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Review

The Emerging Role of FBXL19 in the Prediction and Pathogenesis of Inflammatory Lung Diseases

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ABSTRACT: Inflammatory lung diseases can be caused either by direct pulmonary insults via inhaled pathogens, such as bacteria or virus, or by indirect insults secondary to systemic inflammation, such as sepsis. The pathogenesis of inflammatory lung diseases has been extensively investigated. Recent studies focusing on protein ubiquitination provide mechanistic insights into the regulation of inflammatory responses in lung epithelial and endothelial cells. F-box and leucine-rich repeat protein 19 (FBXL19) is a substrate-recognition component of the SKP1-Cullin-1-F-box (SCF) E3 ubiquitin ligase complex. Previous studies have demonstrated that FBXL19 plays an important role in regulating pulmonary inflammation by targeting multiple inflammatory signaling proteins, including interleukin 33 receptor (IL-33R), CREB-Binding Protein (CBP), and Nuclear Factor-κB subunit p65 (NF-κB p65). Furthermore, FBXL19 overexpression attenuates lung inflammation and injury in experimental models of LPS exposure, bacterial infection, and sepsis. FBXL19 exhibits anti-inflammatory property and regulates cytoskeletal organization by targeting multiple substrates, including IL-33R (ST2L/IL1RL1), CBP, FOXM1, NF-κB p65, and Rho GTPases. In this review, we outline recent advances in FBXL19 research, highlighting its critical role in regulating inflammatory responses within the lungs. This review also highlights current knowledge gaps and future research directions, including the potential therapeutic applications of FBXL19 in inflammatory lung diseases, which require further preclinical and clinical validation.

Keywords: Ubiquitination; Ubiquitin E3 ligase; Lung inflammation; ISGylation; Signal transduction

1. Introduction

Inflammatory lung diseases encompass a group of pulmonary disorders characterized by excessive cytokine production, inflammatory cell infiltration into the lungs, and the development of pulmonary edema [1,2]. The pulmonary epithelial and endothelial barriers constitute the first line of defense against inhaled pathogens or circulating toxins, limiting their penetration into the lung interstitium [3,4]. In addition to serving as physical barriers, pulmonary structural cells actively contribute to immune responses through the production and release of pro-inflammatory cytokines, including interleukin (IL)-6, IL-8, IL-1β, and TNFα, as well as alarmins such as IL-33, thymic stromal lymphopoietin (TSLP), and IL-25 [5–8]. The

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molecular regulation of cytokine and alarmin production, their downstream signaling pathways, and their effects on immune responses and lung dysfunction have been extensively investigated. Recent studies have been focused on the role of protein ubiquitination in the regulation of immune responses [9–16].

Protein ubiquitination is a critical post-translational modification that regulates diverse cellular processes, including protein degradation, intracellular translocation, and enzymatic activity. This process is mediated through a three-step enzymatic cascade involving E1 enzyme-mediated ubiquitin activation, E2 enzyme-mediated ubiquitin conjugation, and E3 ligase-mediated ubiquitin ligation to substrate proteins [17,18]. F-box proteins function as substrate-recognition components of SCF E3 ubiquitin ligase complexes. The F-box domain mediates interaction with SKP1, while the RING-finger protein RBX1 facilitates ubiquitin transfer to target substrates. Based on their C-terminal domains, F-box proteins are classified into three subfamilies: FBXL (leucin rich repeats, LRRs), FBXW (WD40 repeats), and FBXO (other) families [19,20]. *FBXL19* was originally identified as a human gene using bioinformatics and computational biology-based *in silico* analyses [21]. Subsequent genetic studies demonstrated that SNPs within the *FBXL19* locus are associated with susceptibility to psoriasis and psoriatic arthritis [22–25]. Zhao and colleagues showed that FBXL19 forms an SCF E3 ubiquitin ligase complex with Cullin-1, which promotes IL-33 receptor ubiquitination and degradation, thereby limiting pulmonary inflammation [26]. Since this initial discovery, multiple additional FBXL19 substrates have been identified, expanding the biological roles of FBXL19 in cell migration, gene regulation, and immune responses [26–37]. Furthermore, FBXL19 has been shown to possess E3 ligase activity in the ISGylation system [32]. Beyond regulating protein stability and enzymatic activity, FBXL19 has been implicated in the regulation of DNA methylation [38–40], a function that may be independent of its E3 ligase activity. However, its role in DNA methylation during the pathogenesis of lung inflammatory diseases has not been reported.

This review provides a comprehensive overview of FBXL19 research, encompassing its discovery, the identification and functional characterization of FBXL19 substrates, and the molecular regulation of FBXL19. Given that the majority of FBXL19 studies have been conducted in lung epithelial and endothelial cells, particular emphasis is placed on the role of FBXL19 in the pathogenesis of acute inflammatory lung diseases. Finally, we highlight current knowledge gaps and discuss future research directions for investigating the biological and pathological functions of FBXL19.

2. Discovery of *FBXL19* Gene and Structure of FBXL19 Protein

The CXXC family proteins are characterized by a conserved zinc-finger domain that recognizes unmethylated CpG islands and contributes to the regulation of gene expression [41,42]. Through bioinformatics-based analyses, Katoh and Katoh identified FBXL19 as a member of the CXXC family [19]. The *FBXL19* gene is located on chromosome 16p11.2 and encodes a 675-amino-acid protein that shares 97.5% sequence identity with its murine ortholog. FBXL19 contains an F-box domain that mediates interaction with SKP1 and multiple leucine-rich repeat (LRR) domains involved in substrate recognition. Unlike most F-box proteins, FBXL19 also possesses an extended N-terminal region containing a nuclear localization signal (NLS), a CXXC-type zinc-finger domain, and a plant homeodomain (PHD) motif. While the CXXC domain contributes to chromatin-associated gene regulation, the specific function of the PHD motif in FBXL19 remains poorly understood (Figure 1). These structural features suggest that FBXL19 may regulate both protein ubiquitination and chromatin-associated processes. Immunofluorescence analyses have shown that FBXL19 is primarily localized in the nucleus, with lower but detectable expression in the cytoplasm and at the plasma membrane [26,30]. The broad cellular distribution of FBXL19 suggests that it may mediate diverse biological processes.

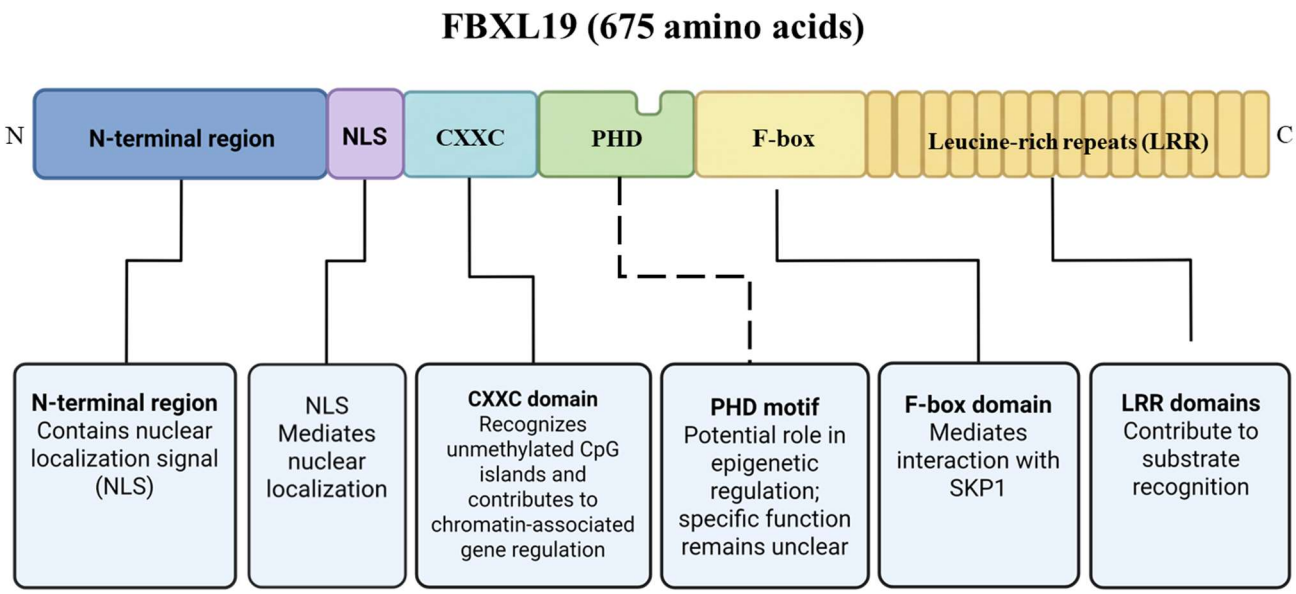


Figure 1. Domain architecture and proposed functions of the FBXL19 protein. The schematic illustrates the domain structure of FBXL19, including an extended N-terminal region, NLS, CXXC-type zinc-finger domain, PHD motif, F-box domain, and LRR domains. The CXXC domain recognizes unmethylated CpG islands and contributes to chromatin-associated gene regulation, whereas the specific function of the PHD motif in FBXL19 remains unclear. The F-box domain mediates interaction with SKP1, while the LRR domains contribute to substrate recognition within the SCF E3 ubiquitin ligase complex (The schematic is not drawn to scale). The figure is created by using BioRender.com.

3. SNPs with *FBXL19* in Allergic Diseases

SNPs are widespread genetic variants distributed throughout the human genome among individuals. Although most SNPs are phenotypically silent and have no effect on health, specific variants can modulate gene expression or alter protein structure and function, thereby affecting an individual's disease risk [43–45]. The first indication that *FBXL19* may contribute to human disease was reported in 2010 by Stuart et al. [22]. Analyzing 4064 psoriasis cases and 4685 controls from multiple international cohorts, the investigators identified rs10782001 within the *FBXL19* locus as a susceptibility variant associated with psoriasis and psoriatic arthritis, providing the first genetic evidence implicating *FBXL19* in human diseases [22]. Furthermore, Assarsson et al. demonstrated that patients with psoriasis carrying three SNPs within *FBXL19* (rs12924903, rs10782001, rs12445568) exhibit a positive correlation between Streptococcus genus abundance and psoriasis severity [25]. More importantly, the polymorphism rs10782001 in *FBXL19* has also been implicated in paradoxical skin reactions induced by anti-TNFα therapy in patients with psoriasis [24], suggesting a potential role for *FBXL19* in modulating therapeutic responses (Figure 2). These studies demonstrate an association between genetic variants within the *FBXL19* locus, psoriasis, and psoriatic arthritis. However, no direct evidence has established an association between *FBXL19* polymorphisms and asthma or other allergic lung diseases. Therefore, the potential role of *FBXL19* genetic variants in these diseases remains unclear.

Asthma is a chronic inflammatory airway disease associated with allergy. Multiple meta-analyses and systematic reviews indicated a positive association between psoriasis and asthma [46,47]. FBXL19 protein has been shown to regulate IL-33 signaling [26] and modulate CREB-binding protein (CBP) ubiquitination [37], which play critical roles in the pathogenesis of asthma.

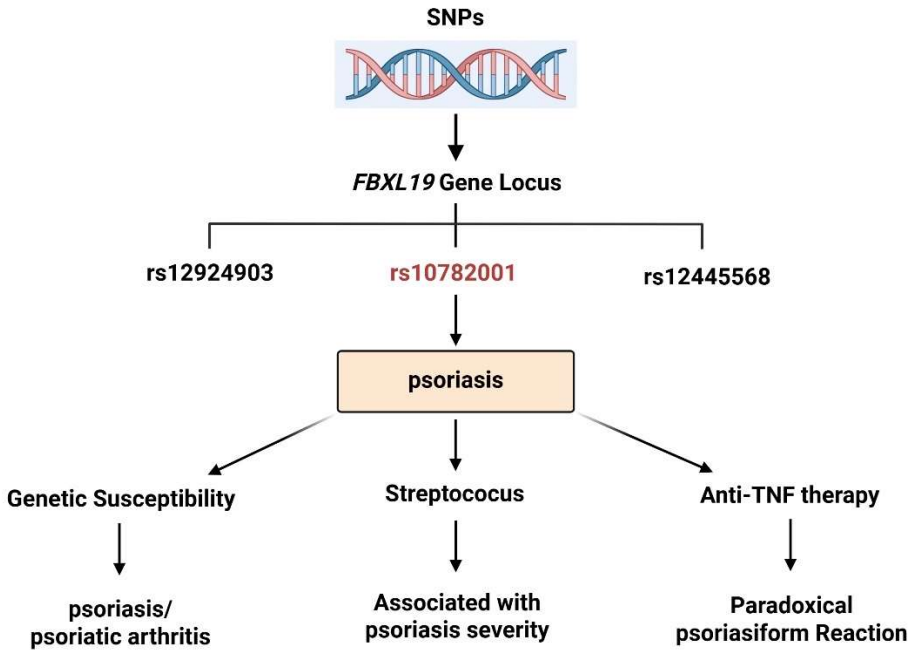


Figure 2. Association of SNPs in the *FBXL19* gene locus with psoriasis. The schematic shows three SNPs (rs12924903, rs10782001, and rs12445568) located within the *FBXL19* gene locus. Among these variants, rs10782001 is highlighted because of its reported association with psoriasis. The figure is created with BioRender.com.

4. FBXL19 Regulates Lung Inflammation

4.1. FBXL19 Regulates Inflammatory Signaling Pathways

Although the *FBXL19* gene has been associated with human disorders through its SNPs, the biological function of FBXL19 remains unclear until Zhao and colleagues showed that it functions as a component of the SCF E3 ligase complex and plays a critical role in limiting IL-33 signaling [26]. IL-33 is an alarmin cytokine released from damaged or necrotic cells that activates inflammatory signaling by binding to its membrane-bound receptor ST2L, encoded by the interleukin-1 receptor-like 1 (*IL1RL1*) gene [48,49]. ST2 also exists in a soluble form (sST2), which acts as a decoy receptor for IL-33. To identify the E3 ligase responsible for ubiquitination and degradation of IL-33R, the authors screened a panel of F-box proteins by overexpression in lung epithelial cells and found that FBXL19 targeted IL-33R, thereby promoting its ubiquitination and subsequent degradation [26]. In human lung endothelial cells, overexpression of FBXL19 attenuated IL-33-induced apoptosis, cytokine release (IL-8 and IL-6), and endothelial hyperpermeability, suggesting an anti-inflammatory role for FBXL19 in the lungs [26]. Moreover, in mouse models of acute lung injury, pulmonary overexpression of FBXL19 reduced lipopolysaccharide (LPS) and *Pseudomonas aeruginosa* strain PA103-induced lung inflammation, as indicated by reduced inflammatory cell infiltration, cytokines level, and lung tissue injury [26], further supporting its protective function in inflammatory lung diseases.

In addition to targeting IL-33R, FBXL19 has been shown to regulate the ubiquitination and stability of CBP, but not p300, thereby limiting histone acetylation [37]. In mouse lung epithelial cells exposed to LPS, FBXL19 mediated CBP degradation reduced histone acetylation and inflammatory cytokine production. Moreover, FBXL19 overexpression attenuated lung inflammation in a mouse model of cecal ligation and puncture (CLP)-induced sepsis [37]. Similar protective effects were reported by Chen et al. in immature mice infected with *Streptococcus pneumoniae*, a Gram-positive bacterium [36]. FBXL19 overexpression reduced lung injury, inflammatory cytokine production, and pulmonary edema [36]. Mechanistically, the authors showed that FBXL19 targets FOXM1, a transcription factor that promotes NF-κB activation and

pro-inflammatory responses, for its ubiquitination and degradation, while FOXM1 overexpression reverses the protective effect of FBXL19 [36]. Beyond its function as an E3 ubiquitin ligase, FBXL19 also acts as an E3 ligase in the ISGylation system [32]. ISGylation is a post-translational modification characterized by the covalent conjugation of ISG15, a ubiquitin-like protein, to substrate proteins [50,51]. Li et al. demonstrated that FBXL19 acts as an ISG15 E3 ligase and promotes NF-κB p65 ISGylation in endothelial cells [32]. In response to inflammatory stimuli, including LPS, TNF-α reduced p65 ISGylation was associated with increased p65 phosphorylation and endothelial inflammation. FBXL19 depletion increased these inflammatory responses, whereas endothelial specific FBXL19 overexpression in transgenic mice reduced acute lung injury [32]. Together, these findings showed that FBXL19 regulates multiple inflammatory pathways through IL-33R, CBP, FOXM1, and NF-κB p65 [26,32,36,37]. In addition to its anti-inflammatory effects, FBXL19 has been shown to regulate antiviral immune responses. Xia et al. demonstrated that endothelial-specific FBXL19 overexpression enhanced interferon signaling and reduced viral levels, cardiac inflammation, and cellular senescence in influenza A virus-infected mice [33]. These findings suggest that FBXL19 may play an important role in endothelial antiviral immunity and host defense during viral infection.

Although most studies suggest that FBXL19 has anti-inflammatory effects, its role may vary depending on the cellular context and target proteins. Li et al. demonstrated that FBXL19 promotes STK11 ubiquitination and degradation through the ubiquitin-proteasome pathway in airway epithelial cells [34]. STK11 overexpression attenuated cigarette smoke extract (CSE)-induced cytotoxicity, whereas STK11 knockdown increased cell injury. Furthermore, lung tissues from smokers with COPD showed reduced STK11 protein expression compared with smokers without COPD. These findings suggest that FBXL19-mediated STK11 degradation may contribute to cigarette smoke-induced airway epithelial injury. However, further studies using FBXL19 gain- and loss-of-function approaches are needed to determine its role in COPD development and progression.

4.2. FBXL19 Regulates Rho GTPases and Cytoskeletal Organization

The Rho family of GTPases comprises a group of small G proteins that belong to the Ras superfamily [52,53]. Among its members, RhoA, Rac1, and Cdc42 are the most extensively studied and have been implicated in a wide variety of cellular processes, including cytoskeletal organization, cell migration, proliferation, and the regulation of cell-cell junctions. Rho GTPase activity is regulated by a molecular switching mechanism in which these proteins alternate between a GTP-bound active state and a GDP-bound inactive state. In addition to the canonical GDP/GTP cycling, ubiquitination also plays an important role in controlling Rho GTPase stability [52,53]. The E3 ubiquitin ligases, HACE1, and members of the inhibitor of apoptosis protein (IAPs) have been shown to selectively target the active, GTP-bound form of Rac1 for ubiquitination and degradation [54,55]. In contrast, FBXL19 has been reported to promote ubiquitination of both the active and inactive forms of Rac1 [28]. Mechanistically, HACE1- and IAPs-mediated ubiquitination occurs at lysine residue 147 of Rac1 [54,55], whereas FBXL19 targets lysine 166 [28]. Wei et al. [37] showed that phosphorylation at serine 71 by AKT facilitates FBXL19-mediated Rac1 ubiquitination and degradation. However, whether this serine phosphorylation is also required for the HACE1- and IAPs-mediated Rac1 degradation remains unclear. Moreover, the molecular basis for the ability of FBXL19 to target both active and inactive Rac1, in contrast to other E3 ligases that preferentially degrade the active form, has yet to be elucidated. One possible explanation is that ubiquitination at distinct lysine residues differentially affects Rac1 conformation, thereby influencing its susceptibility to degradation by specific E3 ligases.

Among these three E3 ubiquitin ligases, HACE1 exhibits the highest degree of substrate specificity, targeting only active Rac1 and no other Rho GTPase members. In contrast, IAPs induce both Rac1 and Cdc42 ubiquitination and degradation [55,56]. FBXL19 appears to possess broader substrate specificity,

functioning as an E3 ubiquitin ligase for multiple Rho GTPases, including Rac1, RhoA, Rac3, and Cdc42 [27–30]. Similar to its regulation of Rac1, FBXL19 targets both the active and inactive forms of RhoA for ubiquitination and degradation [27]. Given the well-established roles of Rho GTPases in regulating cytoskeletal organization, cell migration, and proliferation, FBXL19 overexpression has been shown to suppress cell migration, proliferation, filopodia formation, and cell adhesion in lung epithelial cells [27–30]. In the context of endothelial barrier regulation, individual Rho GTPases exert distinct and often opposing effects. For example, RhoA activation promotes cell contraction and increases endothelial cell permeability [57,58], whereas Rac1 activation enhances the barrier integrity [59,60]. Consequently, Rac1 and RhoA function in a dynamic antagonistic balance to maintain endothelial barrier homeostasis. Given that FBXL19 targets both RhoA and Rac1, an important question is how FBXL19 influences endothelial barrier function. FBXL19-mediated RhoA degradation may protect endothelial barrier integrity, whereas Rac1 degradation could have the opposite effect. However, these potential effects require further investigation, as the role of FBXL19 may depend on the cell type and physiological conditions. Notably, FBXL19 overexpression in human pulmonary endothelial cells did not affect basal barrier integrity under resting conditions but significantly attenuated IL-33-induced hyperpermeability [26], suggesting that FBXL19 preferentially modulates pathological rather than physiological barrier responses. These *in vitro* findings are further supported by multiple *in vivo* studies in murine models of acute lung injury. Overexpression of FBXL19, achieved through a lentiviral gene delivery system or endothelial cell-specific transgenic expression, has been shown to protect against pulmonary edema induced by LPS, PA103, *Streptococcus pneumoniae*, and CLP [26,32,36].

Rho GTPase members exhibit substantial sequence and domain conservation, sharing approximately 40% to 95% amino acid identity. This high degree of homology suggests the presence of a conserved structural docking site for FBXL19 in RhoA, Rac1, Rac3, and Cdc42. To date, however, the docking site has not been mapped (Figure 3). Notably, phosphorylation is required for FBXL19-mediated ubiquitination and degradation of RhoA and Rac1, suggesting that phosphorylation may either create a recognition motif or induce conformational changes that facilitate FBXL19 binding.

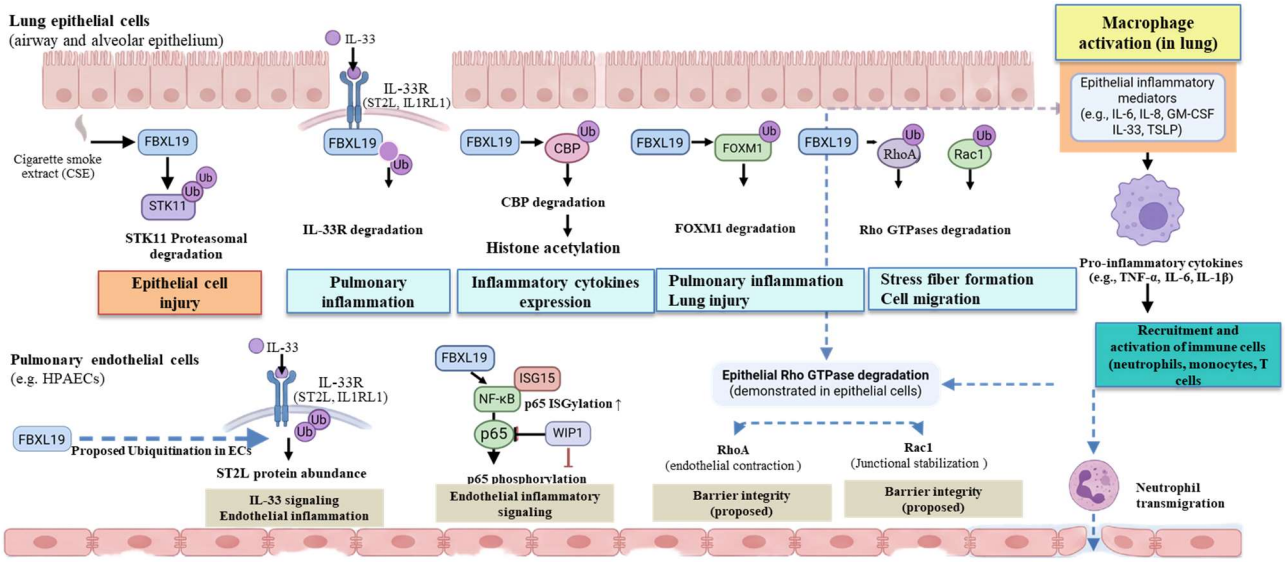


Figure 3. Schematic representation of FBXL19-mediated regulatory pathways in pulmonary epithelial and endothelial cells during lung inflammation and injury. In epithelial cells, FBXL19 promotes STK11 degradation, contributing to epithelial injury, while targeting IL-33R, CBP, and FOXM1 to reduced inflammation. It also regulates stress fiber formation and cell migration through RhoA and Rac1 degradation. In endothelial cells, FBXL19 attenuates IL-33 induced and promotes NF-κB p65 ISGylation. Solid arrows indicate reported mechanisms, whereas dashed arrows represent proposed interactions (Figure is created with BioRender.com)

4.3. Molecular Regulation of FBXL19

Although the protective role of FBXL19 in lung inflammatory diseases has been extensively investigated, the molecular mechanisms regulating FBXL19 remain poorly understood. Reduced FBXL19 expression has been observed in the lungs of *Streptococcus pneumonia*-infected mice [36]. However, the mechanisms underlying this reduction during lung inflammation have not been investigated. Wei et al. demonstrated that FBXL19 is an unstable protein, and its degradation is mediated by the ubiquitin-proteasome pathway [30]. Although CBP was previously identified as a substrate of FBXL19, Wei et al. further revealed that FBXL19 itself is also a substrate of CBP [30]. Specifically, CBP acetylates FBXL19 at lysine 141, and this acetylation enhances FBXL19 stability [30]. Furthermore, FBXW17 was identified as the E3 ubiquitin ligase responsible for FBXL19 ubiquitination and degradation [61]. However, whether CBP and FBXW17 contribute to the regulation of FBXL19 levels in *Streptococcus pneumonia*-infected lungs remains unknown. Notably, the *FBXW17* gene has not been identified in humans. Therefore, the E3 ligase responsible for FBXL19 ubiquitination and degradation in human cells remains to be determined.

Gene expression is regulated at multiple levels, including transcription and mRNA stability. MicroRNAs (miRNAs) are a group of non-coding RNAs, typically 21–23 nucleotides in length, that regulate gene expression by modulating mRNA stability and translation [62,63]. miR-26 and miR-532-3p have been shown to repress FBXL19 expression in adipocyte progenitor cells and glioma cells, respectively [64,65]. However, whether these miRNAs regulate FBXL19 expression in inflammatory lung diseases has not yet been investigated.

5. Current Knowledge Gaps and Future Research Directions

FBXL19 is a substrate recognition component of the SCF^FBXL19 E3 ligase complex. Previous studies have shown that genetic variants within the *FBXL19* locus are associated with psoriasis and psoriatic arthritis [22–25]. However, their association with asthma and other allergic lung diseases has not yet been established. Interestingly, several studies have reported a link between psoriasis and asthma [46,47], suggesting that *FBXL19* genetic variants might also be involved in asthma susceptibility. However, further GWAS and functional studies are needed to investigate this possible association and better understand the role of *FBXL19* genetic variants in allergic lung diseases.

FBXL19 targets a diverse range of substrates involved in inflammatory signaling, transcriptional regulation, and cytoskeletal organization. Future protein-protein interaction/proteomics analyses may uncover additional FBXL19 substrates in lung epithelial, endothelial, and immune cells. Identification of these novel substrates will expand our understanding of the biological functions of FBXL19 in lung homeostasis and disease. Based on the currently identified substrates, artificial intelligence (AI)-assisted protein interaction analyses may help to identify conserved amino acid motifs that mediate FBXL19-substrates recognition. Characterization of the FBXL19 docking site within specific substrates could facilitate the development of substrate-targeting linkers that selectively recruit FBXL19 to proteins of interest, thereby promoting their ubiquitination and degradation. Such a PROTAC-like strategy may minimize the potential adverse effects associated with the multi-substrates of FBXL19. In addition to its role as an E3 ligase component, FBXL19 has been shown to modulate epigenetic processes independently of its E3 ligase activity. The molecular mechanisms underlying FBXL19 regulates DNA methylation remain poorly understood. Future studies should investigate the contribution of FBXL19-mediated epigenetic regulation to the pathogenesis of lung inflammatory diseases, and determine whether these mechanisms represent viable therapeutic targets.

From a translational perspective, the potential clinical relevance of FBXL19 genetic variants in chronic respiratory diseases requires further investigation. Future large-scale GWAS, followed by validation in independent patient cohorts, are needed to determine whether *FBXL19* polymorphisms are associated with

asthma, COPD, and other chronic lung diseases. Additionally, examining FBXL19 expression and activity in patient samples and evaluating their association with disease severity and clinical outcomes may help establish its potential as a biomarker. However, the predictive value of FBXL19 has not yet been clinically established.

Author Contributions

N.S. and J.Z. conducted the literature search and drafted the original manuscript. N.S., J.Z. and C.K. contributed to reviewing and revising the manuscript. All authors read and approved the final version of the manuscript. J.Z. supervised the project and finalized manuscript.

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Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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