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REVIEW ARTICLE

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Activating transcription factor 3: A potential therapeutic target for inflammatory pulmonary diseases

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Abstract

Background: Activating transcription factor 3 (ATF3) is a nuclear protein that is widely expressed in a variety of cells. It is a stress-inducible transcription gene and a member of the activating transcription factor/cAMP responsive element-binding protein (ATF/CREB) family.

Methods: The comprehensive literature review was conducted by searching PubMed and Google Scholar. Search terms used were "ATF3", "ATF3 and (ALI or ARDS)", "ATF3 and COPD", "ATF3 and PF", and "ATF3 and Posttranslational modifications".

Results: Recent studies have shown that ATF3 plays a critical role in many inflammatory pulmonary diseases, including acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis (PF). ATF3 participates in many signaling pathways and complex pathophysiological processes, such as inflammation, immunity, endoplasmic reticulum stress, and cell proliferation. However, the role of ATF3 in current studies is controversial, and there are reports showing that ATF3 plays different roles in different pulmonary diseases.

Conclusions: In this review, we first summarized the structure, function, and mechanism of ATF3 in various inflammatory pulmonary diseases. The impact of ATF3 on disease pathogenesis and the clinical implications was particularly focused on, with an overall aim to identify new targets for treating inflammatory pulmonary diseases.

KEYWORDS

acute lung injury, acute respiratory distress syndrome, ATF3, chronic obstructive pulmonary disease, posttranslational modifications, pulmonary fibrosis

1 | INTRODUCTION

During respiration, the lungs are constantly exposed to various irritants, such as bacteria, viruses, cigarette smoke, and airborne particulates, which makes them highly susceptible to pulmonary diseases. The characteristics of pulmonary diseases include high rates of morbidity and mortality, as well as poor treatment outcomes, making them a significant public health problem worldwide.[1] In studies on the pathogenesis of pulmonary diseases, it has been found that transcription factors directly affect gene expression and play a vital role in the regulation of cellular functions and disease development, and consequently, these have thus become a hot topic of research in recent years.[2,3]

Activating transcription factor 3 (ATF3) is a stress-inducible transcription factor that belongs to the activating transcription factor/cAMP-responsive element-binding protein (ATF/CREB) family, which regulates gene transcription by forming homodimers or heterodimers via the basic leucine zipper (bZIP) structural domain, thereby supporting the biological functions of genes.[4–6] ATF3 mainly functions as an adaptive response gene to maintain genetic integrity and intracellular homeostasis under stress conditions.[7]

The expression of ATF3 is relatively stable under normal physiological conditions, while changes in its expression are associated with multiple pathophysiological responses (e.g., inflammation, oxidative stress, endoplasmic reticulum stress, and cell death).[8–10] This review briefly discusses the mechanism of action of ATF3 and its effects on biological functions and cellular processes, with a special focus on the role of ATF3 in acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis (PF), and with an overall aim to identify new targets for the treatment of inflammatory pulmonary diseases.

2 | STRUCTURE AND BIOLOGICAL FUNCTIONS OF ATF3

2.1 | Structure of ATF3

ATF3 was first identified from a cDNA library of HeLa cells stimulated by serum. ATF3 contains four exons and encodes 181 amino acids (Figure 1). The molecular weight of ATF3 is 22 kDa.[11] ATF3 has the same binding site as other ATF/CREB family transcription factors, which is 5′-TGACGTCA-3′.[12] Among the same family, the more studied ones are ATF1, ATF2, ATF4, and CREB.[13] They interact with target DNA by binding an entire region in the bZIP structural domain.

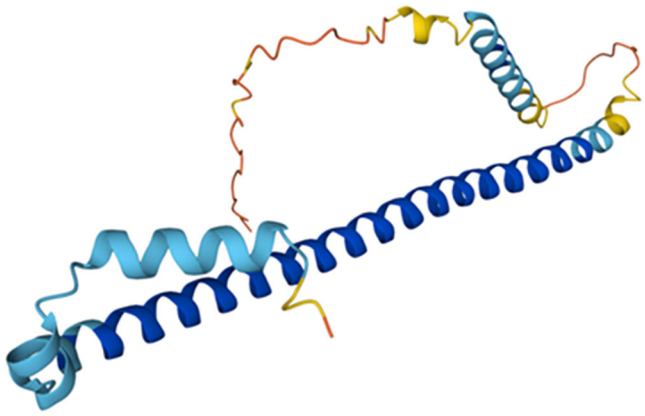

FIGURE 1 The spatial structure of ATF3.

2.2 | Biological functions of ATF3

2.2.1 | Transcriptional regulation of ATF3

The stimulation mode and cell type mainly determine the function of ATF3. Although the ATF3 gene is expressed at low levels in normal conditions, its expression is upregulated when subjected to multiple stimuli, such as hypoxia, cytokines, DNA damage, or chemotherapeutic drugs.[14,15] The ATF3 promoter can bind to the loci involved in cellular stress responses to accomplish the transcriptional regulation of these genes.[16] Thus, ATF3 acts as a regulator in the host defense mechanism.[17]

ATF3 is a star gene of the ATF/CREB family and its dimerization affects gene transcription. ATF3 can not only act with other ATF/CREB family members, such as JDP2, but also with other family transcription factors, such as p53, Nrf2, and nuclear factor-κB (NF-κB), to regulate gene expression.[18–21] ATF3 binds to regulatory sequences within the promoter region of a target gene, which can lead to its transactivation or repression.[16,22,23] The specific mechanisms by which ATF3 regulates transcription remain to be further explored.

2.2.2 | Posttranslational modifications of ATF3

ATF3 can be modified by acetylation, ubiquitination, and ubiquitin-like modification, and these posttranslational modifications change its stability and function (Figure 2).

Acetylation

Protein acetylation modifications are involved in several important physiological functions, such as transcriptional regulation, signaling pathways, metabolic regulation, protein stability, and responses to microbial

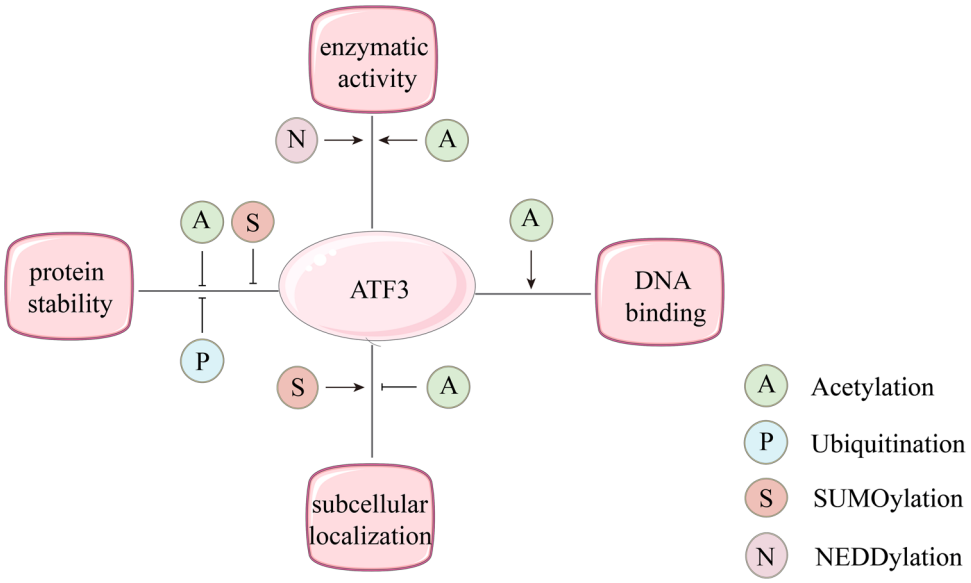

FIGURE 2 Posttranslational modification plays a critical role in regulating ATF3 enzymatic activity, DNA binding, protein stability, and subcellular localization.

infection.[24–26] The mammalian intracellular acetyltransferases that mediate protein acetylation modifications mainly include Tip60 and p300. Tip60 is a transcriptional co-activator, while ATF3 is a regulator of Tip60, and ATF3 acetylation enhances Tip60 activity and stability.[22] Similarly, p300 is a transcriptional co-activator and histone acetyltransferase, and the stimulation of glomerular thylakoid cells by subsoluble complement C5b-9 complexes can upregulate p300 expression and then acetylate ATF3, thereby affecting ATF3 transcriptional activity without altering its sublocalization in the cell.[27]

Ubiquitination

Ubiquitination is the process of the specific modification of target proteins by ubiquitin molecules in the presence of ubiquitin-activating enzymes (E1), ubiquitin-binding enzymes (E2), and ubiquitin ligases (E3), leading to degradation of the target protein. Murine double minute 2 (MDM2) is an essential gene for the ubiquitination of ATF3. The ubiquitination of ATF3 mediated by the ubiquitin ligase MDM2 can lead to both the degradation of ATF3 and degradation of the oncogene p53 in cells, thus promoting tumor formation.[28] In contrast, progesterone X receptors can block MDM2-mediated ATF3 ubiquitination by targeting ATF3 lysine mutations, thereby increasing the stability of ATF3 and p53.[29]

Ubiquitin-like modification

Both ubiquitin-like and ubiquitin modifications are cascade reactions involving multiple enzymes. Ubiquitin-like proteins are homologous and similar to ubiquitin proteins, but each ubiquitin-like protein has its own specific biological function.[30] Two representative examples are the small ubiquitin-like modifier (SUMO) protein and neural precursor cell expressed developmentally downregulated (NEDD) 8 protein. Both SUMO and NEDD8 are small ubiquitin-like peptides that also regulate intracellular processes by modifying specific proteins, and both require E1, E2, and E3, and hence the term "ubiquitin-like proteins."[31] SUMO proteins function mainly in the nucleus and are involved in DNA replication, repair, and transcriptional regulation.[32] The primary role of NEDDylation is to alter protein function, not to degrade it.[33]

ATF3 can be SUMOylated, and lysine 42 of ATF3 is the primary SUMO site. The SUMOylation of ATF3 does not directly interfere with the binding of ATF3 to DNA. However, how the SUMOylation of ATF3 alters its ability to recruit transcription factors remains unknown.[34] In human umbilical vein endothelial cells, the SUMOylation of ATF3 promotes protein degradation caused by ATF3 ubiquitination, decreases ATF3 protein stability, and exacerbates angiotensin II-induced inflammation and cellular dysfunction in endothelial cells. Additionally, SUMOylation controls the subcellular location of ATF3 in endothelial cells.[35]

In the process of NEDDylation, the protein is catalyzed by NEDD8 activase (E1), NEDD8 conjugase (E2), and NEDD8 ligase (E3).[33] The most typical substrate of the NEDDylation pathway is Cullin-RING E3 ubiquitin ligase (CRL). A study showed that the NEDD8-activating enzyme inhibitor MLN4924 significantly enhances ATF3 expression at the protein and RNA

TABLE 1 The role of ATF3 in inflammatory pulmonary diseases.

Diseases	Expression of ATF3	Signaling pathways	Roles of ATF3	References
ALI/ARDS	↑	LPS → ATF3 ↑ → TL1A ↓ /NF-κB ↓ AUF1→Nrf2 ↑ /ATF3 ↓ ATF3 ↑ → DR5 ↑ /Bcl-xL↓	Alleviate LPS/PA induced ALI Promote ferroptosis of alveolar epithelial cells Promote airway epithelium apoptosis	[38–41]
PF	↑	CAE → ATF3 ↑ → PINK1 ↑ Pirfenidone →ATF3 ↓ /p-Smad3↓	Initiate ERS Promote PF	[42, 43]
COPD	↑	CSE → ATF3 ↑ → MUC5AC↑ ATF3 ↑ →p NF- κB ↓	Promote COPD Alleviate COPD	[44, 45]

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ATF3, activating transcription factor 3; AUF1, AU-rich element RNA-binding factor 1; Bcl-Xl, B-cell lymphoma-extra large protein; CAE, citrus alkaline extract; COPD, chronic obstructive pulmonary disease; CSE, cigarette smoke extract; DR5, death receptor 5; ERS, endoplasmic reticulum stress; LPS, lipopolysaccharide; MUC5AC, mucin 5AC; NF-κB, nuclear factor-κB; Nrf2, nuclear factor erythroid 2-related factor 2; pNF-κB, phosphorylated NF-κB; PA, *Pseudomonas aeruginosa*; PF, pulmonary fibrosis; PINK1, phosphatase and tensin homolog (PTEN)-induced putative kinase 1; TL1A, tumor necrosis factor-like ligand 1A.

levels. The stability of ATF3 was further determined using an actinomycin tracking assay after MLN4924 treatment, which revealed that the half-life of ATF3 was not affected by MLN4924-induced NEDD–CRL axis inactivation.[19]

Therefore, an in-depth study of the various modalities of ATF3 posttranslational modifications is necessary to understand their mechanism of action.

3 | ROLE OF ATF3 IN PULMONARY DISEASES

3.1 | ALI/ARDS

ALI and ARDS are common diseases in the intensive care unit. One study reported that the 90-day in-hospital mortality rate of patients with moderate to severe ARDS was as high as 43%.[36] Based on the available statistics, the causes of ARDS are complex, including severe pneumonia, sepsis, aspiration of gastric contents, and significant trauma. The pathogenesis of ARDS is mainly manifested as increased endothelial permeability, death and dysfunction of alveolar epithelial cells, loss of surfactant function, activation of the coagulation cascade, and activation of the pulmonary innate immune pathway.[37] At present, the management of ARDS patients focuses on infection diagnosis and treatment, respiratory support, and fluid management. Moreover, individualized protocols and treatments developed based on these protocols often fail to meet clinical needs. Even so, the patient mortality rate remains high, so advancing precision medicine and gaining insights into the drivers of molecular heterogeneity may help identify new therapeutic targets.

3.1.1 | Effect of ATF3 in lipopolysaccharide (LPS)-induced ALI

In a study exploring the expression profile of genes associated with lipopolysaccharide-induced early ALI, protein–protein interaction network analysis showed that ATF3 was one of the most critical genes.[46] Several studies have demonstrated that ATF3 plays an important role in the development of ALI induced by different factors.

A study found that compared to wild-type mice, ATF3-deficient mice were more likely to develop ALI with enhanced lung permeability, epithelial injury, and inflammation in response to LPS stimulation. ATF3 prevents over-activation of the immune system by repressing the expression of pro-inflammatory genes.

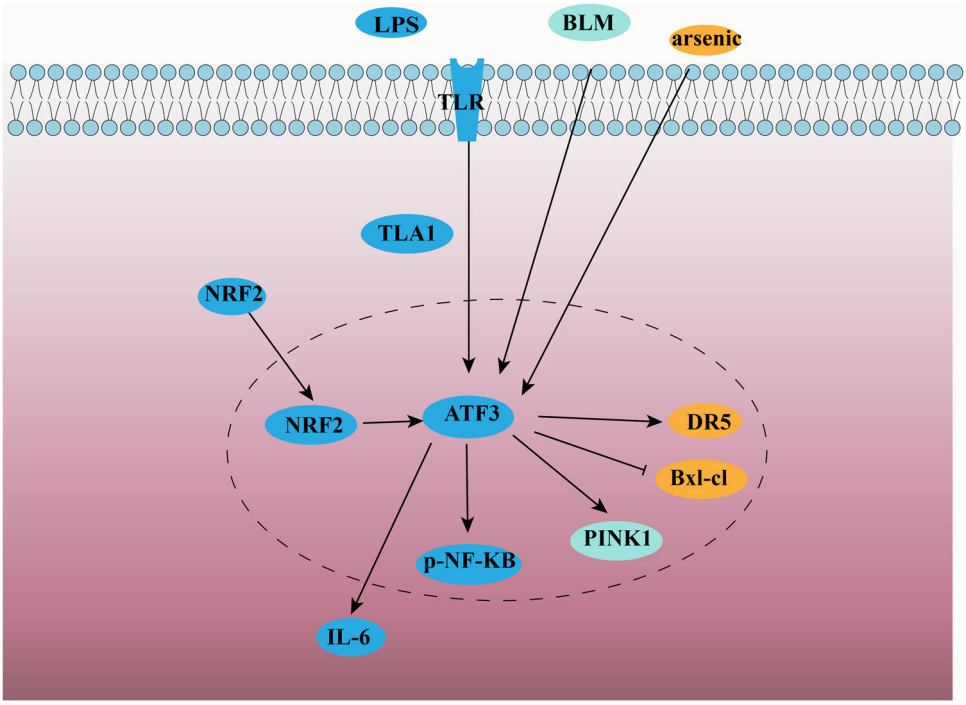

FIGURE 3 Signaling pathway of ATF3 in inflammatory pulmonary diseases.

Tumor necrosis factor (TNF)-like cytokine 1A (TL1A), also called TNFSF15, is a member of the TNF family. Differential gene analysis showed that TL1A was highly expressed in LPS-induced ATF3 knockout mice lung tissues, and that ATF3 downregulated TL1A expression in RAW264.7 cells and lung tissues.[38] Like TL1A, the Toll-like receptor (TLR) family plays a vital role in innate immunity. Upon recognition of their ligands, TLRs trigger complex intracellular signaling pathways and promote the expression of inflammatory cytokines, chemokines, and costimulatory molecules essential for activating adaptive immune responses.[47] ATF3 is a negative regulator of the TLR4 signaling pathway.[48]

The central molecule in the TLR4 pathway is NF-κB, which is translocated to the nucleus in cells to initiate the transcription of inflammatory mediators. The mammalian NF-κB family consists of RelA (p65), c-Rel, RelB, p50, and p52. ATF3 negatively regulates NF-κB by interacting directly with p65.[49] It was found in innate immunity that ATF3 attenuated inflammation by interacting with NF-κB and inhibiting the LPS-induced expression of the pro-inflammatory cytokines IL-6, IL-12B, and TNF-α in mice.[50,51] In contrast, ATF3 overexpression significantly increased p-p65 (the phosphorylated form of p65) production in human bronchial epithelial cells in a particulate matter-induced lung inflammation model, suggesting that ATF3 can act as an activator of the NF-κB pathway in particulate matter-induced inflammation.[8] Thus, ATF3 acts as a critical immunomodulator against pathogen invasion, activating the immune response, and can enhance or suppress inflammation by regulating multiple target genes.[52]

3.1.2 | Effect of ATF3 in pneumonia-associated ALI

Pseudomonas aeruginosa (PA) as an important opportunistic human pathogen can take part in the pathogenesis of pneumonia. Co-immunoprecipitation in one study indicated that ATF3 protected mice against PA-induced ALI in part by interacting with the LPS-binding protein in lung tissue.[39] Besides, enzyme-linked immunosorbent assay results from BALF and peritoneal macrophages showed that ATF3 attenuates the release of inflammatory factors, such as TNF-α, IL-6, and IL-1β. Furthermore, its protective effect may be related to the inhibition of NF-κB activation, suggesting that the ATF3 gene may be a potential target gene for treating PA-induced ALI.[39] In pneumonia caused by *Staphylococcus aureus*, ATF3 regulates the expression of intracellular antimicrobial genes, actin cytoskeleton, and the cell migration of macrophages to ameliorate inflammation.[53] In pneumonia caused by *Streptococcus pneumoniae*, ATF3 positively regulates the innate immunity during pneumococcal infection by enhancing TNF-α, IL-1β, and IFN-γ expression and controlling bacterial clearance.[54] ATF3 in macrophages promotes IL-17A production in γδT cells

for a rapid induction of the host defense during early *S. pneumoniae* infection.[55] ATF3 overexpression after *S. pneumoniae* infection promotes cell proliferation in alveolar type II epithelial cells, which promotes lung epithelial recovery and improves lung function after injury.[56]

3.1.3 | Effect of ATF3 in sepsis-associated ALI

Sepsis is a life-threatening systemic condition and is the leading cause of ALI. Autophagy plays a vital role in regulating the pulmonary inflammatory response during sepsis. Studies have shown that ATF3 is a novel autophagy-regulated gene. In autophagy-deficient mice with the Atg4b gene knocked out, ATF3 is retained in the cytoplasm to prevent its binding to target genes.[57] Ferroptosis is closely related to sepsis-associated ALI. In a mouse model of sepsis induced by cecum ligation puncture (CLP), the inhibition of ferroptosis improved the survival rate of CLP mice and significantly alleviated lung tissue injuries. Further research revealed that AU-rich element RNA binding factor 1 (AUF1) attenuated ferroptosis in alveolar epithelial cells in vitro by upregulating the expression of nuclear factor erythroid two related factors 2 (Nrf2) and downregulating the expression of ATF3.[40] In addition to AUF1, the citrus flavonoid naringenin effectively attenuated lung tissue damage and reduced cytokine levels and leukocyte infiltration in septic mice.[58] The above results suggest that ATF3 has a protective role in ALI.

3.1.4 | Effect of ATF3 on other types of ALI

The etiologies of ALI are complex. In addition to the above-mentioned causes, ALI can also be induced by ischemia–reperfusion, ventilator application, and certain chemical substances. The mechanism of ALI caused by different etiologies is also different. In a rat model of lung transplantation injury, the expression of ATF3 increased significantly with the prolongation of the warm ischemic time (the time from the start of lung implantation to the release of the pulmonary artery clamp).[59] In an ischemia–reperfusion-induced lung injury model, it was found that carnosol (an antioxidant herbal compound) treatment may protect the lung from ischemia–reperfusion injury by regulating the ATF3–IL-6 axis.[60] Ventilator-induced lung injury (VILI) can be triggered by mechanical injury, such as cyclic stretching. A microarray analysis of cyclic stretch response genes in Beas-2B cells showed a significant enrichment of ATF3 in stretch cells. This study was validated in vivo, and the results were correlated and consistent with those from in vitro experiments. The research proves that ATF3 plays a protective role in VILI as an early stress gene.[61] Nrf2 plays a protective role as a transcription factor mediated by antioxidant response elements. It was shown that ATF3 attenuates ventilator-associated lung injury by preventing Nrf2 degradation.[62] Nickel oxide nanoparticles (NiONPs) are commonly produced and used in industry, but are harmful to the lungs, and exposure to NiONPs can lead to apoptosis and ferroptosis in lung epithelial cells, ultimately leading to ALI.[63] ATF3 expression was found to be upregulated in the lung tissue of mice and human lung epithelial cells after exposure to NiONPs. In another study, ATF3-deficient BEAS-2B cells were relatively resistant to apoptosis when exposed to arsenic, showing that ATF3 plays a facilitative role in arsenic-induced apoptosis. ATF3 also prevented transcription of the death receptor 5 (DR5) and B-cell lymphoma extra-large protein (Bcl-xL) by directly binding to the promoter DR5 and Bcl-xL. ATF3 has the potential to serve as an early and sensitive biomarker for lung injury brought on by arsenic by acting as a proapoptotic protein in arsenic-induced airway epithelium apoptosis.[41]

3.2 | Pulmonary fibrosis

Pulmonary fibrosis (PF) is an end-stage alteration of a large group of pulmonary diseases characterized by fibroblast proliferation and massive extracellular matrix aggregation with inflammatory damage and tissue structural destruction.[64,65] Its pathogenesis involves epithelial cell injury, aging, mitochondrial dysfunction, ER stress, and proteostasis imbalance.[66] Although two antifibrotic drugs, nintedanib and pirfenidone, have been approved for the clinical treatment of PF, neither treatment is curative and lung transplantation is the only viable option for patients with PF.[67,68] However, the risks of surgery are high and new therapeutic approaches need to be explored to improve patient prognosis and enhance patients' long-term quality of life.[69]

ATF3 may be a biomarker for PF.[70] ATF3 was found to be significantly upregulated in lung tissues from mice with bleomycin-induced pulmonary fibrosis and in patients with rheumatoid arthritis-associated interstitial lung disease.[71] In addition, the overexpression of ATF3 leads to the accumulation of depolarized mitochondria, increased mitochondrial ROS, and reduced cell viability, whereas the knockdown of ATF3 in type II lung epithelial cells was found to protect mice from bleomycin-induced PF.[66] Pirfenidone has a therapeutic effect on idiopathic pulmonary fibrosis (IPF). It also

significantly reduced ATF3 expression and collagen accumulation in the bleomycin-induced lung tissue of mice. Moreover, in one study where primary human lung fibroblasts (pHLFs) were treated in vitro with ATF3 shRNA-expressing lentiviral vectors, it was found that the knockdown of ATF3 inhibited the production of p-Smad3, an important mediator of pathological fibrosis. This suggests that pirfenidone inhibits myofibroblast differentiation by inhibiting the ATF3/Smad3 signaling pathway.[42] Citrus alkaline extract (CAE) is derived from citrus pericarp and has antifibrotic properties. In one study, CAE inhibited the elevation of proteins downstream of ER stress induced by bleomycin or clathrin and activated the expression of ATF3. It also increased PTEN-induced kinase 1 (PINK1) levels in type II alveolar epithelial cells in vivo and in vitro, suggesting that CAE may improve PF through the ATF3/PINK1 pathway.[43] In studies of pulmonary inflammation and pulmonary fibrosis induced by inhaled silica particles, crystalline silica induced more intense stress-related ATF3 gene expression and cytokine and chemokine secretion in primary human bronchial epithelial cells and mouse alveolar epithelial cells.[72] However, a deeper understanding of the underlying mechanisms of disease development is a prerequisite for curing PF. Therefore, the mechanism of ATF3 in PF needs to be further investigated.

3.3 | COPD

COPD is a clinical syndrome characterized by chronic respiratory symptoms, structural lung abnormalities (airway disease or emphysema), pulmonary dysfunction (mainly incomplete reversible airflow limitation), or any combination of the above. Chronic inflammation, protease-antiprotease imbalance, ER stress, and oxidative stress are involved in the development of COPD.[73,74] The current treatments for COPD include the inhalation of β2-adrenergic receptor agonists, glucocorticoids, and anticholinergics, but while these treatments help slow the progression of COPD, they have little effect in improving lung function and quality of life. Some of these drugs are also associated with toxic side effects, so there is an urgent need to find alternative therapies for COPD. Recent basic and clinical research has focused on the early pathophysiological changes in COPD to improve diagnosis and help identify patients most likely to benefit from early intervention.[75] Although few new treatments have been approved for COPD in the last 5 years, new biomarker-based strategies have made significant progress in targeting specific subgroups in existing therapies.[76]

The nature of COPD is as an inflammatory disease; especially, the acute exacerbation of COPD occurs with the aggregation of inflammatory cells and the massive release of inflammatory factors, which induce cupular cell hyperplasia of the airway epithelium and an increase in airway mucus secretion.[77] The inflammatory factors stimulate the proliferation of smooth muscles and fibroblasts around the airway, leading to a remodeling of the small airways and aggravating the degree of airflow limitation. Excessive mucus secretion is one of the essential pathological features of COPD.[44] Mucin 5AC (MUC5AC) is closely related to COPD mucus secretion. Studies have shown that cigarette smoke and cigarette smoke extract (CSE) stimulate ATF3 expression in mouse lung tissue and airway epithelial cells. ATF3 was found to be a positive regulator of CSE-induced MUC5AC expression in vivo.[45] It was suggested that ATF3 can promote mucus secretion and thus exert pro-inflammatory effects in COPD models. However, the findings of another study were quite different. In animal experiments, ATF3 knockout mice showed significantly increased mucus production and increased peribronchial inflammatory cell infiltration after modeling compared to wild-type mice, suggesting that ATF3 has an attenuating effect on COPD. In vitro experiments showed that ATF3 plays a negative regulatory role in mediating cigarette smoke-induced inflammatory gene transcription, especially IL-6 and IL-8 expression, through the down-regulation of pNF-κB.[78] The above results indicate that further studies on ATF3-targeted therapies may be helpful for the treatment of cigarette smoke-induced COPD.

4 | CONCLUSION

ATF3 plays an important role in the development of multiple inflammatory pulmonary diseases (Table 1). This has been confirmed by a number of cell and animal experiments, but the specific mechanism remains to be explored (Figure 3). At present, studies on the effect of ATF3 in inflammatory pulmonary disease are limited to basic experiments, and there is a lack of in-depth clinical research. In the future, new therapies and their delivery modes should be developed for ATF3, whether these ATF3-targeted therapies need to be used in combination with specific drugs targeting other signaling pathways or alone.

AUTHOR CONTRIBUTIONS

Dandan Li: Conceptualization (equal); investigation (lead); writing—original draft preparation (lead). **Juanjuan Jin**: Investigation (supporting); writing—original

draft preparation (supporting). **Xue Dong**: Visualization (equal). **Chenyang Zhang**: Visualization (equal). **Jia Wang**: Conceptualization (equal); writing—review & editing (supporting). **Xianyao Wan**: Writing—review & editing (lead).

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Figure 1 was obtained from the Uniprot database (https://www.uniprot.org/).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article.

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