is a devastating condition with many kinds of inducements. Alveolar macrophages (AMs) and interstitial macrophages (IMs) are two subsets of macrophages which involve in the inflammatory reaction of pulmonary fibrosis. Traditional Chinese medicine has good effects on the treatment of pulmonary fibrosis. This review is aimed at summarizing the different roles of alveolar macrophages and interstitial macrophages in the pathological process of pulmonary fibrosis progression and anti-fibrosis drugs related to the self-regulation mechanism of these two kinds of cells, furthermore to explain the multiple mechanisms of traditional Chinese medicine for treating pulmonary fibrosis from the self-regulation of macrophages. Searches for keywords “alveolar macrophages”, “interstitial macrophages”, “pulmonary fibrosis” and “IPF” were performed in biomedical databases. The reported incidences of AMs and IMs in the pathological process of pulmonary fibrosis are involved in this article, and the influences of traditional Chinese medicine on the cells are summarized.

A comprehensive analysis of the literature confirms that alveolar macrophages appear to be better equipped for their antimicrobial task, whereas interstitial macrophages have more capacity for immune regulatory functions. Disease-modifying therapy for pulmonary fibrosis based on intervening the macrophages self-regulation relates to chemokines and cytokines. Traditional Chinese herbs for pulmonary fibrosis have different targets on the two kinds of cells. Alveolar macrophages and interstitial macrophages could be used to explore the pathological process and clinical medicine of pulmonary fibrosis, and they are conducive to interpret the multiple mechanisms of TCM for pulmonary fibrosis.

Keywords: Alveolar macrophages; Interstitial macrophages; Pulmonary fibrosis; Chemokines; Cytokines; Traditional Chinese medicine

Abbreviations: AMs: Alveolar Macrophages; IMs: Interstitial Macrophages; IPF: Idiopathic Pulmonary Fibrosis; TCM: Traditional Chinese Medicine; BALF: Bronchoalveolar Lavage Fluid; PDGF: Platelet-Derived Growth Factor; TNF-α: Tumor Necrosis Factor-A; IFN: Interferon; TGF-β1: Transforming Growth Factor-B1; CTGF: Connective Tissue Growth Factor
production of collagen by fibroblasts and the subsequent formation of scar tissue [8]. However, the cause of IPF remains unclear [9].

It is vital that tissue architecture is restored to regain normal function. The early lesions of pulmonary fibrosis mainly appear in the alveolar walls accompanied by a large number of proliferated lung fibroblasts, causing extracellular matrix deposits in alveolar and interstitial excessively [10]. Then the repaired fibrous tissues result in structural disorder and replace the normal tissues [11]. The ultimate outcome is irreversible pulmonary fibrosis [12,13]. An important factor of pulmonary fibrosis occurrence is the function and number of AMs and IMs [14]. Analysis of the different roles of AMs and IMs in the pathological process of pulmonary fibrosis in the field will provide an explanation of the multiple mechanisms for treating pulmonary fibrosis with TCM.

Roles of AMs and IMs in the Pathological Process of Pulmonary Fibrosis

AMs and IMs are getting more and more attention in the treatment of pulmonary fibrosis. The basic functions of macrophages in the immune defence system are phagocytic and bactericidal activities, which is vital in resisting the invasion of pathogenic microorganisms. It is reported that AMs appeared to be better equipped for their antimicrobial task. Whereas IM, although also having antimicrobial potential, show a more pronounced capacity of immunoregulatory functions [15]. As the sole cell population exposed to air, AMs having phagocytic activity of clearing extraneous particles, which is the first barrier of the lung. AMs get damaged after phagocytizing the pathogenic particles, further cause lung damages. IMs in the lung tissue also play a very important role in inflammation and local immune defense reaction of the lung injury, which is the second barrier of the lung (Figure 1).

The form and number of AMs and IMs in the pathological process of pulmonary fibrosis

AMs and IMs are two critical subsets of macrophages. Pulmonary macrophages consist of AMs in the surface and internal of alveolar space, and IMs in pulmonary interstitial next to alveolar septa or next to bronchi and vessels. Normally, there are significant differences between AMs and IMs in morphology, structure, phenotype and function [16]. Under the light microscope, the diameter of AM is about (12.1±1.16) μm which is larger than that of IM with about (9.3±1.1) μm. AM is round or irregular while IM is round and uniform relatively in shape and size. AM HE staining shows the cytoplasm is pink with loose nucleus deviate to the side of the cytoplasm in an oval shape and the nuclear-cytoplasmic ratio is less than 50%. The surface of the AM is uneven with many protrusions and the cells contain more intracellular lysosomes. IM, HE is staining shows that the cytoplasm is dark red, with dense nucleus shape irregularly and the nuclear-cytoplasmic ratio is greater than 50% [17].

The surface of the IM is smooth with almost no protrusions and the cells contain fewer primary and secondary intracellular lysosomes. Differences between AMs and IMs in morphology and structure determine their differences in functions [18]. IMs only accounts for 3%-5% of the total number of various cells throughout the lung tissue, so the isolation of IM is totally a difficult task. Over 90% of the rat bronchoalveolar lavage fluid (BALF) samples are AMs, and a variety of cells including macrophages, neutrophils, endothelial cells and lymphocytes can be obtained by enzymatic dispersal of the lung tissue. Separated by the lymphocyte separation liquid and purified by adherent cell culture, 90% of the cells in culture liquid are IM cells. The number of AMs and IMs in lung tissues under normal physiological conditions is less than that of fibrosis pathological conditions. Studies have found that the number of AMs in BALF reached the highest level on the 7th day after bleomycin injection, and the number and HE stain intensity of positive AMs have reached its peak as well [19]. And AMs increased significantly in the BALF on the 14th and 30th day after Pingyangmycin injection, which is consistent with the pro-inflammatory and
The cell function of AMs and IMs in the pathological process of pulmonary fibrosis

AMs and IMs in the lung are distributed in two different anatomical sites, which result in their different functions [21,22]. Located in the airways and alveoli, AMs are the only cell population exposed to air, which contributes to the first barrier of the lung to clear inhaled microorganisms during breathing [23]. The morphology of the permanent AMs in alveoli is changeable, while the AMs in normal lung tissues are similar to the mature macrophages of other organizations. The microvilli of normal AMs distribute on the cell surface uniformly. The cytoplasmic volume of normal AMs is large with a large number of lysosomes, phagosomes and enzymes [24]. Besides, normal AMs produce cell recruitment factors, active nitrogen and other factors, and result in macrophages and other inflammatory cells gathering. During acute inflammatory periods, AMs become larger and containing quantities of peroxidase with a diameter of 12μm, while they become mature and larger during chronic progress period with a diameter of 14-40μm. The cytoplasmic membrane of AMs under the electron microscope is irregular.

The cytoplasm contains many mitochondria and lysosomes, and the nucleus is more leaflike. The expression and release of membrane receptors in AMs depend on different states. The main role of AMs is to kill pathogenic microorganisms, phagocytize water-soluble poorly organic particles, release inflammatory mediators, present antigens, and express different cytomembrane receptors at the same time. Many studies suggest that AMs are the key cells causing early biological effects on lung [25]. In the initial process of lung injury, cellular infiltration can also be found in AMs from the observation of lung tissue by biopsy. The degree of cellular infiltration is closely related to the cellular infiltration capability of IMs, which confirms that AMs have the function of promoting the inflammatory response. In the process of promoting inflammatory infiltration, it also increases lung damage and causes excessive repair of the tissues, then leads to fibrosis.

IMs also play a very important role in lung inflammation and local immune defence reaction. The IMs are a type of macrophages in the interstitial connective tissue forming the second line of the lung defence, which may have a greater immune function with its special location. But the location of IM can also make it difficult in extracting the cells. IMs in pulmonary interstitial contact with the extracellular matrix and other interstitial cells tightly thus affects pulmonary interstitial metabolism. IMs are often acquired from the pulping lung tissue digested by collagenase, but the separation methods reported in the literature are quite different. IMs have their own unique function and morphology compared with AMs. They have a smaller diameter of 6.6μm, a more folded cell membrane, irregular nucleus and larger nucleoplasm ratio. And the non-specific lipid stain results of them can be positive, less positive or negative.

The filar pseudopod of IMs cell can be seen under the electron microscope. The cytoplasmic membrane of IMs is pleated, and still not extended to its characteristics after cultivating for 24h. Because of the difficulty in getting IMs, more papers focus on the study of AMs. However, recent studies have shown that IMs may have a more important role in lung injury. As the important cells, IMs’ ability to phagocytize particles, produce oxygen radicals and chemotactic complement is weaker than that of AM [15]. But IMs express more MHC II and they are more efficient in stimulating the proliferation of T cells [26].

The phagocytosis and secretory function of IMs are like that of AMs. Although the Fc receptor-dependent cellular phagocytosis capability of IMs is like that of AMs, the Fc receptor-independent cellular phagocytosis capability of IMs is lower than that of AMs significantly. So that IMs show more capable of respiratory immune responses. Existed in pulmonary interstitial, IMs can release inflammatory mediators and cytotoxic mediators, which may be a more direct cause of lung tissue damage [27]. There has also been reported that IMs make more sense in the progression of pulmonary fibrosis than AMs in biological behaviours and active effects [28]. More experiments should be carried out to confirm the function of IMs.

The relationship between AMs and IMs in the pathological process of pulmonary fibrosis

AMs and IMs are two critical subsets of macrophages, which are critical in the pathological process of pulmonary fibrosis process. From the perspective of cells occurrence, AMs are the ultimate development status of macrophages which come from the source of bone marrow monocytes. Blood monocytes grew into AMs in the development of end-stage, while IMs may be the transitional stage of that process [18]. But there are great differences between AMs and IMs in antigen presenting, cytokines secreting and other immune functions. And the effects of endotoxin attacks on them are discrepant. All the differences suggest IMs are not simply the precursor of AMs.

Evidence also shows that platelet-derived growth factor (PDGF) secreted by AMs cannot enter the alveolar interstitial through the epithelia completely. Therefore, it may be concluded that AMs located in the alveolar may have a stronger function of phagocytosis, and IMs in the interstitial are primarily related to the immune regulation. In vitro studies, Adamson found that short fibers (<1μm) and long fibers (> 20μm) asbestos could stimulate macrophages to produce the Fibroblast Growth cytokines. In vivo studies also found that AMs phagocytized almost all short fibers which did not enter the pulmonary interstitial without pulmonary fibrosis lesion when mice inhaled short asbestos fibers. While IMs were activated when the long fiber deposited
on the bronchi furthered into the pulmonary interstitial and caused effector cells accumulate in pulmonary interstitial. Then fibroblast multiplied quickly, eventually led to the formation of pulmonary fibrosis [29].

**The Self-Regulation Mechanism of AMs and IMs in the Pathological Process of Pulmonary Fibrosis**

Pulmonary fibrosis is characterized by the accumulation of fibroblasts. The deposition of inflammatory cells such as macrophages, lymphocytes, and granulocytes are also the hallmark of pulmonary fibrosis. The mechanisms responsible for the migration of fibroblasts and inflammatory cells to the lung in pulmonary fibrosis are not known, but cytokines and chemokines are essentially considered [30]. The self-regulation mechanism of AMs and IMs includes two parts: Firstly, the inflammatory factors stimulate macrophages and other immune cells to secrete chemokines [31], which allow AMs, IMs and other inflammatory cells to accumulate and release a large number of cytokines. Secondly, the release of cytokines stimulates myofibroblast, leading to the accumulation, proliferation and activation of fibroblasts, then pulmonary fibrosis occurs. By further activating signal transduction pathways at the same time, cytokines stimulate inflammatory cells to generate new cytokines and the process cycles [32] (Figure 2).

![Figure 2: The self-regulation mechanism of AMs and IMs in pulmonary fibrosis.](image)

**Chemokines assist in the migration and invasion ability of AMs and IMs**

The CC family and CXC family are two big families of chemokines involving the pulmonary fibrosis. The transfer of fibroblasts and inflammatory cells in the lung requires the participation of various chemokines/chemokine receptors such as CXCL12/CXCR4, CCL21/CCR7, CCL2/CCR2, CCL3/CCR5 [32]. Many biological functions of macrophages play their roles in their cytomembrane mediated action. The cytomembrane receptors of AMs and IMs correspond with their specific binding ligand, triggering the cell signalling pathways. The binding force of the receptor on the cell surface and the number of receptors on the surface of the cytomembrane can affect the signal transduction [33,34]. Phagocytosis is one of the important functions of macrophages, and the interaction between effector cells and the membrane of the target cell is a key factor in macrophages to kill tumor cells [35].

Cell migration is an important reason for adjusting the number of cells. Monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1α (MIP-1α) (also known as CCL2 and CCL3) in-vivo are important chemokines participated in the chemotaxis of the cells, the main chemotactic cells and macrophages are concentrated in the inflammatory regions [36]. Studies have found that inhibiting the activity of MCP-1 and MIP-1α in the early pulmonary fibrosis can reduce the accumulation of alveolar macrophages [37]. MCP-1 mRNA in the lung tissue of rats can be found mainly expressed in alveolar macrophages, airway epithelial cells in Bleomycin-induced pulmonary fibrosis rats [38]. Thus, MCP-1 alters the population of alveolar macrophages through recruitment of blood monocytes into the luminal airspace. MIP-1α can also mobilize the bone marrow monocytes into myeloid precursor cells and enhance the infiltration of macrophages in inflammation areas [39].

According to the general reasoning, the reason for the increase of AMs in the alveoli and IM in the pulmonary interstitial is likely to be under the chemotaxis of chemokines, blood monocytes cells infiltrate or migrate to the inflammatory sites and grow into the macrophages. The increased extent of AMs varies depending on the stage of the pulmonary fibrosis, while IMs increase more obviously in the early period. *In vitro* study of the macrophages migration and invasion chemotaxis of MCP-1 shows that MCP-1 can assist in the migration and invasion ability of macrophages. And the chemotactic efficiency of macrophages related to the concentration of MCP-1 [40]. The growing number of macrophages with enhanced invasion capability can contribute to the pathological process of pulmonary fibrosis.

**AMs and IMs secrete cytokines to regulate fibroblasts and regulate cytokines secretion**

Macrophages are gathered and activated under the chemotaxis of chemokines. AMs secrete platelet-derived growth factor (PDGF) and transform growth factor beta (TGF-β), which can promote the accumulation, proliferation and activation of fibroblasts in lung injury area, causing the extracellular matrix accelerating the synthesis. It can also increase fibroblast by increasing the transfer and adhesion of osteopontin, resulting in pulmonary fibrosis [41]. AMs secrete tumor necrosis factor-α (TNF-α), interferon (IFN), transforming growth factor-β1 (TGF-β1) and other active media that can anti-pathogenic microorganisms strongly, which can effectively kill the pathogens invaded the body. IMs have lower ability to produce these cytokines than AMs, while the ability to secrete cytotoxic medium and interleukin (IL) are high, which cause more direct damages to lung tissue and show higher MHCII class antigen expression activity and stronger supplementary ability.
Cytokines regulate fibroblasts and macrophages involved in a variety of signal transduction pathways such as the MAPK pathway, JAK-STAT pathway, NF-κB pathway, etc [42]. TGF-β, a powerful fibrosis cytokine, rely on Smads and MAPK signal transduction pathway to regulate lung fibroblasts to muscle fibroblasts, produce a large number of extracellular matrix proteins, and lead to pulmonary fibrosis [43]. IL-1, TGF-β, IFN involved in the JAK-STAT pathway to regulate the proliferation of fibroblasts by regulating the gene expression. At the same time, cytokines further activate the signal transduction pathways and stimulate AMs and IMs to produce new cytokines. TNF-α stimulates MAPK/ERK pathway, increases transcription of the TGF-β1 Gene and stabilizes TGF-β1mRNA to induce the expression of TGF-β1 [44,45]. On the other hand, TNF-α activates NF-κB pathway to accelerate the new TNF-α secretion of macrophages [46]. The upgraded cytokines create new biological effects.

**Disease-Modifying Therapy for Pulmonary Fibrosis Based on Intervening the Self-Regulation of AMs and IMs**

Clinical medicinal therapies of pulmonary fibrosis including symptom-focused therapy and disease-modifying therapy. Randomised controlled trials show that various therapies (eg. prednisolone and azathioprine, acetylcysteine, and warfarin) were ineffective or harmful, but disease-modifying therapies with nintedanib and pirfenidone are effective [47]. Both drugs are currently approved worldwide. Thus, therapies focusing on modifying pulmonary fibrosis are promising.

AMs and IMs primarily regulate the pulmonary fibrosis with cytokines TNF-α and TGF-β. Clinically recommended medicines for the treatment of pulmonary fibrosis are related to these cytokines. TNF-α can induce the adsorption of inflammatory cells and promote the occurrence of the inflammatory response. It can also regulate the production of other cytokines, deposit collagen, and promote the proliferation of fibroblasts, which plays an important role in the progress of pulmonary fibrosis. TNF-α inhibitors include etanercept, infliximab and adalimumab [48]. TGF-β can cause direct and effective stimulation to collagen synthesis, which makes an important impact on the development of pulmonary fibrosis. It takes action by enhancing the activity of connective tissue growth factor (CTGF), promoting the formation of muscle fiber cell type, as well as producing collagen and proteoglycan. Its action mechanism is associated with stimulating the Smads protein pathways. Clinical antifibrotic drugs Pirfenidone can reduce the proliferation of fibroblasts and inhibits collagen synthesis through regulation of TGF-β [49]. And some under-developmental TGF-β inhibitors such as GC1008, BG00011 and STX-100 can take actions by inhibiting the TGF-β pathway [50].

The NF-κB and MAPK pathways are important pathways to cytokine upregulation. The inhibition of these two pathways can reduce cytokines cycle and ease the fibrosis reaction. SP100030 is a type of underdeveloped NF-κB pathway inhibitor. Experiments showed that SP100030 inhibit the protease isomerized to block NF-κB pathway and reduces the degree of inflammation and pulmonary fibrosis. Current p38MAPK inhibitors under clinical trials include BIRR796, SB203580, TAK715, etc. BIRR796 shows good inhibition of all p38 MAPK isoforms in-vitro and in vivo [51].

There are no clinical chemokine inhibitors in the treatment of pulmonary fibrosis. Experiments showed that fluorofenidone (a me-too drug of pirfenidone) can inhibit the expression of MCP-1 and TNF-α in mice macrophages induced by dead cells, which show the anti-inflammatory action. And fluorofenidone has the influence on NF-κB and MAPK pathway as well [52]. CNTO 888 (Carlumab), an under-developmental human anti-CCL2 antibody, is a monoclonal antibody that binds and neutralizes CCL2, can reduce the migration of macrophages [53]. Binding of CCL2 to its receptor CCR2 triggers chemotaxis. Inhibition of the CCR2 can reduce macrophages migration and accumulation in experimental models [5-4].

**The Effect on AMs and IMs of TCM Treatment of Pulmonary Fibrosis**

Large quantity of experiments showed that TCM had an influence on the expression of cytokines such as TNF-α, TGF-β, PDGF, CTGF, HGF, INF-γ, etc. [55]. Studies have found that macrophages are main cells which secrete tumor necrosis factor (TNF-α) in bleomycin-induced pulmonary fibrosis [56]. Experimental results of the buyanghuanwu decoction effect on the AMs of pulmonary fibrosis rats were also found the model group had higher levels of TNF-α than that of the control group. The levels of TNF-α in the model group reached its peak on the 7th day, and fell on the 28th day, with higher levels than the control group. The result showed that TNF-α has an important role in the pathological process of pulmonary fibrosis. The experiment showed that buyanghuanwu decoction can inhibit AMs of lung fibrosis rats to release TNF-α. So we can conclude that the mechanism for buyanghuanwu decoction preventing pulmonary fibrosis may be associated with its function of suppressing the TNF-α releasing of AMs [57].

In the study of discussing the mechanism of Pneumonia Mixture (containing ephedra 60g) in the treatment of pulmonary fibrosis, researchers found that after the formation of bleomycin-induced pulmonary fibrosis in rats, TGF-β1 mRNA expressed in AMs and IMs in the model group increased more significantly than that in the control group. Therefore, we can infer that the mechanism of Pneumonia Mixture interfering the pulmonary fibrosis process is possibly associated with the reduction of the TGF-β1 expressing...
in AMs and IMs. The main components of Pneumonia Mixture are Astragalus, leeches, Polygonum cuspidatum, etc. Combined treatments of these drugs in all aspects of pulmonary fibrosis remediation inhibit the aggregation of inflammatory cells and reduces the synthesis of TGF-β1, as well as reduces abnormal tissues repairing and fibrosis progression [59]. The pathological process of lung diseases including pulmonary fibrosis is called “Xuansu disordered in lung” according to TCM theory. Ephedra and Schisandra are commonly used in the treatment of lung diseases.

Our laboratory has completed ephedra and Schisandra drug-containing serum on normal rat AMs and IMs secrete TGF-β1. In vitro experiments found that ephedra, Schisandra could inhibit the TGF-β1 secretion of AMs and IMs. Ephedra-containing serum has a stronger inhibition of AM secretion compared to ephedra-containing serum, whereas Schisandra-containing serum has a stronger inhibition of IM secretion compared to Ephedra-containing serum [60]. The results showed that ephedra and Schisandra may have different influences on pulmonary fibrosis. Ephedra may have a major role in the acute inflammation period while Schisandra may have a major role in pulmonary fibrosis period.

Many experiments also elucidated the mechanism of treating pulmonary fibrosis from the regulation of chemokines. Xuejun Li showed the concentration of MIP-1α and MCP-1 in the plasma of the Panax Notoginseng, the treating group began to rise on the 3rd day and reached the peak on the 7th day in rats of bleomycin-induced pulmonary fibrosis, then gradually decreased [61]. The concentration of both MIP-1α and MCP-1 in the plasma of the treating group had been significantly lower than that of the model group since the 7th day. Zhanshuai Song used Yifei-Huaxian granules in the treatment of paraquat-induced pulmonary fibrosis in rats showed the concentration of MCP-1 reached the peak on the 7th day and kept lower than the model group all through the experiment [62]. The result suggests that Chinese medicine reduces the migration of fibroblasts and inflammatory cells by suppressing the macrophages to express MIP-1α and MCP-1, thereby reducing the degree of pulmonary fibrosis.

Conclusion

In conclusion, AMs and IMs are vital regulatory macrophages in the pathological process of pulmonary fibrosis. Because of the anatomical site and cell function of AMs and IMs, anti-fibrosis drug options related to them have higher targeting ability than anti-inflammatory therapy drugs. And AMs and IMs can also be used to explore the multiple mechanisms of traditional Chinese medicine treatment for pulmonary fibrosis.

TCM has made great progress in the experimental study of pulmonary fibrosis prevention. Drugs involving enriching yin and nourishing the blood, clearing up heat and toxin, fortifying the spleen to boost qi, invigorating blood to dissolve stasis, supplementing the lung to boost the kidneys, relieving a cough and panting and many other aspects, meanwhile, the effective components of Chinese medicine provide a larger space and treatment basis for the clinic. Single herb showed good results in fighting against pulmonary fibrosis. At the same time, traditional Chinese medicine decoctions and Chinese patent medicines can have significant effects on pulmonary fibrosis [63,64]. Overall, the mechanisms explanation of the Chinese medicines on pulmonary fibrosis is still in its infancy.

The current studies were largely restricted to animal experiments rather than clinical studies, which focused on anti-inflammatory, immune and cytokines without systematic measurements and standards [65]. Because of the complicated compositions of single Chinese herbs, there is no clear scientific research basis for the effective compositions in the treatment of pulmonary fibrosis. And some therapeutic mechanisms are built on the hypothesis with a lack of rigorous experimental verification. Small samples, different clinical diagnosis and efficacy evaluation criteria result in the no convincing results. Although the research on the molecular and genetic level has been increasing in recent years, it is still limited to a few kinds of Chinese medicines. In this context, some experiments from the perspective of AMs and IMs in the pulmonary fibrosis rats and the influence of some common herbs for lung diseases on the AMs and IMs by using drug-containing serum were conducted. Thus, we can explore the pathological process of pulmonary fibrosis and explain the multiple mechanisms of TCM to guide clinical medication better, which is conducive to the succession and development of traditional Chinese medicine.

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