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Knockdown of STAU1 inhibits inflammation and autophagy in *in vitro* chronic obstructive pulmonary disease model by regulating AMPK-mTOR signaling pathway

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Abstract
Chronic obstructive pulmonary disease (COPD) is characterized by chronic inflammation, airway obstruction, and lung damage, often triggered by cigarette smoke. Dysregulated autophagy and inflammation are key contributors to its progression. Although double-stranded RNA-binding protein Staufen homolog 1 (STAU1), a multifunctional protein primarily involved in mRNA transport and localization, is identified as a potential biomarker, its role in COPD pathogenesis remains unclear. This study investigates the effects of STAU1 knockdown on inflammation and autophagy in an *in vitro* COPD model. We found that STAU1 expression was significantly elevated in the *in vitro* COPD model. Knockdown of STAU1 led to a marked reduction in inflammation in cigarette smoke extract (CSE)-induced non-tumorigenic human bronchial epithelial cells (BEAS-2B). Additionally, STAU1 knockdown suppressed autophagy in CSE-induced BEAS-2B cells. Mechanistically, it inhibited the activation of the adenosine monophosphate-activated protein kinase–mechanistic target of rapamycin (AMPK/mTOR) pathway. In summary, STAU1 knockdown inhibits inflammation and autophagy by modulating the AMPK/mTOR axis. Targeting STAU1 could provide new avenues for the treatment of COPD.
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Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent and life-threatening respiratory condition characterized by persistent airway obstruction, chronic inflammation, and progressive deterioration of lung tissue.[1] As one of the leading causes of global deaths, COPD presents a significant global health burden, particularly in aging populations, where morbidity and mortality rates are alarmingly high. Exposure to cigarette smoke is recognized as a major contributing factor to the development of COPD, triggering a cascade of pathological processes that affect the respiratory system.[2] Among these, enhanced inflammation, oxidative stress, and apoptosis have been documented widely. Additionally, recent findings highlight that autophagy, a key cellular process responsible for degrading and recycling damaged components, is dysregulated in COPD.[3] While autophagy typically serves a protective role in maintaining cellular homeostasis, excessive activation of autophagic pathways can lead to autophagic cell death, contributing to the destruction of lung tissue and the development of emphysema, a characteristic feature of advanced COPD.

The staufen double-stranded RNA binding protein 1 (STAU1), a multifunctional protein primarily involved in mRNA transport and localization, has recently emerged as a potential biomarker in COPD.[4] It has been implicated in various cellular processes, including autophagy and stress responses. Previous studies linked STAU1 to neurodegenerative diseases, where its overexpression was shown to disrupt autophagy and regulate the mechanistic target of rapamycin (mTOR), which plays a critical role in cellular growth and survival.[5-7] Despite these insights, the specific role of STAU1 in COPD remains largely uncharted.

Autophagy, a cellular process responsible for the degradation and recycling of damaged cellular components, plays a critical role in maintaining cellular homeostasis.[5-7] However, in the context of COPD, dysregulated autophagy contributes to the destruction of lung tissue, promoting the progression of emphysema and airway remodeling. Excessive autophagy leads to autophagic cell death, further aggravating COPD pathology.[5-7] Recent studies have suggested a connection between STAU1 and the regulation of autophagy in neurodegenerative diseases, where its overexpression disrupted normal autophagic processes.[5-7] In our COPD model, the elevated levels of STAU1 specifically correlated with increased autophagic activity, suggesting that STAU1 can play a direct role in modulating autophagy, rather than other cellular activities.

Among the pathways known to influence progression of COPD, the adenosine monophosphate-activated protein kinase (AMPK)–mTOR pathway is studied extensively. The AMPK/mTOR axis is crucial for regulating cellular energy metabolism, autophagy, and inflammation, processes that are central to COPD development.[8] Dysregulation of this axis is associated with increased inflammation and aberrant autophagy in COPD, making it a key focus of research.[9] Given the potential involvement of STAU1 in autophagy and mTOR signaling, investigating its role in the AMPK/mTOR pathway could yield important insights into the molecular mechanisms underlying COPD.

The purpose of this study was to investigate the role of STAU1 in COPD pathogenesis, particularly in relation to its effects on inflammation and autophagy. Understanding these mechanisms can open up opportunities to target STAU1 as a novel intervention for managing the complex progression of COPD.

Materials and Methods

Cell Culture

Non-tumorigenic human bronchial epithelial cells (BEAS-2B) were purchased and cultured in Dulbecco's Modified Eagle Medium (DMEM)/nutrient mixture F-12 medium (11320033; Gibco, Miami, FL, USA), supplemented with 10% fetal bovine serum (10099141; Gibco) and 1% penicillin–streptomycin (15140122; Gibco). Cells were maintained in a humidified incubator at 37°C with 5% CO_2.

Cigarette Smoke Extract (CSE) Treatment

Cigarette smoke extract was prepared by bubbling smoke from two commercially available cigarettes through 10 mL of culture medium at a flow rate of 5 mL/min. The medium was filtered through a 0.22-μm filter and diluted to 5% before use. BEAS-2B cells were exposed to CSE for 24 h to induce a COPD-like model.The flow rate and exposure time of CSE were determined based on previous studies that optimized these parameters for inducing COPD-like conditions *in vitro*, using a flow rate of 5 mL/min for 10 min to generate a 5% CSE solution. The successful establishment of the *in vitro* COPD model was confirmed by elevated levels of pro-inflammatory cytokines (tumor necrosis factor-α [TNF-α], interleukin 6 [IL-6], and IL-1β) and increased autophagic activity, consistent with key pathological features of COPD. BEAS-2B cells were cultured for 48 h after CSE treatment, and STAU1 expression was detected at this time point using immunoblot analysis.

Small interfering RNA (siRNA) transfection

Small interfering RNAs targeting STAU1 and negative control siRNA (si-NC) were purchased from RiboBio (si-STAU1: 123456; si-NC: 789012). Transfection was performed using Lipofectamine 2000 (11668019; Invitrogen, Carlsbad, CA, USA). BEAS-2B cells were transfected with 50-nM siRNA and incubated for 48 h before further analysis.

Immunoblot

Samples were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene fluoride (PVDF) membranes (IPVH00010; Millipore, MA, USA). Membranes were blocked in 5% non-fat milk for 1 h and incubated overnight at 4°C with primary antibodies: STAU1 (ab123456, 1:1000; Abcam, Cambridge, UK), LC3B (ab51520, 1:1000; Abcam), phosphorylated(p)-AMPK (ab133448, 1:1000; Abcam),

phosphor(p)-mTOR (ab109268, 1:1000; Abcam), and glyceraldehyde 3-phosphate dehydrogenase (GAPDH, AF0006, 1:5000; Beyotime, Shanghai, China). After washing, membranes were incubated with horseradish peroxidase (HRP)-conjugated secondary antibodies (A0208, 1:5000; Beyotime) for 1 h at room temperature. Blots were visualized using an enhanced chemiluminescence (ECL) detection system (P0018S; Beyotime), and quantification was performed using the ImageJ software.

Immunofluorescence

BEAS-2B cells were fixed with 4% paraformaldehyde (P0099; Beyotime) for 15 min, permeabilized with 0.1% Triton X-100, and blocked with 5% bovine serum albumin (BSA, ST023; Beyotime) for 30 min. Cells were incubated with LC3B primary antibody (ab48394, 1:200; Abcam) overnight at 4°C, followed by incubation with Alexa Fluor 488-conjugated secondary antibody (A-11008, 1:1000; Invitrogen) for 1 h. Images were captured using a Zeiss fluorescence microscope, and LC3B puncta were quantified using ImageJ.

Enzyme-linked-immunosorbent serologic assay (ELISA)

The levels of inflammatory cytokines (TNF-α, IL-6, and IL-1β) in cell culture supernatants were measured using ELISA kits (PT512, PI330, and PI305; Beyotime) according to the manufacturer's protocols. Absorbance was read at 450 nm using a microplate reader.

Cell viability assay

Cell viability was assessed using the cell counting kit-8 (CCK-8) assay (C0038; Beyotime). BEAS-2B cells were seeded in 96-well plates and treated as indicated. After treatment, 10 μL of CCK-8 solution was added to each well and incubated for 2 h. Absorbance was measured at 450 nm using a microplate reader.

Statistical analysis

Data were presented as mean ± SD from at least three independent experiments. Statistical analyses were performed using the GraphPad Prism 8.0 software. Group differences were analyzed using one-way ANOVA, followed by Tukey's *post hoc* test; $P < 0.05$ was considered statistically significant.

Results

STAU1 expression was significantly elevated in the in vitro *COPD model*

To investigate whether STAU1 expression is altered in a COPD model, BEAS-2B cells were treated with CSE.

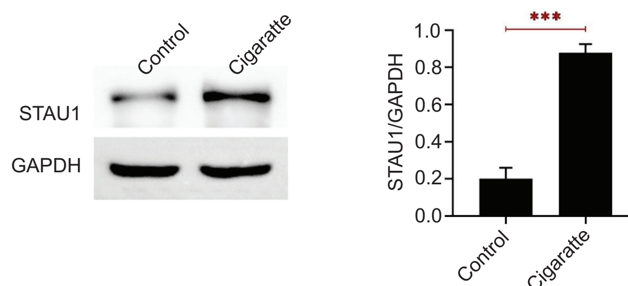

Figure 1 STAU1 expression is significantly elevated in the *in vitro* COPD model. Immunoblot analysis of STAU1 expression in control and cigarette smoke extract (CSE)-treated BEAS-2B cells. Quantification of STAU1 expression relative to GAPDH. Data are expressed as mean ± SD. $^{***}P < 0.001$ versus control.

As shown in Figure 1, immunoblot analysis revealed that STAU1 expression was significantly upregulated in cigarette smoke-treated cells, compared to control BEAS-2B cells. This suggests that STAU1 is upregulated and may play a role in cigarette smoke-induced inflammation and progression of COPD.

Knockdown of STAU1 led to a marked reduction in inflammation in cigarette smoke extract-induced BEAS-2B cells

To determine the role of STAU1 in cigarette smoke-induced inflammation, immunoblot analysis confirmed efficient knockdown of STAU1 in si-STAU1-transfected cells, compared to negative control siRNA (si-NC) cells (Figure 2A). Cell viability, assessed using the CCK-8 assay, was significantly reduced in cigarette smoke-treated cells but improved upon STAU1 knockdown (Figure 2B). Furthermore, STAU1 knockdown significantly reduced the secretion of inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, in the cigarette smoke-exposed BEAS-2B cells (Figure 2C). These results indicate that STAU1 contributes to cigarette smoke-induced inflammation, and its knockdown alleviates the inflammatory response.

STAU1 knockdown suppressed autophagy in cigarette smoke extract-induced BEAS-2B cells

Next, we assessed the effect of STAU1 on autophagy, a process involved in COPD pathogenesis. CSE increased autophagy in BEAS-2B cells, as evidenced by elevated LC3-II-LC3-I ratios and reduced P62 levels (Figure 3A). Knockdown of STAU1 significantly reversed these effects, reducing autophagy LC3-II-LC3-I ratios and restoring P62 levels (Figure 3A). Immunofluorescence staining for LC3B further confirmed these findings, showing a decrease in LC3B-positive autophagosomes in si-STAU1-transfected cells, compared to si-NC-transfected cigarette smoke-treated cells (Figure 3B). These results demonstrate that STAU1 knockdown inhibits autophagy in CSE-induced BEAS-2B cells.

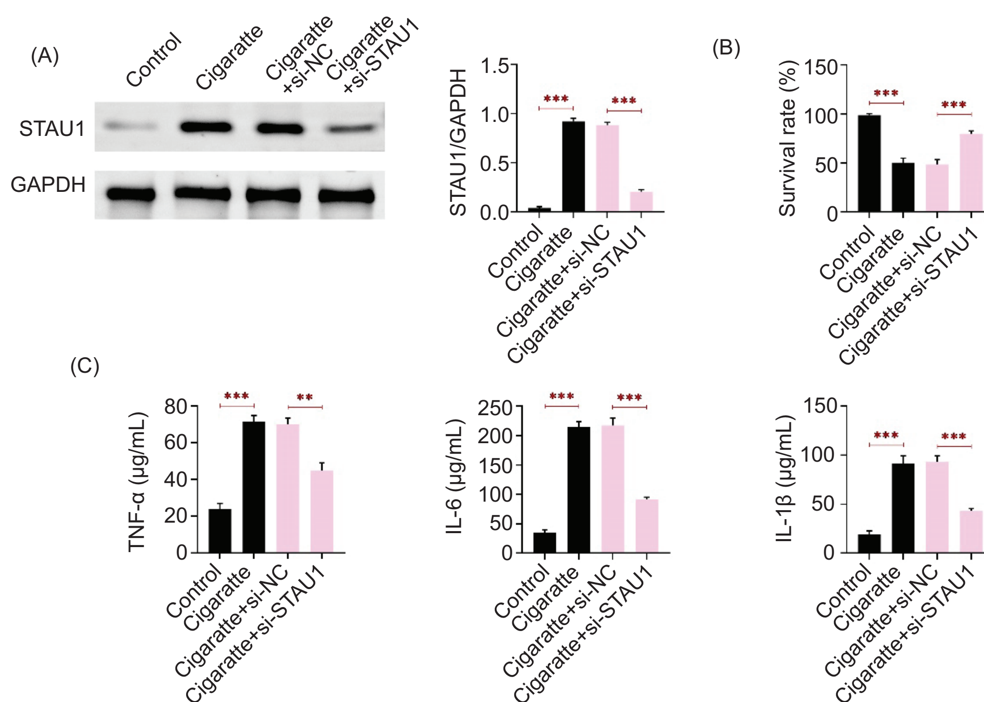

Figure 2 Knockdown of STAU1 leads to a marked reduction in inflammation in smoke extract-induced BEAS-2B cells. (A) Immunoblot analysis is performed to assess the expression levels of STAU1 and GAPDH in BEAS-2B cells treated with control, cigarette smoke extract (CSE), CSE+si-NC, or CSE+si-STAU1. Quantification of STAU1 expression is shown on the right. (B) CCK-8 assay is used to evaluate the survival rate of BEAS-2B cells under different treatment conditions: control, CSE, CSE+si-NC, and CSE+si-STAU1. (C) ELISA is employed to measure the levels of inflammatory cytokines TNF-α, IL-6, and IL-1β in the BEAS-2B cells across the same four treatment groups: control, CSE, CSE+si-NC, and CSE+si-STAU1. Data are expressed as mean ± SD. **$P < 0.01$, ***$P < 0.001$.

STAU1 inhibited the activation of the AMPK/mTOR pathway in cigarette smoke extract-induced BEAS-2B cells

To elucidate the molecular mechanisms through which STAU1 regulates inflammation and autophagy, we analyzed the effects of STAU1 depletion the AMPK/mTOR axis in CSE-induced BEAS-2B cells. CSE treatment led to the activation of AMPK/mTOR, as indicated by increased phosphorylated(p)-mTOR levels, and p-AMPK levels (Figure 4). Knockdown of STAU1 reversed these effects, resulting in decreased AMPK and mTOR phosphorylation (Figure 4). These findings suggest that STAU1 modulates the AMPK/mTOR axis, promoting autophagy and inflammation in COPD. Therefore, STAU1 inhibited the activation of the AMPK/mTOR pathway in CSE-induced BEAS-2B cells.

Discussion

Chronic obstructive pulmonary disease is a progressive and life-threatening respiratory condition characterized by chronic inflammation, airway obstruction, and tissue remodeling.[10] The pathogenesis of COPD involves a complex interplay of cellular processes, such as inflammation, oxidative stress, and autophagy dysregulation. Inflammatory responses and excessive autophagy are key drivers of COPD progression, contributing to lung tissue damage and the development of emphysema.[11] These pathological mechanisms highlight the importance of identifying critical proteins and signaling pathways involved in the regulation of inflammation and autophagy, as they may offer novel therapeutic targets for COPD management.[12] In this context, our study investigates the role of STAU1 in modulating these processes, particularly through the AMPK/mTOR signaling pathway, offering new insights into COPD pathogenesis and potential treatment strategies.[13]

The BEAS-2B cell COPD model, induced by exposure to CSE, serves as a reliable *in vitro* model for studying COPD mechanisms. Human bronchial epithelial cells play a crucial role in the lung's inflammatory response and are directly impacted by exposure to cigarette smoke.[14] By using this model, we can closely mimic the inflammatory and autophagic responses observed in COPD. The need to intervene in the COPD model, specifically in the context of inflammation, is critical for exploring potential therapeutic approaches. In our study, we observed that knocking down STAU1 in BEAS-2B cells led to a significant reduction in inflammation, demonstrating the relevance of targeting inflammation in COPD and suggesting that modulating STAU1 could have therapeutic benefits.

STAU1 is a multifunctional protein primarily involved in mRNA transport and localization.[15,16] It has been implicated in various cellular processes, such as autophagy, stress

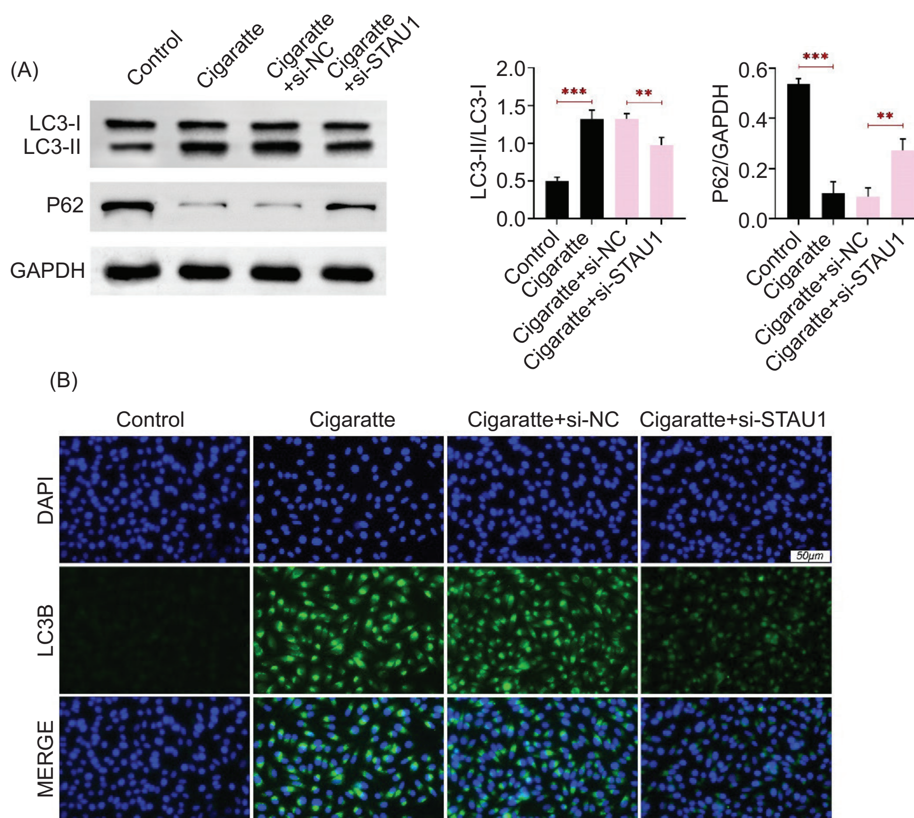

Figure 3 STAU1 knockdown suppresses autophagy in smoke extract-induced BEAS-2B cells. (A) Immunoblot analysis is conducted to assess the expression levels of autophagy-related proteins LC3-I, LC3-II, P62, and GAPDH in BEAS-2B cells under control, cigarette smoke extract (CSE), CSE+si-NC, and CSE+si-STAU1 conditions. Quantification of LC3-II/LC3-I and P62/GAPDH is shown on the right. (B) Immunofluorescence staining for microtubule-associated protein 1A/1B-light chain 3 (LC3B, green) and nuclei (4',6-diamidino-2-phenylindole [DAPI], blue) is performed to observe autophagic response in BEAS-2B cells across the same four treatment groups. Scale bar: 50 μm. Data are expressed as mean ± SD. $^{**}P < 0.01$, $^{***}P < 0.001$. NC: negative control.

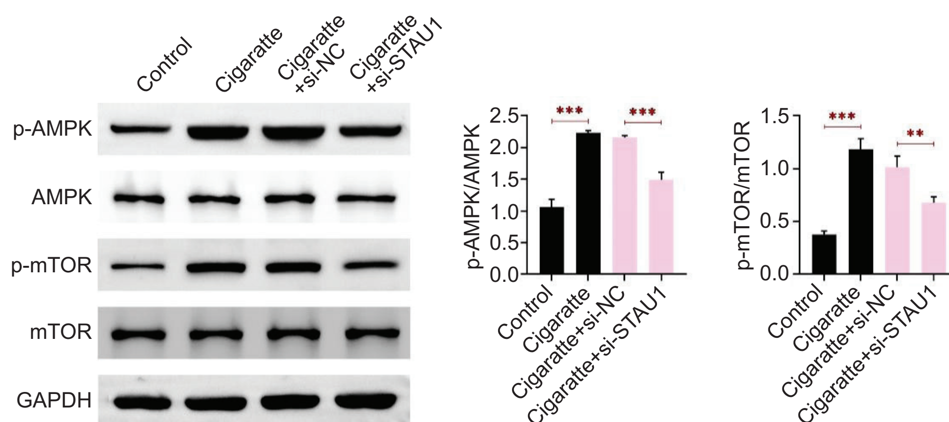

Figure 4 STAU1 inhibits the activation of the AMPK/mTOR pathway in smoke extract-induced BEAS-2B cells. Immunoblot examines the expression levels of phosphorylated AMPK (p-AMPK), total AMPK, phosphorylated mTOR (p-mTOR), total mTOR, and GAPDH in BEAS-2B cells treated under the following conditions: control, cigarette smoke extract (CSE), CSE+si-NC, and CSE+si-STAU1. Quantifications of p-AMPK/AMPK and p-mTOR/mTOR are displayed on the right. Data are expressed as mean ± SD. $^{**}P < 0.01$, $^{***}P < 0.001$.

response, and gene expression regulation. Previous studies associated STAU1 with neurodegenerative diseases, where it has been shown to disrupt autophagy and affect mTOR signaling. However, the role of STAU1 in lung diseases, particularly COPD, remains unclear. Our study reveals that knockdown of STAU1 leads to reduced inflammatory and autophagic responses in a COPD model, suggesting that STAU1 can play a critical role in regulating these cellular processes during progression of disease.

Although our current findings provide substantial evidence of STAU1's regulatory effect on the AMPK/mTOR pathway, we acknowledge that future studies using mTOR activators could offer deeper insights into the mechanistic role of STAU1 in modulating inflammation and autophagy. This approach would help further elucidate the intricate interactions between STAU1 and the AMPK/mTOR axis, particularly in the context of COPD pathogenesis.

Inflammation and autophagy are intimately linked processes, and both are central to the development of inflammatory diseases, such as COPD.[17] STAU1's involvement in autophagy regulation suggests that it may be a key modulator of cellular homeostasis in response to stressors such as cigarette smoke.[18] In our study, STAU1 knockdown not only reduced inflammation but also inhibited autophagy in BEAS-2B cells. This dual regulation of inflammation and autophagy positions STAU1 as a potential therapeutic target for managing COPD and other inflammation-driven diseases, providing a mechanistic link between these processes.

While autophagy is typically considered a protective mechanism, in the context of COPD, excessive or dysregulated autophagy can contribute to tissue damage and progression of disease. In our study, the inhibition of autophagy through STAU1 knockdown likely targets this harmful, overactive autophagic response that is exacerbated by exposure to cigarette smoke. Excessive autophagy in COPD models is shown to promote autophagic cell death, leading to lung tissue destruction. Therefore, reduction in autophagy observed in the treatment group CSE+si-STAU1 reflects the inhibition of this detrimental autophagic activity while maintaining a balance that may preserve cellular homeostasis.

The AMPK/mTOR axis is a well-established regulator of cellular energy metabolism, autophagy, and inflammation.[19] AMPK activation promotes autophagy and inhibits mTOR, a key regulator of cell growth and proliferation. In COPD, dysregulation of the AMPK/mTOR axis contributes to excessive inflammation and aberrant autophagy, exacerbating progression of disease.[20-22] Our findings demonstrate that STAU1 knockdown in BEAS-2B cells modulates this pathway, leading to increased AMPK activation and reduced mTOR activity. This suggests that STAU1 may act upstream of the AMPK/mTOR axis, influencing both autophagy and inflammation, thus offering a new perspective on the molecular mechanisms driving progression of COPD.

Despite the significant findings in our study, several limitations are addressed. First, our research is based on an *in vitro* COPD model using BEAS-2B cells, which may not fully capture the complexity of COPD *in vivo*. Additionally, while we demonstrated the regulatory role of STAU1 in inflammation and autophagy, the precise molecular mechanisms remain to be elucidated, particularly in the context of how STAU1 interacts with other key signaling molecules. Future studies should aim to validate these findings in animal models and explore the potential of STAU1 as a therapeutic target in clinical settings.

Conclusions

This study provides new insights into the role of STAU1 in COPD pathogenesis. By regulating inflammation and autophagy through the AMPK/mTOR axis, STAU1 plays a critical role in the cellular processes underlying progression of COPD.

Competing Interests

The authors stated that there was no conflict of interest to disclose.

Data Availability

The authors declare that all data supporting the findings of this study are available in the paper and any raw data can be obtained from the corresponding author upon request.

Author Contributions

Rixi Xie and Fang Wang designed the study and carried it out. Both authors supervised data collection, analyzed and interpreted the data, prepared the manuscript for publication, and reviewed the draft of the manuscript. Both authors had read and approved the final manuscript.

Conflict of Interest

None.

Funding

None.

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