The Role of Immune Cells in the Progression of Idiopathic Pulmonary Fibrosis

Xiaxue Wang *

Jilin Agricultural University, China

* Corresponding Author Email: 2721516926@qq.com

Abstract. Idiopathic Pulmonary Fibrosis (IPF) is a progressive interstitial lung disease of unknown etiology, characterized by the excessive deposition of fibrotic tissue in the lungs. The global incidence of IPF is on the rise, and the disease is associated with a poor prognosis and high mortality rate, with a median survival time of only 2 to 5 years after diagnosis. Pathologically, IPF is most commonly classified into two subtypes: Usual Interstitial Pneumonia (UIP) and Non-Specific Interstitial Pneumonia (NSIP). Current research suggests that injury to alveolar epithelial cells plays a pivotal role in the initiation of IPF. Damaged epithelial cells secrete a variety of cytokines and chemokines, which recruit immune cells, including macrophages, T cells, B cells, and neutrophils, to the lung tissue. These immune cells contribute to local immune dysregulation, leading to further irreversible epithelial injury and the activation of myofibroblasts, which in turn accelerates the progression of fibrosis. This review focuses on the roles of different immune cell populations in the pathogenesis and progression of idiopathic pulmonary fibrosis.

Keywords: Idiopathic pulmonary fibrosis; immunity; lymphocytes; macrophages; neutrophils.

1. Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a type of interstitial lung disease characterized by progressive fibrosis of lung tissue with an unknown etiology. The normal structure and function of lung tissue are disrupted, leading to abnormal deposition of extracellular matrix (ECM), which gradually replaces the lung parenchyma with fibrotic tissue. This results in impaired lung function, compromised gas exchange, and a severe threat to patients' health and survival [1]. The incidence of IPF is increasing globally, with an estimated prevalence ranging from 2 to 29 cases per 100,000 individuals in the general population [2]. Patients with IPF have a poor prognosis and high mortality rate, with a median survival time of only 2 to 5 years and a 5-year survival rate of approximately 20% to 40% [3]. Among the pathological subtypes of IPF, the most common are Usual Interstitial Pneumonia (UIP) and Non-Specific Interstitial Pneumonia (NSIP). UIP is characterized by honeycombing changes and the presence of fibroblastic foci, which are critical markers of disease progression. In contrast, NSIP exhibits uniform inflammation and fibrosis in the alveolar septa, with relatively milder fibrosis and the absence of honeycombing or prominent fibroblastic foci [4].

The pathogenesis of IPF is a complex process [5]. Injury to alveolar epithelial cells is considered a key initiating event, triggered by various harmful factors such as oxidative stress and viral infections. Damaged epithelial cells release a variety of cytokines and chemokines, recruiting immune cells, including macrophages and lymphocytes, to the lung tissue. These inflammatory cells release mediators that further damage lung tissue and activate fibroblasts. Activated fibroblasts differentiate into myofibroblasts, which excessively produce and secrete ECM, ultimately leading to the formation of pulmonary fibrosis [6]. During the development and progression of pulmonary fibrosis, multiple immune cells, including macrophages, T cells, B cells, and neutrophils, play a role in disrupting local immune homeostasis. This exacerbates irreversible epithelial injury and myofibroblast activation, accelerating the progression of IPF. Immune cells are thus critical regulators in the pathogenesis of IPF [7]. Therefore, this review focuses on the roles of different types of immune cells in the progression of idiopathic pulmonary fibrosis.

2. Different immune cells and IPF

2.1. Macrophages and IPF

2.1.1. M1/M2 macrophages and IPF

During the progression of pulmonary fibrosis, macrophages can polarize into two main phenotypes, M1 and M2, depending on the specific stimulatory factors [8]. These phenotypes exhibit significant differences in their functions and their impact on pulmonary fibrosis. M1 macrophages, also known as classically activated macrophages, are typically induced by factors such as lipopolysaccharide (LPS) and interferon-gamma (IFN-γ). In the early stages of lung inflammation, pathogen invasion or tissue injury triggers the production of these stimulatory factors. Once activated, M1 macrophages highly express inducible nitric oxide synthase (iNOS), generating large amounts of nitric oxide (NO). NO possesses potent antimicrobial and antiviral properties, effectively eliminating pathogens that invade the lungs [9]. Additionally, M1 macrophages secrete pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which play a critical role in the initial inflammatory response [10]. However, excessive or sustained activation of M1 macrophages can lead to the overproduction of pro-inflammatory cytokines, amplifying lung inflammation and causing tissue damage, thereby laying the groundwork for the development of pulmonary fibrosis.

In contrast, M2 macrophages, or alternatively activated macrophages, are primarily induced by factors such as interleukin-4 (IL-4) and interleukin-13 (IL-13) [11]. M2 macrophages are involved in tissue repair and pro-fibrotic processes [12]. They typically express markers such as arginase-1 (Arg-1), chitinase-3-like protein-1 (Ym1), mannose receptor C type 1 (CD206), and cluster of differentiation 163 (CD163). Arg-1 metabolizes arginine into ornithine and polyamines, with ornithine contributing to collagen synthesis, a process critical for tissue repair but also accelerating fibrosis. Ym1 acts as an alarmin, mitigating inflammatory responses and regulating extracellular matrix (ECM) deposition. Dysregulation of Ym1 can lead to excessive ECM deposition, exacerbating pulmonary fibrosis. Macrophages with high CD206 expression promote fibrosis progression, and CD206 serves as a valuable marker for studying phenotypic and functional changes in macrophages during pulmonary fibrosis. CD163 exerts anti-inflammatory and pro-fibrotic effects. Furthermore, M2 macrophages secrete transforming growth factor-beta (TGF-β), which activates fibroblasts and myofibroblasts, leading to excessive ECM synthesis and deposition. This process gradually forms fibrotic lesions, disrupting the normal structure and function of the lungs [13].

The balance between M1 and M2 macrophages is crucial during the progression of pulmonary fibrosis. Under normal physiological conditions, these two phenotypes maintain a relative equilibrium. During inflammation, M1 macrophages are initially activated to clear pathogens and damaged cells. As inflammation progresses, M2 macrophages become dominant, promoting tissue repair [14]. However, when this balance is disrupted, M2 macrophages may become excessively activated, leading to excessive tissue repair and fibrosis, ultimately resulting in the progressive loss of lung function.

2.1.2. Mo-M/TR-M and IPF

Based on their origin, macrophages can be broadly classified into tissue-resident macrophages (TR-M) and monocyte-derived macrophages (Mo-M). These two types of cells exhibit significant differences in their origin, characteristics, and impact on pulmonary fibrosis [15]. TR-M settle in the lungs during embryonic development and maintain their population through self-renewal. They possess unique transcriptomic and epigenetic features, allowing them to adapt closely to the lung microenvironment. TR-M play a crucial role in maintaining lung homeostasis by continuously monitoring the pulmonary environment, clearing inhaled pathogens, foreign particles, and apoptotic cells, and secreting anti-inflammatory cytokines such as IL-10 to suppress excessive inflammatory responses. These functions are essential for preserving the normal structure and function of lung tissue [16]. However, during lung inflammation, TR-M can be abnormally activated, releasing pro-fibrotic

factors such as TGF-β, which induce fibroblast activation and excessive extracellular matrix (ECM) deposition, thereby promoting pulmonary fibrosis. Additionally, some TR-M may become functionally impaired, losing their ability to effectively suppress inflammation, indirectly contributing to the progression of fibrosis.

In contrast, Mo-M originate from hematopoietic stem cells in the bone marrow and circulate in the blood. During lung inflammation, circulating monocytes are recruited to the lungs, where they differentiate into macrophages. A lineage-tracing study demonstrated that as pulmonary fibrosis progresses, monocytes are recruited to lung tissue and differentiate into Mo-M under the fibrotic microenvironment. These Mo-M persist in the lung tissue throughout the lifespan. Furthermore, the depletion of monocytes in Ccr2-deficient mice effectively alleviated bleomycin (BLM)-induced pulmonary fibrosis [17]. Subsequent single-cell RNA sequencing studies revealed that a subset of monocytes exhibits highly activated macrophage colony-stimulating factor (M-CSF) signaling, facilitating their migration to fibrotic lesions and differentiation into Mo-M, which promote disease progression. Targeted inhibition of M-CSF signaling in these Mo-M has been shown to effectively mitigate BLM-induced pulmonary fibrosis [18]. Additionally, Mo-M express high levels of marker proteins such as CCR2, CX3CR1, and ApoE, which are highly infiltrated in lung tissue. The overexpression of these markers promotes fibroblast proliferation, differentiation, and ECM synthesis, exacerbating pulmonary fibrosis [19]. Collectively, these studies highlight that Mo-M play a significant role in driving the progression of idiopathic pulmonary fibrosis (IPF).

2.2. T cells and IPF

2.2.1. Role of helper T cells in IPF

Helper T cells (Th cells) primarily consist of three subsets: Th1, Th2, and Th17. The functional imbalance of these subsets is closely associated with disease progression [20]. Th1 cells predominantly secrete interferon-gamma (IFN-γ), which exhibits anti-inflammatory and immunomodulatory effects under normal physiological conditions. However, during pulmonary fibrosis, overactivated Th1 cells may trigger aberrant immune responses [21]. IFN-γ can induce macrophage polarization toward the M1 phenotype, enhancing their capacity to release inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β). These inflammatory factors persistently stimulate the proliferation and activation of fibroblasts in lung tissue.

In the early stages of pulmonary fibrosis, increased Th2 cytokines promote the recruitment and activation of eosinophils. The release of various toxic proteins and inflammatory mediators from eosinophils disrupts the normal structure of lung tissue [22]. IL-4 and IL-13 can induce the transformation of fibroblasts into myofibroblasts, increasing the synthesis of extracellular matrix (ECM) components such as collagen and fibronectin, leading to excessive ECM deposition in the pulmonary interstitium. Additionally, Th2 cells can activate alveolar epithelial cells through paracrine signaling, inducing epithelial-mesenchymal transition (EMT), which further increases the number of myofibroblasts and exacerbates the progression of pulmonary fibrosis.

Th17 cells are characterized by their secretion of interleukin-17 (IL-17) [23]. IL-17 acts on various cell types, including fibroblasts, epithelial cells, and endothelial cells, inducing the production of chemokines such as CXCL1 and CXCL8 [24]. These chemokines attract neutrophils to infiltrate lung tissue. Neutrophils release substances such as elastase and myeloperoxidase, which directly damage lung tissue cells and promote the proliferation and activation of fibroblasts. Furthermore, IL-17 enhances the sensitivity of fibroblasts to transforming growth factor-beta (TGF-β) [25], further promoting fibroblast proliferation, differentiation, and ECM synthesis. This creates a vicious cycle that accelerates the progression of pulmonary fibrosis.

2.2.2. The role of regulatory T cells in IPF

Regulatory T cells (Tregs) are a subset of T lymphocytes with immunosuppressive functions, playing a critical role in maintaining immune homeostasis and suppressing excessive immune

responses [26]. Their functional changes during pulmonary fibrosis significantly influence disease progression [27]. Tregs primarily exert their immunosuppressive effects through cell-to-cell contact and the secretion of inhibitory cytokines such as transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10).

In the early stages of pulmonary fibrosis, an appropriate increase in Treg numbers helps to suppress excessive inflammatory responses and prevents immune cells from over-attacking lung tissue. TGF-β inhibits the proliferation and activation of effector T cells, reduces the release of inflammatory cytokines, and promotes extracellular matrix (ECM) remodeling during tissue repair, thereby maintaining the normal structure of lung tissue [28]. IL-10 suppresses the activation of macrophages and dendritic cells, reducing their antigen-presenting capacity and secretion of inflammatory mediators, which alleviates pulmonary inflammation.

However, during the progression of pulmonary fibrosis, Treg function may undergo abnormal changes. On one hand, the persistent elevation of pro-fibrotic factors such as TGF-β in the lung tissue microenvironment may induce phenotypic and functional plasticity in Tregs, partially impairing their immunosuppressive capacity and even potentially transforming them into pro-fibrotic cell subsets [29]. On the other hand, in the disease state, the migration, homing, and survival mechanisms of Tregs are disrupted, leading to an imbalance in their numbers and function within lung tissue. This prevents Tregs from effectively inhibiting fibroblast activation and proliferation as well as excessive ECM deposition, thereby promoting the progression of pulmonary fibrosis.

2.3. The relationship between B cells and pulmonary fibrosis

2.3.1. Autoantibodies involved in IPF progression

In the pathogenesis of pulmonary fibrosis, B cells primarily influence disease progression through two key mechanisms: autoantibody-mediated attacks on lung tissue and cytokine secretion [30]. In patients with pulmonary fibrosis, B cells are abnormally activated, producing a large number of autoantibodies such as antinuclear antibodies (ANA), anti-topoisomerase I (anti-Scl-70), and anticentromere antibodies (ACA). These autoantibodies specifically recognize and bind to self-antigens in lung tissue, forming antigen-antibody complexes.

On one hand, antigen-antibody complexes can activate the complement system. The cleavage products generated during complement activation, such as C3a and C5a, exhibit potent chemotactic effects, attracting a large number of inflammatory cells [31], including neutrophils and macrophages, to the site of pulmonary inflammation. These inflammatory cells release a significant amount of inflammatory mediators locally, further damaging lung tissue and disrupting its normal structure, thereby laying the foundation for the development of pulmonary fibrosis.

On the other hand, antigen-antibody complexes can directly stimulate resident cells in the lung [32], such as alveolar epithelial cells and fibroblasts, causing abnormal functional changes. When alveolar epithelial cells are damaged, their barrier function is compromised, leading to the leakage of extracellular matrix (ECM) components into the alveolar space. Additionally, epithelial cells secrete cytokines and chemokines, recruiting more inflammatory and interstitial cells, which further promotes the progression of pulmonary fibrosis. Activated fibroblasts proliferate extensively and synthesize and secrete excessive ECM, leading to the gradual worsening of lung tissue fibrosis.

2.3.2. Cytokines involved in IPF progression

B cells secrete a variety of factors, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which also contribute to the progression of pulmonary fibrosis [33]. IL-6 is a cytokine with broad biological activities that promotes the activation and proliferation of T cells and B cells, enhancing the function of immune cells. During pulmonary fibrosis, IL-6 secreted by B cells stimulates the proliferation and differentiation of fibroblasts, leading to increased synthesis and secretion of extracellular matrix (ECM) [34]. Additionally, IL-6 can indirectly promote pulmonary fibrosis by modulating the expression of other cytokines, such as transforming growth factor-beta

(TGF-β). Specifically, IL-6 upregulates the expression of TGF-β, thereby amplifying its pro-fibrotic effects.

TNF-α is another critical pro-inflammatory cytokine that induces apoptosis, promotes inflammatory responses, and regulates immune cell function. In pulmonary fibrosis, TNF-α secreted by B cells directly damages alveolar epithelial cells and endothelial cells, disrupting the normal structure of lung tissue. Furthermore, TNF-α activates the nuclear factor-kappa B (NF-κB) signaling pathway, promoting the infiltration of inflammatory cells and the release of inflammatory mediators, which exacerbates pulmonary inflammation and fibrosis [35].

In addition, B cells can secrete chemokines such as CXCL12, which recruit immune cells and interstitial cells to sites of pulmonary inflammation, further driving the progression of pulmonary fibrosis.

2.4. Neutrophils and pulmonary fibrosis

2.4.1. Neutrophil recruitment is involved in IPF progression

Neutrophils (Neutrophilic granulocytes, NEUs) play a critical role in pulmonary fibrosis, and their recruitment is the initial and essential step in this process [36]. When the lungs are subjected to injurious stimuli such as inflammation or oxidative stress, the damaged site rapidly releases a series of chemokines, including interleukin-8 (IL-8) and complement component C5a. These chemokines act as "signaling flares," guiding neutrophils to the site of injury. Under normal physiological conditions, neutrophils remain in a "standby" state within the bloodstream. However, upon receiving chemokine signals, they quickly respond.

First, neutrophils interact with the corresponding ligands on the surface of vascular endothelial cells through adhesion molecules, such as integrins, causing them to "marginate" from the bloodstream and tightly adhere to the endothelium. This process is known as margination. Subsequently, under the continuous attraction of chemokines, neutrophils migrate through the gaps between endothelial cells via diapedesis and enter the inflammatory region of the lung tissue.

In the context of pulmonary fibrosis, persistent injurious stimuli lead to the continuous release of chemokines, resulting in the ongoing recruitment of neutrophils to the lungs. The accumulation of a large number of neutrophils not only alters the cellular composition of the pulmonary microenvironment but also sets the stage for subsequent pathological responses [37].

2.4.2. Degranulation of NEU is involved in IPF progression

Degranulation of neutrophils (NEUs) is another critical mechanism through which they influence pulmonary fibrosis [38]. NEUs contain various types of granules, including primary, secondary, and tertiary granules, each storing unique bioactive substances [39]. When neutrophils are activated, these granules fuse with the cell membrane, releasing their contents into the extracellular environment. Primary granules are rich in myeloperoxidase (MPO) and elastase. MPO catalyzes the production of highly oxidative substances, such as hypochlorous acid, which play a crucial role in defending against pathogen invasion. However, in the context of pulmonary fibrosis, these strong oxidants excessively damage normal lung tissue cells and the extracellular matrix (ECM) [40]. Elastase degrades structural proteins such as elastic fibers in lung tissue, disrupting its normal structure and function. Secondary granules contain lactoferrin and collagenase. Lactoferrin can modulate inflammatory responses to some extent, but its function becomes dysregulated in the complex environment of pulmonary fibrosis. Collagenase, which breaks down collagen—a major component of the lung ECM—can lead to abnormal collagen degradation when excessively released. This disrupts the balance between ECM synthesis and degradation, promoting the development of pulmonary fibrosis. Tertiary granules, which contain enzymes such as cathepsins, also participate in ECM metabolism, further influencing the progression of pulmonary fibrosis.

In summary, tissue-resident macrophages (TR-M) and monocyte-derived macrophages (Mo-M) collaborate and counteract each other during pulmonary fibrosis, jointly influencing its initiation, progression, and outcomes. Helper T cells (Th) and regulatory T cells (Treg) play significant roles in

the development of pulmonary fibrosis. B cells contribute through autoantibody-mediated attacks on lung tissue and the secretion of various cytokines and chemokines. Neutrophils exert their effects via direct inflammatory damage and ECM destruction. A deeper understanding of their mechanisms and interrelationships may provide new insights and strategies for the prevention and treatment of pulmonary fibrosis.

3. Conclusion and outlook

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive disease with a complex pathogenesis involving the abnormal activation and interaction of various immune cells. In recent years, with in-depth research into the role of the immune system in pulmonary fibrosis, increasing evidence has demonstrated that immune cells play a critical role in the initiation, progression, and prognosis of pulmonary fibrosis. Innate immune cells, such as macrophages and neutrophils, are pivotal in the early stages of pulmonary fibrosis. They initiate and amplify inflammatory responses by releasing pro-inflammatory factors and reactive oxygen species (ROS), promoting the activation and proliferation of fibroblasts. Adaptive immune cells, including T cells and B cells, exhibit dual roles in pulmonary fibrosis. On one hand, pro-inflammatory T cell subsets such as Th1 and Th17 exacerbate inflammation and tissue damage. On the other hand, regulatory T cells (Tregs) exert immunosuppressive effects, limiting inflammation and tissue injury. B cells contribute to the development of pulmonary fibrosis by producing autoantibodies and pro-inflammatory factors. A complex interaction network exists between immune cells and lung parenchymal cells, such as fibroblasts and epithelial cells. Immune cells regulate the activation, proliferation, and differentiation of lung fibroblasts through the secretion of cytokines, growth factors, and other mediators, promoting extracellular matrix (ECM) deposition and the formation of pulmonary fibrosis. Advanced technologies, such as single-cell sequencing, have enabled further elucidation of the functional and phenotypic changes in different immune cell subsets during pulmonary fibrosis, providing a theoretical foundation for precision-targeted therapies. Based on the understanding of the roles of various immune cells in pulmonary fibrosis, therapeutic strategies targeting specific immune cells or signaling pathways—such as immune cell adoptive therapy and immune checkpoint inhibitors—offer new hope for patients with IPF.

In summary, immune cells play a complex and crucial role in pulmonary fibrosis. Further research into the interactions between immune cells and pulmonary fibrosis, as well as the underlying molecular regulatory mechanisms, will help identify key regulatory nodes and signaling pathways. This could provide novel insights for the diagnosis, treatment, and development of new therapeutic targets for pulmonary fibrosis.

Reference

[1] Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence - based guidelines for diagnosis and management [J]. American journal of respiratory and critical care medicine, 2011, 183(6): 788 - 824.

[2] Corte TJ, Raghu G, Wuyts WA, et al. Epidemiology and natural history of idiopathic pulmonary fibrosis[J]. Respirology, 2011, 16(2): 225 - 234.

[3] Tolle, Leslie B., et al. "Idiopathic pulmonary fibrosis: What primary care physicians need to know." *Cleve Clin J Med* 85.5 (2018): 377-386.

[4] Khalil N, O'Connor R. Idiopathic pulmonary fibrosis: current understanding of the pathogenesis and the status of treatment [J]. Cmaj, 2004, 171(2): 153-160.

[5] Wang H, Sun K, Peng H, et al. Emerging roles of noncoding RNAs in idiopathic pulmonary fibrosis[J]. Cell Death Discovery, 2024, 10(1): 443.

[6] Mayr C H, Sengupta A, Asgharpour S, et al. Sfrp1 inhibits lung fibroblast invasion during transition to injury-induced myofibroblasts[J]. European Respiratory Journal, 2024, 63(2).

[7] Lv J, Gao H, Ma J, et al. Dynamic atlas of immune cells reveals multiple functional features of macrophages associated with progression of pulmonary fibrosis [J]. Frontiers in Immunology, 2023, 14: 1230266.

[8] Liu G, Zhai H, Zhang T, et al. New therapeutic strategies for IPF: Based on the "phagocytosis-secretion-immunization" network regulation mechanism of pulmonary macrophages [J]. Biomedicine & Pharmacotherapy, 2019, 118: 109230.

[9] Mehta D R, Ashkar A A, Mossman K L. The nitric oxide pathway provides innate antiviral protection in conjunction with the type I interferon pathway in fibroblasts [J]. PLoS One, 2012, 7(2): e31688.

[10] Kishore A, Petrek M. Roles of macrophage polarization and macrophage-derived miRNAs in pulmonary fibrosis [J]. Frontiers in immunology, 2021, 12: 678457.

[11] Scott T E, Lewis C V, Zhu M, et al. IL-4 and IL-13 induce equivalent expression of traditional M2 markers and modulation of reactive oxygen species in human macrophages [J]. Scientific Reports, 2023, 13(1): 19589.

[12] Huang J G, Ren J X, Chen Y, et al. M2 macrophages mediate fibrotic scar formation in the early stages after cerebral ischemia in rats[J]. Neural Regeneration Research, 2023, 18(10): 2208-2218.

[13] Xu Y, Ying L, Lang J K, et al. Modeling mechanical activation of macrophages during pulmonary fibrogenesis for targeted anti-fibrosis therapy[J]. Science Advances, 2024, 10(13): eadj9559.

[14] Shenderov K, Collins S L, Powell J D, et al. Immune dysregulation as a driver of idiopathic pulmonary fibrosis[J]. The Journal of clinical investigation, 2021, 131(2).

[15] Arteel G E. When is a Kupffer cell not a Kupffer cell? Novel insight into macrophage fate and function in hepatic fibrosis [J]. 2024.

[16] Steen E H, Wang X, Balaji S, et al. The role of the anti-inflammatory cytokine interleukin-10 in tissue fibrosis [J]. Advances in wound care, 2020, 9(4): 184-198.

[17] Misharin A V, Morales-Nebreda L, Reyfman P A, et al. Monocyte-derived alveolar macrophages drive lung fibrosis and persist in the lung over the life span [J]. Journal of Experimental Medicine, 2017, 214(8): 2387-2404.

[18] Osterholzer J J, Olszewski M A, Murdock B J, et al. Implicating exudate macrophages and Ly-6Chigh monocytes in CCR2-dependent lung fibrosis following gene-targeted alveolar injury[J]. The Journal of Immunology, 2013, 190(7): 3447-3457.

[19] Boorsma C E, Draijer C, Melgert B N. Macrophage heterogeneity in respiratory diseases [J]. Mediators of inflammation, 2013, 2013(1): 769214.

[20] Wang Y H, Li W, McDermott M, et al. IFN-γ–producing TH1 cells and dysfunctional regulatory T cells contribute to the pathogenesis of Sjögren's disease [J]. Science Translational Medicine, 2024, 16(778): eado4856.

[21] Paun A, Bergeron M E, Haston C K. The Th1/Th17 balance dictates the fibrosis response in murine radiation-induced lung disease [J]. Scientific Reports, 2017, 7(1): 11586.

[22] Gieseck III R L, Wilson M S, Wynn T A. Type 2 immunity in tissue repair and fibrosis [J]. Nature Reviews Immunology, 2018, 18(1): 62-76.

[23] Gagliani N, Vesely M C A, Iseppon A, et al. Th17 cells transdifferentiate into regulatory T cells during resolution of inflammation [J]. Nature, 2015, 523(7559): 221-225.

[24] Cavagnero K J, Li F, Dokoshi T, et al. CXCL12+ dermal fibroblasts promote neutrophil recruitment and host defense by recognition of IL-17[J]. Journal of Experimental Medicine, 2024, 221(4): e20231425.

[25] Fabre T, Kared H, Friedman S L, et al. IL-17A enhances the expression of profibrotic genes through upregulation of the TGF-β receptor on hepatic stellate cells in a JNK-dependent manner[J]. The Journal of immunology, 2014, 193(8): 3925-3933.

[26] Zhang H, Jiang D, Zhu L, et al. Imbalanced distribution of regulatory T cells and Th17. 1 cells in the peripheral blood and BALF of sarcoidosis patients: relationship to disease activity and the fibrotic radiographic phenotype [J]. Frontiers in Immunology, 2023, 14: 1185443.

[27] Bargagli E, Refini R M, d'Alessandro M, et al. Metabolic dysregulation in idiopathic pulmonary fibrosis[J]. International journal of molecular sciences, 2020, 21(16): 5663.

[28] Saito A, Horie M, Nagase T. TGF-β signaling in lung health and disease [J]. International journal of molecular sciences, 2018, 19(8): 2460.

[29] Celada L J, Kropski J A, Herazo-Maya J D, et al. PD-1 up-regulation on CD4+ T cells promotes pulmonary fibrosis through STAT3-mediated IL-17A and TGF-β1 production [J]. Science translational medicine, 2018, 10(460): eaar8356.

[30] Zoz D F, Lawson W E, Blackwell T S. Idiopathic pulmonary fibrosis: a disorder of epithelial cell dysfunction [J]. The American journal of the medical sciences, 2011, 341(6): 435-438.

[31] Bavia L, Lidani K C F, Andrade F A, et al. Complement activation in acute myocardial infarction: An early marker of inflammation and tissue injury?[J]. Immunology Letters, 2018, 200: 18-25.

[32] Platzer B, Stout M, Fiebiger E. Antigen cross-presentation of immune complexes [J]. Frontiers in immunology, 2014, 5: 140.

[33] Ali M F, Egan A M, Shaughnessy G F, et al. Antifibrotics modify B-cell–induced fibroblast migration and activation in patients with idiopathic pulmonary fibrosis [J]. American journal of respiratory cell and molecular biology, 2021, 64(6): 722-733.

[34] Roman J, Chiba H. B cells in idiopathic pulmonary fibrosis: Targeting immune cells with antifibrotic agents [J]. American Journal of Respiratory Cell and Molecular Biology, 2021, 64(6): 652-654.

[35] Shang G S, Liu L, Qin Y W. IL-6 and TNF-α promote metastasis of lung cancer by inducing epithelial-mesenchymal transition [J]. Oncology letters, 2017, 13(6): 4657-4660.

[36] Leslie J, Millar B J M, del Carpio Pons A, et al. FPR-1 is an important regulator of neutrophil recruitment and a tissue-specific driver of pulmonary fibrosis[J]. JCI insight, 2020, 5(4).

[37] Ueki H, Wang I H, Kiso M, et al. Neutrophil adhesion to vessel walls impairs pulmonary circulation in COVID-19 pathology [J]. Nature Communications, 2025, 16(1): 455.

[38] Zhang F, Yan Y, Cao X, et al. TGF-β-driven LIF expression influences neutrophil extracellular traps (NETs) and contributes to peritoneal metastasis in gastric cancer [J]. Cell Death & Disease, 2024, 15(3): 218.

[39] Greten F R, Arkan M C, Bollrath J, et al. NF-κB is a negative regulator of IL-1β secretion as revealed by genetic and pharmacological inhibition of IKKβ[J]. Cell, 2007, 130(5): 918-931.

[40] Rahman I. Oxidative stress and gene transcription in asthma and chronic obstructive pulmonary disease: antioxidant therapeutic targets [J]. Current Drug Targets-Inflammation & Allergy, 2002, 1(3): 291-315.