

Pathological Mechanism and Targeted Drugs of COPD

Peng Guo¹, Rui Li², Tie Hua Piao³, Chun Lan Wang³, Xiao Lu Wu³, Hong Yan Cai³

¹College of Traditional Chinese Medicine, Changchun University of Chinese Medicine, Changchun, 130000, People's Republic of China; ²Graduate School, Beijing University of Chinese Medicine, Beijing, 100000, People's Republic of China; ³Pulmonology Department, The First Clinical Hospital of Jilin Academy of Traditional Chinese Medicine, Changchun, 130000, People's Republic of China

Correspondence: Hong Yan Cai, The First Clinical Hospital of Jilin Academy of Traditional Chinese Medicine, Changchun, 130000, People's Republic of China, Email 774009408@qq.com

Abstract: Chronic obstructive pulmonary disease (COPD) includes chronic bronchitis, emphysema, and small airway obstruction. Incompletely reversible airflow limitation, inflammation, excessive mucus secretion and bronchial mucosal epithelial lesions are the main pathological basis of the disease. The prevalence of COPD is increasingly worldwide, which has caused the burden on individuals and society. This paper summarizes the pathogenesis of COPD and clarifies the effect and mechanism of the latest targeted drugs for COPD. Besides, we focus on NOD-like receptor thermal protein domain associated protein 3 inflammasome (NLRP3 inflammasome). NLRP3 can promote production of interleukin-1 β (IL-1 β) and interleukin-18 (IL-18). NLRP3 is an important factor in the migratory aggregation of macrophages and neutrophils and the generation of oxidative stress. Inhibition of NLRP3 inflammasome indirectly blocks the inflammatory effects of IL-1 β and IL-18, which may be regarded as an ideal target for COPD treatment.

Keywords: chronic obstructive pulmonary disease, pathogenesis, targeted drugs, NLRP3

Introduction

COPD is an incurable chronic lung disease, which is also complicated by pulmonary heart disease and respiratory failure in some individuals with a tremendous burden on individuals and society. At present, it is not clear whether the pathological mechanisms of COPD are mainly thought to be the result of genetic and environmental interactions. Moreover, smoking is considered to be the main environmental factor to trigger COPD.^{1–3} Except for genetics, gender,⁴ occupation,^{4,5} airway hyperresponsiveness,⁶ lung growth and development,^{3,7} and infection⁸ also play an important role in the development of COPD. It is easily understood that gender may influence the history of smoking and the particulate environment in which the occupation is located. However, the status of lung growth and development determines the susceptibility to COPD, which seems to have a close relationship with genetics.^{9,10} We should focus on airway hyperreactivity, which is an independent predictor of COPD and can exist independently without asthma and bronchitis, suggesting that the inflammatory response in COPD is different from asthma.^{6,11} In addition to the above causes, inflammatory mechanisms, oxidative stress, and protease-antiprotease imbalance are also involved in the development of COPD. Various reasons for bronchial mucosal epithelial cell degeneration, necrosis, squamous metaplasia and recurrent injury-repair airway wall eventually lead to the occurrence of structural repeated remodeling of the airways and scar formation.^{12,13}

Currently, there is still no specific treatment for COPD, and palliative regimens to improve airflow limitation are the mainstay methods. We generally do not advocate drug intervention for COPD in the stable period, but in the acute attack stage, antibiotics, inhaled corticosteroids, bronchodilators, and other medicines are widely used in clinical practice. However, the negative effects of these drugs should not be ignored. For example, frequent use of inhaled corticosteroids can cause side effects such as osteoporosis, immunosuppression and increased probability of infection, especially infection that promotes the recurrence of COPD,^{8,14} while bronchodilators, for example, the anticholinergic agents and

β_2 agonists commonly used in clinical practice have side effects such as heart rate disturbance, impact on vision, urinary retention, and metabolic disorders, which cannot be ignored.^{15,16} With the development of molecular biology, targeted drugs for treatment by blocking COPD development are gradually being developed. This paper not only reviews the pathogenesis of COPD and the pharmacological mechanisms of COPD-related targeted drugs but also elaborates the concerned contribution of NLRP3 to COPD and the effectiveness of NLRP3 inhibitors and related advances.

Pathogenesis of COPD

Oxidative Stress Response

Oxidative stress is involved in the development of several inflammatory conditions and is an important pathogenetic factor in COPD. Stimulation of patients with smoke or dust leads to lung cell damage. Excessive mucus secretion and accumulation of neutrophils produce a large amount of reactive oxygen species (ROS). Oxidative inactivation of antiproteases loses inactivation and the structure of lung tissue is destroyed due to ROS.¹⁷ The aggregation of neutrophils also leads to activation of a large number of inflammatory factors to produce more ROS, and aggravates the oxidative stress response.^{18,19} The oxidative system involves the secretion of the airway epithelial mucus, and the stimulation of noxious gases such as cigarettes²⁰ generates oxidative stress, which causes a large accumulation of ROS and regulates the relevant mucus genes, such as Muc5b²¹ and Mu5ac.²² In addition, epidermal growth factor²³ is also involved in the production of mucus. The signaling pathway of this kind of factor often resides in the oxidants' activation of airway cells, and then involves in COPD. Regarding the structural destruction of lung tissue caused by protease-antiprotease imbalance, due to α_1 -antitrypsin²⁴ is the most active one, its inactivation is the most critical one. And the large amount of oxidants released by noxious gases, oxidative stress also makes the antiprotease inactivated and finally the protease-antiprotease imbalance occurs. Oxidative stress also enhances the inflammatory response in the lung by regulating redox-sensitive transcription factors such as nuclear factor kappa-B (NF- κ B) and activator protein 1 (AP-1), releasing amounts of cell factors such as IL-1 β , tumor necrosis factor- α (TNF- α). In addition,²⁵ the accumulation of ROS decreases the activity of histone deacetylases (HADC) and increases the activity of histone acetyltransferase, which can lead to a further aggregation of inflammatory cells, especially neutrophils.²⁶ So, we always observe a large number of neutrophil infiltrates during COPD pathological sections. If COPD worsens, the excessive oxidative stress will cause inflammatory cells to generate large amounts of ROS after accumulating. Then, a systemic response will occur.²⁷ Nuclear factor E2 (Nrf2)²⁸ can regulate antioxidant genes. In oxidative stress response, Nrf2 will dissociate. It is then transported to the nucleus to activate the transcription of antioxidant genes. Patients with COPD go through a diminished self-protective mechanism due to reduction of Nrf2 in level, resulting in lower endogenous antioxidant production.^{29,30}

Inflammatory Cells, Inflammatory Mediators Cell Factors

Neutrophils and macrophages play a significant role in the oxidative stress response in COPD and are involved in the remodeling of COPD's airway. Neutrophils⁷ accumulate in large numbers in the airways of COPD patients under oxidative stress, and this cell can secrete serine proteases,³¹ including matrix metalloproteinase (MMP) and neutrophil elastase (NE). And MMP is significantly increased in patients with emphysema, and goes through the extracellular matrix of the lung destroyed by serine proteases, leading to the remodeling of the airway.³² Neutrophils are sensitive to the infection response. When COPD patients are stimulated by infection, neutrophils will leave the circulation to aggregate in the lungs and protect the cells and surrounding tissues by phagocytosing the infectious agent to form proteases and bactericidal proteins, and produce ROS, which is the necessary mechanism to protect the body from free radical damage and the inductor of oxidative stress. In addition, the accuracy of neutrophil migratory aggregation is affected by physical fitness. Therefore, COPD is more common in the elderly population, which is associated with the expression of phosphatidylinositol 3-kinase (PI3K).³³ The accuracy of neutrophil migration can be improved by inhibiting type I PI3K- δ or PI3K- γ .³⁴

Activation of macrophages³⁵ can regulate the beginning and the end of multiple inflammation. For COPD patients, the combination of Interferon- γ (IFN- γ) secreted by Th1, CD8+ cells, and B cells with the IFN- γ receptor will trigger a series of signaling cascades that lead to the activation and differentiation of M1 macrophages, which then³⁶ produce

a large number of cytokines such as TNF- α , IL-1 β , interleukin-6 (IL-6) depending on the tissue site. M2 macrophages, on the other hand, are activated by a variety of cell factors (interleukin-4 (IL-4), interleukin-10 (IL-10) and interleukin-13 (IL-13) et al), and help the remodeling of airway by remodeling and repairing damaged tissues.³⁷ The inflammatory factor IL-6, produced by neutrophils and macrophages, can induce the production of elastase and oxygen radicals, which will increase the permeability of pulmonary vascular and aggravate the destruction of lung tissue.^{38,39} TNF- α , on the other hand, can modulate endothelial adhesion molecules, which will make polymorphonuclear leukocytes accumulate, and then release large amounts of elastase and ROS's destroyed alveolar epithelium. And during the progression of COPD, TNF- α will generate an inflammatory cascade⁴⁰ with IL-1 β . In COPD patients, macrophages and neutrophils, entering the airways and upregulating chemokines such as monocyte chemotactic proteins (MCP-1, CCL-2),⁴¹ and releasing large amounts of inflammatory factors, all indicate their contribution to the development of COPD.

Access Mechanism

NF- κ B Access

NF- κ B plays a role in systemic inflammation, such as rheumatoid arthritis and bronchial asthma. Activation of NF- κ B is achieved by activating protein inhibitor kappa B (I κ B)⁴² to make ubiquitination of I κ B. Because of I κ B ubiquitination, NF- κ B is released from the NF- κ B/I κ B complex, activates, exposes the nuclear localization domain, forms a p50/RelA dimer, and binds to target genes via the p50 subunit, thereby initiating the expression of target genes, such as TNF- α and IL-1, causing inflammatory responses.⁴³ In addition, the inhalation of mixtures, such as ozone, cigarette smoke and so on, leads to the migration of inflammatory cells such as neutrophils into the lungs, and generates ROS that is also a kind of factor in the activation of (NF- κ B).⁴⁴ It will promote helper T cell type 1 (Th1)⁴⁵ to produce cell factors such as TNF- α , IL-1, IL-6, and so on which promote the maturation of resting monocytes into mature dendritic cells, which then provides autoantigens to self-reactive T lymphocytes, causing them to move to target tissues and the destruction of inflammation and lung tissue. All of these suggest that activation of the NF- κ B pathway drives the release of inflammatory factors, leads to further enhancement of the oxidative stress response and exacerbates lung injury in patients. In respiratory tests in COPD patients, it is confirmed that the NF- κ B expression is higher than in normal people. And in the case of smoking patients, the NF- κ B expression is even higher. In addition, factors such as MCP-1,⁴⁶ IL-6, and CXCL-5⁴⁷ are released in large amounts during COPD exacerbations, and hypomethylation of NF- κ B-mediated pathway gene DNA has also been observed to contribute to COPD exacerbation.⁴⁸

MAPK

Mitogen-activated protein kinase (MAPK)⁴⁹ is an important signaling pathway that transmits signals from the cell membrane to the nucleus. The pathway can be activated by the stimulation of cytokines, neurotransmitters, serine proteases, and oxidative stress to participate in stress adaptation and inflammatory responses.⁵⁰ In COPD, mitogen-activated protein kinase (p38MAPK)⁵¹ plays an important role. The release of inflammatory factors caused by various environmental and genetic factors can lead to the activation of p38MAPK, while IL-8 and TNF- α , which are key factors associated with the development of COPD, are regulated by p38MAPK. The excessive release of these inflammatory factors eventually leads to aggregation of neutrophils, secretion of serine proteases, and destruction of lung structures. And all of p38MAPK isoforms (α , β , δ , γ)⁵² in COPD patients occur with high expression and mediate lung inflammation⁵³ together. In addition, IL-8 and TNF- α , which are regulated by p38MAPK, appear to mediate glucocorticoid insensitivity in COPD patients. And these factors impair the function of glucocorticoid receptor (GR) by phosphorylating the GR, while the anti-inflammatory effects of glucocorticoids are exerted by GR. The endogenous p38MAPK antagonist MAPK-phosphatase-1 (MKP-1)⁵⁴ may be central to the reversal of glucocorticoid insensitivity in COPD patients. And it is found that glucocorticoid insensitivity could be reversed by blocking p38MAPK- α , γ and thus upregulating MKP-1.⁵⁵

PI3K/Akt

The PI3K/Akt⁵⁶ pathway plays an important role in inhibiting cell proliferation and apoptosis. The activation of this pathway is mainly related to tyrosine kinase and G protein-coupled receptors.⁵⁷ Upon receiving the signal, the p85⁵⁸

regulatory subunit in PI3K aggregates to the plasma membrane site. The p110 and p85⁵⁹ subunit converts the substrate phosphatidylinositol 2 phosphate (PIP2) to phosphatidylinositol 3 phosphate (PIP3). And PIP3 binds to the N-terminal end of protein kinase B (Akt) and translocates to the cell membrane for activation.⁶⁰ It is an important mechanism of airway remodeling in COPD³³ that regulates the PI3K/Akt pathways and promote apoptosis through the tumor suppressor gene encoded by chromosome 10 negatively. In COPD patients, low expression of Nrf2 is closely associated with the oxidative stress response and the release of inflammatory factors and Nrf2 is a PI3K/Akt downstream signaling target.⁶¹ In addition, when neutrophil migration is influenced by PI3K expression the persistent lung inflammation triggers neutrophil aggregation by activating the PI3K/Akt pathways. And the aggregation of associated cells generates large amounts of ROS to stimulate further exacerbation of oxidative stress. The activation of the PI3K/Akt pathways downregulates HADC activity, leading to the activation of inflammatory gene. Thus, inactivation of HADC is associated with glucocorticoid insensitivity.⁶²

Molecularly Targeted Drugs for COPD

As the pathogenesis of COPD has become better understood, research on molecularly targeted drugs has increased. Here, we will describe most (we only list those that have been registered in clinical trials and published results) of the targeted drugs used in COPD treatment and introduce the mechanisms of these drugs.

Antioxidants

Oxidative stress is an important mechanism in the development of COPD. The application of antioxidants is feasible in COPD patients, because the significantly elevated level of airway oxidative stress markers (eg, H2O2) and has been validated in in vivo experiments.⁶³ It is proved that N-acetylcysteine (NAC) can control COPD patients' airway function in clinical trials.^{64,65} However, data from various studies are inconsistent, possibly due to oral administration affecting bioavailability. Other trials, such as superoxide dismutase, have a good anti-inflammatory effect achieved in animal studies, but still lack more clinical evidence.

Sulforaphane can attenuate oxidative stress by activating Nrf2 and regulating reactive nitrogen and ROS.⁶⁶ However, in a 4-week clinical trial,⁶⁷ no evidence was found to improve clinical outcomes in COPD (including Nrf2 expression, levels of relevant inflammatory markers). Therefore, the ability of turnip-sulfur as a therapeutic agent for COPD lacks the support of clinical evidence. The drugs are shown in Table 1.

Cytokine-Targeted Drugs

Numerous cytokines are involved in the development of COPD. High expression in COPD patients is also an important factor in activating various inflammatory signaling pathways, and oxidative stress responses. TNF- α plays an important role in interstitial lung disease. As a TNF- α targeting agent, Infliximab has been shown in animal studies⁶⁸ to prevent smoke-induced emphysema in rats, and reduce the percentage of neutrophils and the level of IL-8 and TNF- α in rats. However, clinical trials^{69,70} had less favorable outcomes and did not find an improvement in clinical outcomes in COPD patients. It has even been reported that it is possible to increase in the incidence of lung malignancies in COPD patients. Also, as an antagonist of TNF- α , the outcomes reported by etanercept⁷¹ were slightly better, but still not as effective as

Table 1 Antioxidants

Drugs	Type	Clinical Outcomes
NAC	Controlling oxidative stress	ClinicalTrials.gov, NCT01136239 (1-year high-dose NAC improved small airway function in COPD and reduced the frequency of exacerbations) ClinicalTrials.gov, NCT01739790 (The trial was 8 weeks and did not find that high-dose NAC improved respiratory clinical outcomes in COPD)
Sulforaphane	Targeting the Nrf2 gene	Clinicaltrials.gov, NCT01335971 (4 weeks of sulforaphane in COPD patients was not found to stimulate Nrf2 gene expression and was not found to improve inflammatory marker levels)

those of inhaled corticosteroids. Due to the lack of clinical evidence, whether TNF- α antagonists can be used as a treatment for COPD remains to be discussed.

IL-5 is in high expression in COPD patients. It seems feasible to inhibit IL-5 to achieve suppression of inflammatory and oxidative stress responses. Although mepolizumab is a target drug for IL-5, clinical evidence points to COPD with increased eosinophilia, probably because of the close association between IL-5 and the aggregation and differentiation of eosinophil.⁷² Clinical trials have also demonstrated a reduction in COPD and exacerbation and a more pronounced reduction in eosinophil percentage than with placebo.⁷³ However, the FDA has not approved mepolizumab for COPD and trials related to it still have to be planned. Benralizumab, also an IL-5 antagonist, is approved for asthma with eosinophilia. However, clinical trials reported that benralizumab did not reduce the frequency of exacerbations in moderate-to-severe COPD.^{74,75} So, there is still a lack of more evidence to support it.

MK-7123 is a CXCR2 inhibitor, which can decrease neutrophil chemotaxis to reduce inflammatory manifestations in COPD patients. And in a clinical trial of 616 patients,⁷⁶ it was shown that MK-7123 at a 50 mg dose was effective in improving lung function and reducing lung inflammation in patients. Those drugs are shown in Table 2.

Enzyme Inhibitors

Protease-antiprotease imbalance is the main cause of lung damage in COPD patients. Protection against lung tissue damage and suppression of inflammation by inhibited NE seem feasible; however, clinical evidence^{77,78} seems unsatisfactory, AZD9668, an NE inhibitor, failed to improve the lung function and the airway structure in patients. MMP inhibitors are one of the targets of anticancer drugs, but the clinical value of MMP inhibition for COPD remains unknown. MMP-9 and MMP-12 are significantly associated with airway inflammatory damage, both enzymes have enhanced activity in COPD patients, and their inhibition has been found to achieve better anti-inflammatory efficacy in animal model species of COPD,⁷⁹ however, no valuable outcomes have been reported in clinical trials.⁸⁰

Phosphodiesterases-3 and phosphodiesterases-4 (PED3 and PED4) are involved in the development of COPD, and they regulate cellular activity by hydrolyzing intracellular cAMP and cGMP.⁸¹ PED3 is widely distributed in T lymphocytes, and lymphocyte function can be regulated by inhibition of PED3; inhibiting PED4 can reduce IL-4 and 5 gene expression in TH2 cells, decreases levels of inflammatory factors and has a synergistic effect with PED3 inhibitors in T cells.⁸² Clinical evidence^{83,84} also indicated that PED3/4 inhibitors (RPL-5 and roflumilast) both improve the lung function in COPD patients. However, when these patients simultaneously use standard bronchodilators, the function of RPL-554 and roflumilast benefits little. So, it did not justify the clinical efficacy in RPL-554 and roflumilast. Besides, roflumilast also reported side effects of severe gastrointestinal reactions (diarrhea and nausea)⁸⁵ and headache. Those drugs are shown in Table 3.

Signaling Pathway Inhibitors

In COPD patients, activation of related pathways can enhance oxidative stress and cytokines, chemokines were massive release, which can further COPD development. Vitro trials⁸⁶ demonstrated that verproside can achieve inflammation

Table 2 Cytokine-Targeted Drugs

Drugs	Type	Clinical Outcomes
Infliximab	TNF- α inhibitor	ClinicalTrials.gov, NCT00056264 (In the treatment of COPD, infliximab has a higher probability of causing lung malignancy) ClinicalTrials.gov, NCT00244192 (6 weeks of treatment in COPD patients, had not any evidence pointed that it can improve clinical outcomes)
Etanercept	TNF- α inhibitor	ClinicalTrials.gov, NCT00789997 (It can improve lung function in COPD patients, it was less compared to prednisolone)
Mepolizumab	IL-5 inhibitor	ClinicalTrials.gov, NCT02105948, NCT02105961 (It can reduce COPD exacerbation with elevated eosinophils)
Benralizumab	IL-5 inhibitor	ClinicalTrials.gov, NCT02138916, NCT02155660 (Addition of benralizumab does not reduce annual exacerbation rates in patients with moderate or severe COPD with a history of frequent exacerbations)
MK-7123	CXCR2 inhibitor	ClinicalTrials.gov NCT01006616 (It can significantly improves lung function in COPD patients treated by 50mg dose)

Table 3 Enzyme Inhibitors

Drugs	Type	Clinical Outcomes
AZD9668	NE inhibitor	ClinicalTrials.gov NCT01054170 (After 12 weeks of treatment with 60 mg dose of AZD9668, not found of that CT airway structure were improved in COPD patients) ClinicalTrials.gov, NCT01023516 (AZD9668 three months treatment, no significant improvement in lung function found in COPD patients)
AZD1236	MMP-9, MMP-12 inhibitors	6 weeks of AZD1236 in COPD patients, had not found any valuable clinical outcomes ⁸¹
RPL554	PED3/4 inhibitors	ClinicalTrials.gov, NCT02542254, NCT03028142 (Combined with that standard bronchodilators, it improves peak FEV1 in COPD patients)
Roflumilast	PED4 inhibitor	ClinicalTrials.gov, NCT00313209, NCT00424268 (Can improve lung function in COPD patients, but has the side effect of headache)

suppression by blocking the TNF- α /NF- κ B pathway, but no clinical trials related to verproside have been seen, and no clinical evidence has been found for other inhibitors related to the NF- κ B pathway.

p38MAPK inhibitors have recently received wide attention and have shown beneficial anti-inflammatory effects in smoke-induced pneumonia models,⁸⁷ in addition, inhibiting p38MAPK also reduces the production of associated cytokines by macrophages, whose aggregation is an important cell for oxidative stress and inflammatory factor release in COPD patients⁸⁸ Currently, some clinical evidence^{89,90} also confirmed that p38MAPK inhibitors (PH-797804, SB-681323) improve lung function and inflammatory factor levels (TNF- α) in COPD patients and perform well in hormone-insensitive classes of patients.

Inhibited PI3K can activate Nrf2, improve HDAC activity, modulate oxidative stress and improve inhaled corticosteroids resistance.^{61,62} In clinical trials,^{91–94} the PI3K inhibitor GSK2269557 can improve lung function and related inflammatory factor levels (IL-8, IL-6) in COPD patients, but it has also been reported that it cannot change the clinical outcome. In addition, some studies⁹⁵ pointed out that excessive PI3K inhibition may lead to immunosuppression. Nrf2, as a downstream target of PI3K, although there is no evidence of clinical effectiveness at this time. It remains to be validated and developed the medicine of downstream target of PI3K. Those drugs are shown in Table 4.

Relation of NLRP3 and Inflammatory Factors/Cells

Studies on NLRP3 in COPD, animal and in vitro experiments demonstrated that reducing NLRP3 expression can improve lung inflammation, inflammatory factor levels, and immune system function in COPD patients and so on, which also appears to improve glucocorticoid-insensitive classes of airway disease.

NLRP3 was demonstrated in mice experiments⁹⁶ that Chlamydia and Haemophilus can increase NLR3, IL-1 β responses and develop drug-resistant neutrophil inflammation. This experimental blockade of airway inflammation was

Table 4 Signaling Pathway Inhibitors

Drugs	Type	Clinical Outcomes
Verproside	NF- κ B inhibitor	ClinicalTrials.gov, NCT02272634 (It blocked TNF- α / NF- κ B pathway in human airway epithelial cells NCI-H292)
SB-681323	p38MAPK inhibitor	ClinicalTrials.gov, NCT00380133 (Reduced TNF- α levels in COPD patients)
PH-797804	p38MAPK inhibitor	ClinicalTrials.gov, NCT00559910 (Improved lung function in patients with moderate to severe COPD)
GSK2269557 (nemalisib)	PI3K inhibitor	ClinicalTrials.gov, NCT02294734 (Improved FEV ₁ in patients with moderate to severe COPD), ClinicalTrials.gov, NCT02130635 (Inhaled GSK2269557 can effectively reduce IL-6 and IL-8 levels in COPD patients) ClinicalTrials.gov, NCT02522299 (Altered sputum neutrophil transcription and improved neutrophil migration phenotype) ClinicalTrials.gov, NCT03345407 (12 weeks of treatment had not found that can improved clinical outcomes in acute exacerbations of COPD)

made possible by NLRP3 inhibitor (MCC950), airway inflammation in asthma and the degree of glucocorticoid resistance were all related with IL-1 β and NLRP3 expression. In in vitro models, NLRP3 expression is similarly elevated in models of COPD and exacerbated COPD, and IL-1 β is similarly elevated.⁹⁷ In addition, experiments by Yang⁹⁸ et al verified that in a tobacco-made COPD mouse model, knockdown of NLRP3 caused mice to lose evidence of lung inflammation and did not show pathological damage, while in NLRP3 knockdown mice, IL-1 β , IL-18, macrophage, neutrophil, and lymphocyte levels were significantly lower than in COPD model mice. Although also affected by tobacco, NLRP3 knockdown significantly alleviated lung inflammation in mice, providing us with evidence that NLRP3 is a target for COPD treatment.

Relation of NLRP3 and Oxidative Stress

Research pointed⁹⁹ that NLRP3 deficiency can reduce oxidative stress and scavenge damaged mitochondria, and it seems to play an important role in neuroinflammation. After activation of NLRP3 inflammasome, the release of IL-1 β , IL-18 and other inflammatory factors will activate the polymorphonuclear neutrophils, produce a large number of ROS, and initiate the inflammatory response.¹⁰⁰ Furthermore, studies¹⁰¹ suggest that in smog-induced responses, activation of NLRP3 can induce apoptosis through the p53-Bax mitochondrial pathway. These results demonstrate the importance of NLRP3 inflammasome in the cell injury and apoptosis.

Conclusions

The pathogenesis of COPD is complex, mainly related to oxidative stress, inflammatory factors and over-expression or activation of signaling pathways. We found that these factors often co-exist, and it is difficult for us to achieve treatment of COPD through a single target among these interacting factors. Although some targeted drugs have achieved therapeutic efficacy, there are unknown consequences for the interaction of inflammatory factors and signaling pathways that inhibit only a single pathway. Therefore, most targeted drugs are still at a hypothetical stage in clinical practice. We need to reexamine the mechanisms of COPD and study each targeted pathway in depth to assess the safety of new targets through extensive in vitro and animal experiments. NLRP3 is highly correlated with the development of COPD and achieves therapeutic effects in COPD by controlling inflammation to inhibit the production of inflammatory factors by blocking the activation of related pathways. It is also effective in harmonic tolerant patients. Inhibited NLRP3 has not been reported any adverse effects in animal studies. Therefore, we believe that the targeted drugs have implications for continued development in the treatment of COPD.

Disclosure

The authors report no conflicts of interest in this work.

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