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The Role of Neutrophil Extracellular Traps in Chronic Airway Inflammatory Diseases and Research Advances

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Abstract: Chronic airway inflammatory diseases are a group of diseases in which inflammation involves the upper and/or lower airways, mainly triggered by infections or immune abnormalities, and common types include asthma and chronic obstructive pulmonary disease. Recent studies have revealed that neutrophil extracellular traps (NETs) play an important role in the pathophysiology of several chronic inflammatory airway diseases. Under normal circumstances, the formation of NETs is beneficial for neutrophils to limit the invasion of pathogens in the body, thereby effectively controlling the range of inflammation and reducing the inflammatory response. However, when NETs are over-formed and their clearance is obstructed, it can cause damage to the airway epithelium, thereby exacerbating the level of airway inflammation. This article elaborates on the overview of NETs, the formation mechanism of NETs, the relationship between NETs and chronic airway inflammatory diseases, and the role and research progress of targeted regulation of NETs in the prevention and treatment of chronic airway inflammatory diseases. The aim is to provide effective reference ideas for the prevention and treatment of chronic airway inflammatory diseases.

1. Introduction

Chronic airway inflammatory diseases are a category of inflammatory disorders involving the upper and/or lower airways[1], mainly triggered by immune abnormalities or infections, such as asthma and chronic obstructive pulmonary disease (COPD). Although the pathological mechanisms of these two diseases differ, their common features are chronic airway inflammation leading to airway hyperresponsiveness, airflow limitation and airway remodeling[2].Recent studies have revealed that NETs are widely present in various chronic airway inflammatory diseases. They are closely associated with the occurrence and development of such diseases. Under normal conditions, the appropriate production of NETs are beneficial for neutrophils to limit and enclose pathogens. It is an effective way to controll the range of inflammation. However, when NETs are overproduced and their

clearance is obstructed, it may precipitate pathological responses including damage to airway epithelial tissue, impaired mucociliary clearance, diminished antimicrobial capacity, and exacerbated airway inflammation. This paper explores the role of NETs in chronic airway inflammatory diseases, investigating novel therapeutic targets and treatment strategies for such conditions. Its aim is to provide an effective reference framework for developing new therapeutic approaches to chronic airway inflammatory diseases.

2. Definition of NETs

Neutrophils, as a vital component of the human innate immune system, are the vanguard that first mobilises to sites of inflammation to initiate the immune defence mechanism[3].When pathogens invade the body, neutrophils which are in the peripheral blood migrate to the site of infection. They neutralise pathogens by phagocytosing them, degranulating, and releasing NETs to encapsulate and immobilise the pathogens[4]. Among these, NETs are chromatin fibre networks that are released by neutrophils following stimulation by factors such as infection or inflammation. It features a DNA backbone encircled by a network of antimicrobial proteins, including circulating cell-free DNA (cf-DNA), cathepsin G, neutrophil elastase (NE), myeloperoxidase (MPO), and citrullinated histone H3 (Cit-H3),matrix metalloproteinase-9 (MMP-9), leukotriene B4 (LTB4). Under normal circumstances, appropriately generated NETs can help neutrophils enclose and encapsulate pathogens, thereby effectively controlling the extent of inflammation. However, when NETs are produced in excessive amounts or cleared insufficiently, they may induce tissue damage and even accelerate disease progression.

3. The Formation Mechanism of NETs

NETs can be stimulated by various pathogens and inflammatory factors, such as pathogenic microorganisms like bacteria, fungi, and viruses, as well as small molecules which include lipopolysaccharide (LPS), phorbol myristate acetate (PMA), tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8), and granulocyte-macrophage colony stimulating factor (GM-CSF) and so on [5] . Research reveals that the formation of NETosis is primarily categorised into two types: suicidal NETosis and vital NETosis.

3.1 Suicidal NETosis

Suicidal NETosis can be induced by factors such as bacteria, fungi and viruses. It is characterised by increased cytoplasmic membrane permeability, nuclear membrane rupture and disintegration, and chromatin fragmentation[6]. The fragmented chromatin subsequently binds to granular proteins such as NE and MPO, leading to neutrophil death. At the same time, the decondensed chromatin combines with granular proteins[6]. Suicidal NETosis is primarily related to reactive oxygen species (ROS) and protein arginine deiminase 4 (PAD4). When neutrophils are stimulated by PMA, autoantibodies and cholesterol crystals, they can activate nicotinamide adenine dinucleotide phosphate oxidase (NADPH-oxidase, NOX) through PKC and RAF-MEK-ERK pathways. After NOX is activated, a large amount of ROS are rapidly produced and the concentration of Ca^{2+} in the cytoplasm increases significantly[7] (Figure 1). On the one hand, ROS promotes the production of NE and MPO, accelerating chromatin decondensation. Under normal conditions, NE resides within the azurophilic granules of quiescent neutrophils, with a portion bound to MPO and anchored to the granule membrane, while the remainder remains within the lumen[8]. Under ROS stimulation, NE is released from azide complexes containing MPO into the cytoplasm. Subsequently, by binding to and degrading F-actin filaments, it inhibits neutrophil phagocytosis and ultimately translocates to the nucleus[8].

Within the nucleus, NE cleaves lysine- and arginine-rich histones, weakening their binding to DNA and promoting chromatin depolymerisation into cf-DNA[9]. MPO binding to chromatin further accelerates this depolymerisation to induce NETosis[10]. On the other hand, PAD4 also facilitates chromatin disassembly. Under the drive of high-concentration Ca^{2+}, PAD4 is activated. The activated PAD4 catalyzes the deamination of histones H2A, H3 and H4, converting arginine residues into citrulline. This leads to the loss of positive charges on arginine residues in histones, significantly reducing their electrostatic interaction with negatively charged DNA and promoting chromatin decondensation[11]. Under the synergistic action of NE and MPO, the nuclear membrane ruptures and decomposes, and citrullinated histones and DNA are released into the cytoplasm together. These released DNA are further modified in the cytoplasm by granular proteins (NE, MPO) and cytoplasmic proteins. In addition, NE cleaves Gasdermin D (GSDMD) into its active form (GSDMD-nt), increasing the permeability of the cytoplasmic membrane and azurophilic granule membrane. Upon the disruption of the plasma membrane, NETs are discharged into the extracellular environment. This discharge occurs concurrently with the demise of neutrophils [12].

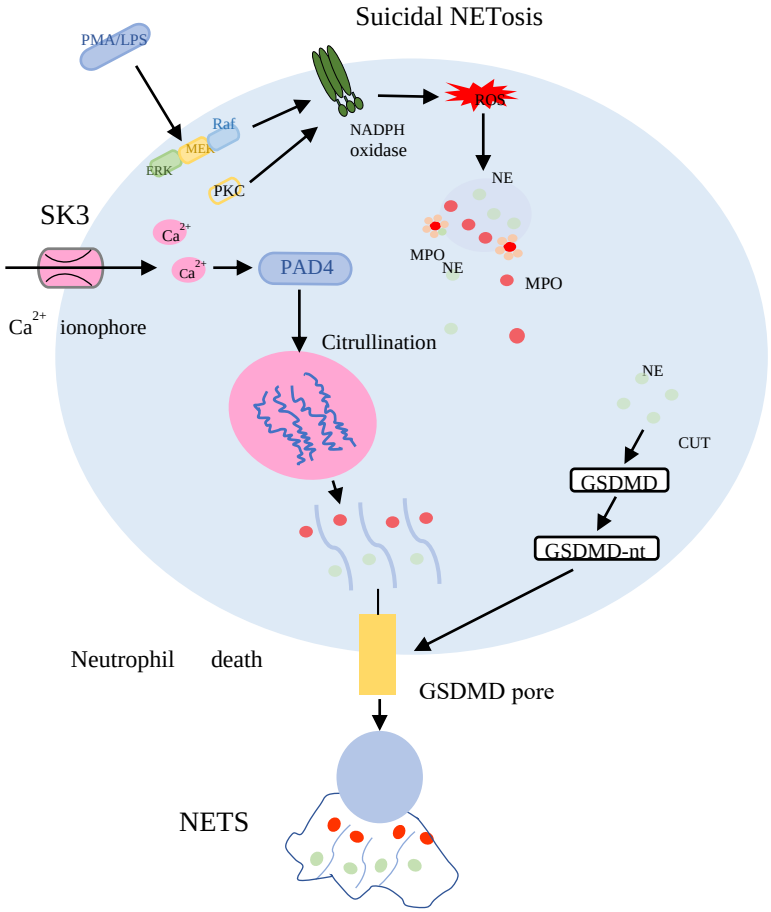

Figure 1 Mechanism of suicidal NETosis

3.2 Vital NETosis

In vital NETosis, the structure of neutrophils remains intact. They still retain their chemotaxis and phagocytosis, as well as other functions. When stimulated by pathogens such as Staphylococcus aureus and Escherichia coli, neutrophils can initiate signal transduction through surface TLR2, TLR4, and complement receptors[13]. The multilobed nucleus of neutrophils rapidly rounds up and condenses, with the inner and outer layers of the nuclear membrane separating. Chromatin and proteases are

released outside the cell through the budding of vesicles, forming NETs. At this time, the nucleus and cytoplasmic membrane remain intact. Under the regulatory effect of small conductance potassium channel member 3 (SK3), mitochondrial reactive oxygen species (mROS) are rapidly generated. The high concentration of Ca^{2+} in the cytoplasm can promote the occurrence of mitochondrial oxidative phosphorylation reactions and simultaneously activate the activity of PAD4, leading to the citrullination of histone arginine residues. After the binding force between histones and DNA decreases, chromatin depolymerizes. In the cytoplasm, DNA combines with granular proteins such as NE and MPO and is eventually released outside the cell[14] (Figure 2). Concurrently, the mitochondrial membrane pore remains persistently open, allowing mROS to be released from mitochondria into the cytoplasm. However, the precise mechanism by which mROS functions in the vital NETosis process remains a subject of ongoing debate.

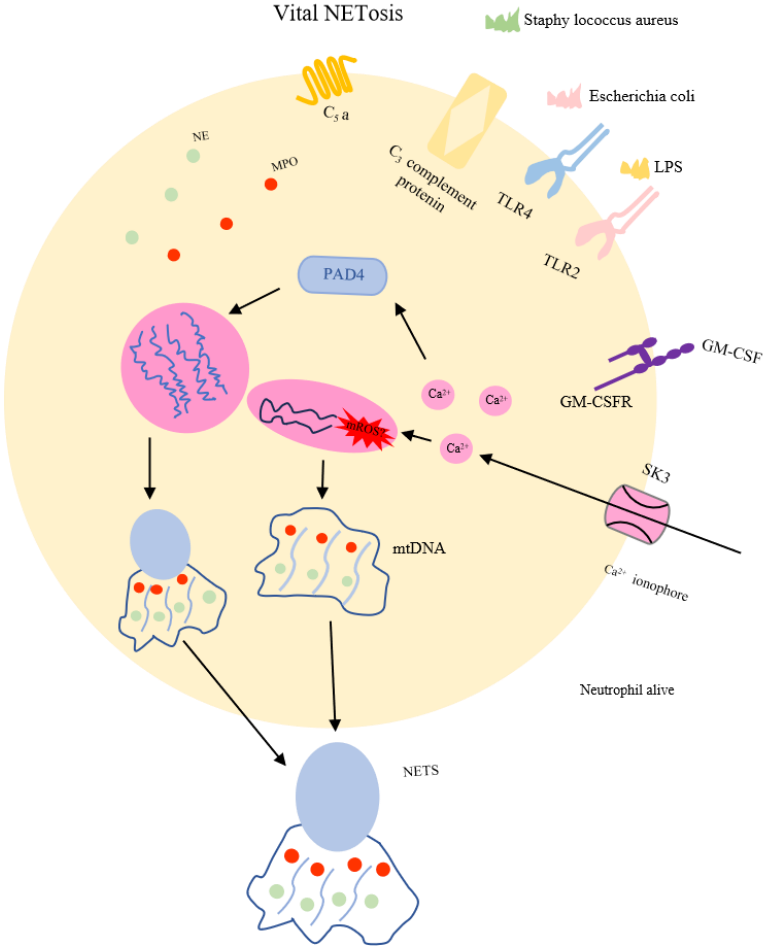

Figure 2 Mechanism of vital NETosis

4. NETs and Chronic Airway Inflammatory Diseases

4.1 Asthma

Asthma is a medical condition mainly distinguished by long - term inflammation of the airways, reversible blockage of the air passages, an exaggerated response of the airways, and remodeling of the airway structure[15]. Clinically, it manifests chiefly through recurrent episodes of chest tightness, coughing, wheezing, and breathlessness, and is typically associated with a protracted course and persistent, difficult-to-cure symptoms[15]. Based on its immunological characteristics, asthma can be

categorised into type 2 and non-type 2 subtypes. Different from the classic Th2 cell-dependent eosinophilic airway inflammation, the inflammatory response in some asthma patients is mainly driven by neutrophils, and this subtype is classified as low Th2 type asthma in clinical practice[16]. The condition of these patients is more severe and they are insensitive to glucocorticoids[17]. NETs play an important role in the disease process of this type of asthma. Studies have found that NETs are widely present in the sputum of asthma patients[18]. In addition, studies have also found that the concentration of CitH3 in the peripheral blood of asthma patients significantly increases, and the level of this marker is significantly negatively correlated with the decline in the lung function index FEV_1/FVC[5]. In severe asthma patients, cf-DNA is closely related to the increased frequency of corticosteroid use, neutrophilic inflammatory response and inflammasome activation [19]. These studies indicate that NETs are involved in the pathogenesis of asthma and may even be associated with the severity or acute exacerbation of asthma.

NETs exert a dual role in the progression of asthma. Under normal circumstances, NET formation enhances the body's resistance, but excessive accumulation of NETs exacerbates disease progression. NETs disrupt the integrity of bronchial epithelium, causing neutrophils to exudate. This increases the viscosity of the mucus, causing damage to the clearance of the mucus and the transport rate of the lower airway[20], eventually leading to the accumulation of mucus in the lungs and having a negative impact on lung function[20]. Some cytotoxicity of NETs can directly damage the airway epithelial cells, causing airway injury and making the inflammatory response more severe[21]. It will stimulate epithelial cells to secrete cytokines such as IL-1, IL-6 and IL-8. These cytokines can promote the aggregation of neutrophils to the inflammatory site, thus promoting the occurrence of airway inflammation[22]. IL-8 will bind to the receptors CXCR1/CXCR2 on the surface of neutrophils. Activating the migration and chemotaxis of neutrophils can also induce the formation of NET [23,24], thus establishing an inflammatory positive feedback loop that continuously amplifies. NETs can also activate airway epithelial cells through the TLR4 receptor pathway, stimulate the release of various inflammatory mediators, amplify Th2-type immune responses, and mediate the occurrence of chronic inflammation[20]. Histones are the main components of NETs, which can directly damage respiratory epithelial cells and vascular endothelial cells, making the inflammatory response more severe[22]. Excessive production of cf-DNA can promote increased airway secretion, increase the viscosity of mucus, and aggravate inflammation by activating proteases and pro-inflammatory cytokines, eventually causing airway obstruction[18]. ROS plays a key role in inflammation, inducing the release of pro-inflammatory cytokines and is closely related to the occurrence of airway hyperresponsiveness. NE can stimulate the proliferation of goblet cells, causing excessive mucus secretion and exacerbating airway obstruction. NE and MPO can promote the generation of ROS through positive feedback mechanisms, increase the level of oxidative stress in lung tissue, damage the airway epithelial barrier function, and make asthma inflammation more severe[25]. Neutrophils abnormally secrete proteolytic enzymes such as MMP-9 and NE[26], which directly participate in the pathological process of airway wall structure remodeling and promote the development of this process. These enzymatic substances can degrade the extracellular matrix components, alter the normal tissue structure of the airway wall, and ultimately cause irreversible damage to airway function.

The components of NETs may have the function of autoantigens. They can activate immune cells such as B lymphocytes and T lymphocytes, disrupt immune tolerance, and thus promote the continuous development of autoimmune diseases[27]. During the formation of NET, the intracellular components of neutrophils are released outside the cells. This process presents autoantigens to the host immune system while releasing damage-associated molecular patterns (DAMPs), thereby amplifying inflammation and immune responses[28]. In a mouse model of asthma induced by lipopolysaccharide house dust mite (LPS-HDM), NETs enhance antigen presentation in dendritic cells (DCs) and induce th2 dominant inflammatory responses. This eventually leads to the

development of characteristic asthma pathologies, including inflammation, excessive mucus secretion and airway hyperresponsiveness [29].

4.2 COPD

COPD is a chronic respiratory disease closely related to smoking and environmental factors. Its characteristic pathological changes include small airway stenosis with emphysema formation, as well as irreversible airflow limitation and airway remodeling[23]. In recent years, the prevalence of COPD has been increasing year by year worldwide. It is predicted that by 2030, the number of deaths in China due to this disease will reach 1,055,400, which means approximately 73.85 people per 100,000 will die from it[30]. Research has found that various stimuli such as bacteria, viruses, cigarette smoke and oxidative stress may all trigger the onset of COPD. These factors induce the secretion of chemokines (CXCL) and inflammatory mediators by lung epithelial cells and macrophages, which in turn stimulate the recruitment and infiltration of neutrophils and monocytes, thereby triggering an inflammatory response[31]. These infiltrating neutrophils exacerbate airway inflammation and mucus secretion levels by releasing a reticular structure containing cf-DNA, granular proteins, and LTB4, playing a crucial role in the acute exacerbation of COPD[32]. Studies have shown that the levels of NETs in induced sputum increase in both stable and acute exacerbation COPD patients[33]. This suggests a close association between NETs and the pathogenesis of COPD.

Under physiological conditions, the NETs, with its unique reticular structure, can capture and encapsulate pathogenic microorganisms, effectively preventing their spread. The net can also utilize extracellular killing mechanisms to suppress infections and significantly reduce the inflammatory response in the body. In addition, key components of NETs such as histones and NE also exhibit strong antibacterial activity[4]. However, when NETs are excessively deposited, they can cause tissue damage. Under normal circumstances, alveolar macrophages secrete deoxyribonuclease I (DNase I) to degrade the DNA skeleton of NETs, effectively clearing NETs from tissues. However, the number of macrophages in the sputum of COPD patients is significantly reduced, and the phagocytic function of the remaining macrophages is impaired[4]. Therefore, it is reasonable to infer that due to the scarcity of macrophages in COPD patients, NETs accumulate in the lung tissue, exacerbating the inflammatory response and increasing the degree of lung injury. Moreover, long-term accumulation of NETs in the body can trigger programmed cell death in epithelial and endothelial cells, leading to destruction of lung parenchyma and functional decline, and accelerating the deterioration of the disease[34]. NE, as a core effector molecule of NETs, can degrade host defense proteins in airway epithelium, damage the defense barrier of lung tissue, and promote the occurrence and development of emphysema[35]. NE also has the effect of promoting airway mucus secretion, further aggravating the damage to lung parenchyma[23]. Currently, the specific mechanism by which NETs participate in the pathophysiological process of COPD is not yet clear and requires further in-depth exploration through more basic experiments and clinical trials.

5. NETs as potential therapeutic targets

NETs play a significant role in numerous chronic pulmonary diseases. Their function in chronic airway diseases can be modulated by inhibiting NETs formation or promoting NETs degradation.

5.1 Inhibition of NET formation

ROS and PAD4 are key molecules triggering NETosis. NADPH oxidase can induce the production of a large amount of ROS. Therefore, by inhibiting the activity of NADPH oxidase, ROS generation can be blocked, and the release of NETs can be inhibited. Diphenyleneiodonium chloride

(DPI), a specific inhibitor of NADPH oxidase, plays an anti-inflammatory role in the development of asthma[36]. In the ovalbumin (OVA)-induced asthma mouse model experiment, we found that after treatment with the NADPH oxidase inhibitor apocynin, the formation of NADPH oxidase in asthmatic mice decreased, the production of Th2 cytokines, TNF-α and IL-12 decreased, and the levels of airway hyperresponsiveness and pulmonary inflammatory infiltration were reduced[37], further demonstrating the feasibility of inhibiting NETs generation by using NADPH oxidase inhibitors to weaken the inflammatory response in asthma. PAD4, as a key enzyme in the formation of NETs, can catalyze the citrullination of histone arginine residues, causing the loss of positive charge on histones and weakening their interaction with negatively charged DNA, ultimately leading to chromatin decondensation. In the neutrophilic asthma model, the PAD4-specific inhibitor Cl-amidine can reduce NETs generation by inhibiting PAD4 enzyme activity and lowering CitH3 expression levels, thereby alleviating airway hyperresponsiveness, reducing inflammatory cell accumulation and mucus obstruction, and improving inflammatory damage[31]. Thiam's research team[38] found in a severe asthma animal model that simvastatin treatment could effectively inhibit PAD4 activity and significantly reduce NETs generation levels, thereby significantly improving asthma clinical symptoms. In a COPD rat model, it can be found that simvastatin can alleviate pulmonary inflammation in rats, reduce the expression of inflammatory factors, and improve lung function[39].

In addition, NE, as a key component of NETs, can be transferred from azurophilic granules to the nucleus after activation, cleave histones, drive chromatin decondensation, and thereby accelerate NET formation[40]. NE itself can stimulate the proliferation of goblet cells, the accumulation of inflammatory cells, leading to excessive mucus secretion, aggravating airway obstruction and tissue damage. It can also reduce the defense ability of epithelial cells by degrading host defense proteins in airway epithelium, making patients more susceptible to bacterial infections. Inhibiting NE activity can eliminate the main proteolytic activity of NETs and subsequently disrupt the core function of NETs. Studies have found that in an in vitro human neutrophil test induced by cigarette smoke extract (CSE), the NE inhibitor GW311616A prevented NET formation by blocking NE nuclear translocation and chromatin decondensation[40]. At the same time, this compound also reduced CSE-induced ROS levels, suggesting that its inhibition of ROS production may also be involved in the regulation of NETosis[40].

Therefore, by inhibiting the activity of NADPH oxidase and NE and blocking histone citrullination, NET production can be reduced at the source. This strategy helps to alleviate excessive immune responses and inflammatory damage, providing a new direction for the prevention and treatment of chronic airway inflammatory diseases.

5.2 Promoting NET Degradation

DNA, serving as the core framework of NETs. Abnormal accumulation of DNA in the airways may affect the development process of chronic lung diseases. Studies have shown that degrading DNA can destroy the reticular structure of NETs, thereby reducing the cytotoxicity caused by histones and granular proteins. In the end, it will lead to a very significant improvement in airway hyperresponsiveness and inflammatory levels[41]. In the mouse model of asthma, after intervention with the DNA degrader DNase I, airway allergic reactions decreased, oxidative stress levels also dropped, and airway resistance was significantly reduced[41]. In the animal model of eosinophilic asthma (OVA)-induced by ovalbumin, recombinant human deoxyribonuclease I (rhDNase I) was exogenous administered to it. It can reduce the production of reactive oxygen species (ROS), increase the activity ratio of superoxide dismutase (SOD)/ catalase (CAT), and also enhance the activity of glutathione peroxidase (GPx), thereby increasing the content of thiol groups. In this way, the level of

oxidative stress was significantly improved, and it also promoted the repair of damaged epithelium[42]. These studies together demonstrated that it is feasible to improve airway inflammation by promoting DNA hydrolysis and accelerating NET degradation. This approach eliminates toxic structures and restores the REDOX balance at the same time. It is very crucial for controlling the development of chronic inflammation and may directly promote the repair of airway tissues.

6. Conclusions

NETs is a reticular fibrous structure released by neutrophils when they capture and kill pathogens. It is a crucial part of the innate immune system. These Nets play a key role in the entire process of the human body's resistance against pathogenic microorganisms. However, if there is an excessive production of Nets or they are not fully eliminated, they will make the inflammatory response more severe, causing a series of pathological reactions such as airway epithelial damage, excessive mucus secretion, airway hyperresponsiveness, airway remodeling, restricted ventilation function and ciliary movement disorders. Studies have shown that NETs are highly active in various chronic airway inflammatory diseases and play specific roles at different stages of disease development. For this reason, intervention with NETs has become an effective strategy for treating chronic airway inflammatory diseases and preventing their further progression. This article will systematically discuss the molecular mechanism of NETs in chronic airway inflammation and its therapeutic potential. At the same time, it will summarize the current pharmacological mechanisms by which Western medicines regulate NETs to treat related diseases, in order to provide some new ideas for the future development of drugs for chronic airway inflammation. Although the existing research has not yet fully clarified the mechanism of action of net, it has already clearly demonstrated its application potential in the clinical field. This breakthrough points out a key direction for the development of new anti-inflammatory drugs and has a very broad prospect in the field of translational medicine. It can be imagined that as research continues to deepen, the development of airway inflammation treatment drugs based on the NETs intervention strategy will achieve significant breakthroughs, providing new options for clinical treatment.

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