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REVIEW

NOD2-NLRP3 Axis and Asthma

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Abstract: Patients with asthma frequently experience recurrent symptoms including coughing, wheezing, shortness of breath, and chest tightness. Asthma is a common public health concern. It is characterized by chronic airway inflammation. However, The pathogenesis of asthma is complex. Inflammasomes are signaling platforms that regulate the inflammatory response. There is a correlation between inflammasomes and asthma. Pattern recognition receptors recognize danger signals and participate in inflammasome activation. Nucleotide-binding and oligomerization domain-containing 2 (NOD2), a pattern recognition receptor, senses microbial components and triggers immune responses. There have been studies showing a correlation between NOD2 and asthma. The nucleotide-binding oligomerization domain-like receptor containing pyrin domain 3 (NLRP3) participates in the formation of inflammasomes. NLRP3 are involved in asthma pathogenesis. In this review, we discuss the roles of NOD2 and NLRP3 in the pathogenesis of asthma.

Keywords: NOD2, NLRP3, inflammasome, asthma

Introduction

Asthma is a common chronic respiratory disease in the world, which increases the burden to family and society. Asthma impacts nearly 300 million globally, with around 1000 daily deaths attributed to this critical health challenge.[1] Asthma attacks often result in coughing, wheezing, shortness of breath, and tightness.[2] Recurrent asthma attacks significantly impair patients' quality of life. Common triggers of asthma include air pollution, allergens, viral respiratory infections, weather changes and exercise.[3–7] Chronic airway inflammation is a pathological feature of asthma.[8] Asthma is believed to be a heterogeneous disease that is affected by the environment and heredity.[9] Cells involved in airway inflammation include T helper cells, lymphocytes, eosinophils, mast cells, basophils, macrophages, epithelial cells, dendritic cells, goblet cells, fibroblasts, smooth muscle cells, neuronal cells, and endothelial cells.[10,11]

NOD-like receptors (NLRs) are a group of pattern recognition receptors. The NLRs family has 22 members in humans and 34 in mice.[12] The expression of NLRs in the cell nucleus and cytoplasm plays an important role in inflammation and immune response.[13,14] NLRs can induce an inflammatory immune response by sensing molecules associated with infection and tissue damage.[14] Previous studies have suggested that NLRs based inflammasomes exhibit an immune response mechanism that enhances the response to pollutants.[3] This suggests that NLRs may be involved in asthma pathogenesis.

The nucleotide-binding oligomerization domain-like receptor containing pyrin domain 3 (NLRP3) and nucleotide-binding and oligomerization domain-containing 2 (NOD2) are members of the NLRs family.[15] Recent studies have suggested that pathogens and allergens can activate NLRP3.[16] Interestingly, NLRP3 contributes to Th2 cell differentiation.[17] Both NLRP3 and NOD2 are involved in the immune defence response to viral infection.[18,19] In fact, viral infection of the respiratory tract is one of the triggers for asthma attacks. It has been confirmed that NOD2 and NLRP3 are closely associated with asthma pathogenesis of asthma.[20,21] In this review, we describe the functional characteristics of NOD2 and NLRP3 in asthma pathogenesis and explore the functional relationship between NOD2 and NLRP3. We propose a new approach to explore the pathogenesis of asthma through the NOD2-NLRP3 signalling pathway.

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NOD2 and Immune Reaction

Functional characteristics of NOD2 were first identified in 2001.[22] NOD2 is located on human chromosome 16 q12, and contains 18 coding exons. NOD2 is widely expressed in human tissues. NOD2 is a cytoplasmic protein mainly expressed in monocytes.[23] Some studies have found that other cells could express NOD2, including epithelial cells, eosinophils, basophils, and neutrophils.[24–27] It had been reported that NOD2 responds to microbial infections. SLC15A3 transports microbial products across endosomal membranes to NOD2.[28] Additionally, some studies have explored the relationship between B cells and endoplasmic reticulum inflammation. The IRE1α/TRAF2 signaling pathway provides a new connection between endoplasmic reticulum stress inflammation and NOD2 in innate immune responses.[29] Singh et al found that parkin targets NOD2 in astrocytes to regulate endoplasmic reticulum stress and inflammatory responses.[30]

NOD2 deficiency enhances the ability of mouse CD4+ T cells to produce IL-17, which promotes inflammation and participates in the pathogenesis of asthma.[31] Compared with wild-type mice, the microbial composition of the intestinal tract of mice with NOD2 deficiency is altered.[32] The expression level of NOD2 mRNA in the central nervous system is increased in mice infected with *Streptococcus pneumoniae*.[33] Travassos et al suggested that NOD2 recruits the autophagy protein ATG16L1 to defend against invading bacteria in the plasma membrane.[34] Respiratory syncytial virus infection enhances NOD2 signal transduction in an IFN-β-dependent manner in primary human cells.[35] The question of whether NOD2 effects the microecology of the lung microenvironment warrants further exploration.

Moreover, NOD2 has been reported to be involved in eosinophil activation.[24] A study demonstrated that bacterial infection activated NOD2, which triggered allergic asthma by promoting eosinophil-bronchial epithelial cell interactions in inflamed airways.[36] In ovalbumin-induced mouse models, NOD2 agonist promoted increased IgE levels.[37] These indicate the mechanism by which NOD2 is involved in allergic reactions.

NOD2 and Airway Allergen Tolerance

There is tolerance in the airway when exposed to harmful environmental antigens.[38] However, in the case of asthma, environmental antigens can cause airway eosinophilia, mucus hypersecretion, and airway hyperresponsiveness.[39] It has been suggested that the induction of airway tolerance is blocked by nod2 through the OX40 ligand IL-25 and Thymic stromal lymphopoietin (TSLP).[40,41] Regulatory T Cells play an important role in airway allergen tolerance.[42] The NOD2 ligand changes the balance between regulatory T and TH2 cells, which subsequently leads to increased susceptibility to eosinophilic airway inflammation.[40] Poole et al designed a study in which monocytes/macrophages were exposed to an organic dust extract from a swine facility and explored the role of NOD2 in complex organic dust reactions.[43] The expression of NOD2 induced by organic dust depends on NF-κB signalling, and NOD2 is a negative regulator of dust-induced inflammatory cytokines produced by monocyte phagocytes. Therefore, NOD2 might play an important role in airway allergic tolerance. At present, it is the mechanism of antigen immune tolerance that is used to desensitize and reduce the incidence of asthma.[44] Therefore, NOD2 could be a potential target for the treatment of allergic asthma.

NOD2 and Asthma

NF-κB contributes to the pathogenesis of airway inflammation in asthma.[45] NOD2 recognizes muramyl dipeptide (MDP), which is the basic bacterial structure that activates the NF-κB pathway and induces an immune response in the host.[46–48] Activation of NF-kB by NOD2 depends on a common downstream regulatory molecule receptor interacting serine/threonine kinase 2 (RIP2).[49] Subsequently, the produced pro-inflammatory mediators (such as iNOS, COX-2, TNF-α, and IL-1β) are involved in airway inflammatory responses.[50] Several studies have investigated the relationship between NOD2 and asthma. A previous study confirmed that bacterial infection mediates the activation of Nod1/2 to trigger allergic asthma by the interaction of eosinophils and bronchial epithelial cells in the inflamed airway.[36] Genetic polymorphisms have suggested that the rs3135499 polymorphism of the NOD2 gene might be associated with susceptibility to asthma in the Chinese Han population.[51] It was found that the expression of NOD2 was down regulated in CCR3+ granulocytes of patients with asthma.[52] Gaballah et al showed that compared with the healthy control group, the expression of NOD2 mRNA in peripheral blood mononuclear cells decreased in patients with atopic asthma, and downregulation of NOD2 expression was related to the severity of asthma.[20] However, another study suggested that

upregulation of NOD2 expression was observed in lung tissue and airway smooth muscle cells in patients with asthma.[53] In addition, a study with different results showed that there were no significant differences in the levels of NOD2 mRNA and protein between asthma and healthy groups.[54] Heterogeneity in results could be influenced by the patient populations, clinical phenotypes, and the types of specimens examined. Whether there is a difference in the expression of NOD2 between different asthma phenotypes requires further investigation.

NLRP3 and Immune Reaction

NLRP3 plays an important role in innate immunity.[55] There were results indicate that NLRP3 played a key transcription factor in the process of Th2 differentiation.[17] Further studies have revealed that NLRP3 is involved in the inflammatory response of Th2 and Th17 in asthmatic mice by inducing the expression and secretion of high-mobility group B1 (HMGB1).[56] Activated NLRP3 recruits apoptosis-associated speck-like protein containing a caspase recruitment domain (PYCARD) and cysteinyl aspartate-specific proteinase-1 (Caspase-1) to form a protein complex called NLRP3 inflammasome.[57] NLRP3 inflammasome, a molecular platform, was discovered in 2002.[57] Upon detecting environmental changes, the NLRP3 inflammasome activates and induces IL-1β and IL-18 secretion.[58,59] Interestingly, Nek7 is involved in the downstream discharge of potassium and plays an important role in the assembly and activation of NLRP3 inflammasome.[60,61] As an RNA binding protein, tristetraprolin may regulate NLRP3 transcription by reactive oxygen species (ROS) level during metabolism.[62] NLRP3 inflammasome is related to a variety of inflammatory diseases and involves the following four categories: genetic-related autoimmune diseases, metabolic disorders, diseases driven by the formation of crystals or aggregates, acute tissue injury, and chronic inflammation.[63]

NLRP3 and Acute Lung Injury

Grailer et al showed that the NLRP3 inflammasome plays a positive feedback role in the mechanism of inflammatory transmission in acute lung injury in mice.[64] Research has demonstrated for hyperoxia-induced acute lung injury that inflammatory response and apoptosis of lung epithelial cells were inhibited in NLRP3 deficient mice.[65] It had been found that the mechanism of NLRP3 inflammasome in acute lung injury was regulated by a series regulatory factors, such as melatonin, vimentin, Heme oxygenase-1, p120-catenin, PTEN-induced putative kinase 1 (PINK1) and carbon monoxide-releasing molecule-2 (CORM-2).[66–71] NLRP3 can be used as a therapeutic target for the inflammatory response to lung injury via various regulatory factors.

NLRP3 and Asthma

A previous study showed that NLRP3 participates in ovalbumin-mediated allergic airway inflammation independently of the inflammasome.[21] However, Allen et al suggested that NLRP3 had no significant effect on alum-free ovalbumin-induced allergic airway inflammation in mice.[72] The inconsistency in the experimental results above may stem from differences in the induced model methodologies. A study using antibiotics to disrupt commensal bacteria suggested that certain commensal bacteria could aggravate OVA-induced allergic asthma through NLRP3/IL-1β signalling.[73] In OVA-induced asthmatic mice, inhibitors, including atractylenolide III and Apolipoprotein, significantly inhibit the activation of the NLRP3 inflammatory response.[74,75] Further studies on NLRP3 and allergic asthma will be helpful in understanding the pathogenesis of asthma.

Studies of neutrophilic asthma have also been conducted. Studies have shown that NLRP3 inflammasome expression is upregulated in neutrophilic asthma phenotype.[76–79] The NLRP3 inflammasome-mediated IL-1β response contributes to neutrophilic inflammation and airway hyperresponsiveness in severe, steroid-resistant asthma.[80] MiR-223 target NLRP3, and neutrophil airway inflammation can be relieved in a mouse model of neutrophilic asthma.[81] These studies suggest that NLRP3 is involved in the pathogenesis of neutrophil asthma and may be used as a therapeutic target.

Other studies have confirmed that NLRP3 is also associated with asthma. Kim et al suggested that the highly selective NLRP3 specific inhibitor MCC950 may contribute to the treatment of severe hormone-resistant asthma.[80] Han et al found that NLRP3 inflammasome is involved in the molecular mechanism of rhinovirus-induced asthma exacerbation.[82] Without dependence on the functional platform of the inflammasome, NLRP3 can promote the polarization of M2 macrophages by upregulating the expression of IL-4 and thus participates in the regulation of asthma.[83]

Airway hyperresponsiveness is a characteristic manifestation of asthma. Activation of the NLRP3 inflammasome is regulated by Apolipoprotein E and ATP/P2X7 axis to participate in the mechanism of airway hyper-responsiveness in mouse models.[56,75] The rs4612666 polymorphism of NLRP3 is related to the symptoms of airway hyperresponsiveness induced by aspirin in Japanese patients with asthma.[84] However, Allen et al revealed that NLRP3 had no significant effect on airway hyperresponsiveness in allergic asthmatic mice.[72] In mouse models, the results of studies on NLRP3 and airway hyper-responsiveness have been inconsistent. The discrepancies may be related to experimental conditions and disease severity. The correlation between NLRP3 and airway hyperresponsiveness requires more systematic and comprehensive studies.

Relationship Between NOD2 and NLRP3

A previous study suggested that the biological mechanism of IL-1 β production induced by MDP requires NOD2 and NLRP3.[85] Under the same conditions, Wagner et al applied the comprehensive yeast two-hybrid method to analyze Nod-like receptor (NLR) protein-protein interactions.[86] The results showed that the CARD domains (CARD1+2) of NOD2 interacted with the PYD domain and linker region of NLRP3. RIPK2-mediated autophagy induction in influenza A virus-infected cells and mice inhibits NLRP3 inflammasome activation, reduces inflammatory cytokine production, and attenuates neutrophil recruitment.[87] Another study has confirmed this result. Lupfer et al suggested that the NOD2-RIP2 pathway may contribute to the inhibition of NLRP3 inflammasome activation during intestinal pathogen infection.[88] Other studies have also explored the relationship between NOD2 and NLRP3.

Kim et al demonstrated that TLR2 and NOD2 contribute to the induction of pro-IL1β and NLRP3 in dendritic cells infected with H. pylori.[89] In a mouse model, the absence of the NOD2 gene was related to a decrease in NLRP3 expression induced by Coxsackievirus B3.[90] Shi et al suggested that NOD2 positively regulates NLRP3.[91] Additionally, the NOD2 ligand MDP upregulates human beta-defensin 2 (hBD2) and inflammatory cytokines, which are dependent on the NLRP3 inflammasome in human dental pulp cells.[92] These studies indicate a close correlation between NOD2 and NLRP3.

mtDNA can act as a signal from the mitochondria to the nucleus to activate the main innate immune signaling pathway, which indicates that cells are undergoing major damage, thus reminding them of major damage. The mitochondrial outer membrane is a platform for the signal transduction of the mitochondrial antiviral signaling protein (MAVS) and the NLRP3 inflammasome.[93] Indeed, the N-terminal residue of NLRP3 constitutes the minimum sequence that mediates NLRP3-MAVS interaction.[94] As a mitochondrial-related adaptor molecule, MAVS mediates the recruitment of NLRP3 to the mitochondria, activation of the NLRP3 inflammasome, and promotion of IL-1β and IL-18 production.[94] Interestingly, after virus-induced asthma attacks, elevated levels of IL-1β and IL-18 were detected.[95–97] IL-1β is involved in steroid-resistant neutrophilic inflammation and airway hyperresponsiveness in asthma.[80] IL-18 is involved in airway inflammation (Th1 inflammatory pathways and Th2 inflammatory pathways), airway hyperresponsiveness and mucus metaplasia in asthma.[98] A previous study suggested that Sendai virus-induced the activation of MAVS promotes NLRP3 activation by enhancing mitochondrial reactive oxygen species (ROS) sensing.[99] Viral infection triggers elevated mitochondrial ROS production, which depends on NOD2.[100,101] Another study found that virus infection promoted the interaction between NOD2 and MAVS to activate antiviral response.[102] These results suggest that MAVS may act as a bridge between the NOD2 and NLRP3 signaling pathways (Figure 1).

Conclusion

NLRs are essential for the recognition of molecular patterns related to microorganisms and danger signals, and have the ability to elicit immune responses through the formation of inflammasomes and activation of inflammatory signaling pathways. NOD2 and NLRP3, as typical members of the NLRs family, are closely associated with asthma. There may be an NOD2-NLRP3 signaling pathway that is mediated by MAVS. Therefore, it is valuable to investigate the relationship between oxidative stress-induced lung damage and the NOD2-NLRP3 signaling pathway in harmful factor-induced asthma exacerbations. Further investigation of the NOD2-NLRP3 signaling pathway's biological functions may contribute to identifying novel therapeutic targets for asthma.

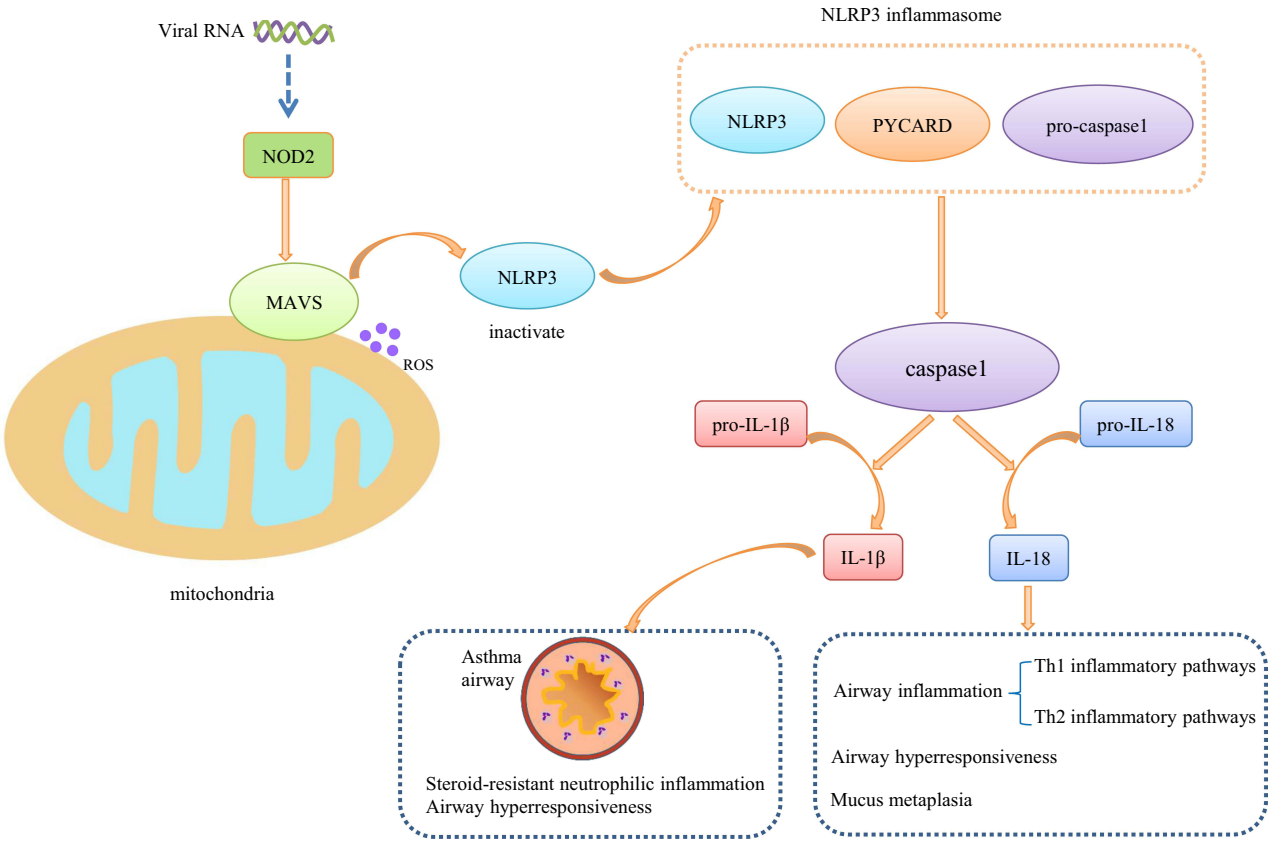

Figure 1 NOD2 identifies virus related dangerous molecules and transmits the signal to MAVS. MAVS mediates the recruitment of NLRP3 to mitochondria and promotes the activation of NLRP3. Activated NLRP3 recruits PYCARD and pro-caspase1 to form NLRP3 inflammasome. Subsequently, activated caspase1 promotes the release of IL-1β and IL-18.

Abbreviations

NOD2, nucleotide-binding and oligomerization-domain containing 2; NLRP3, nucleotide-binding oligomerization domain-like receptor containing pyrin domain 3; NLRs, NOD-like receptors; PYCARD, apoptosis-associated speck-like protein containing a caspase recruitment domain; Caspase-1, cysteinyl aspartate-specific proteinase-1; MDP, muramyl dipeptide; RIP2, receptor interacting serine/threonine kinase 2; ROS, reactive oxygen species; PINK1,PTEN-induced putative kinase 1; CORM-2, carbon monoxide-releasing molecule-2; hBD2, human beta defensin 2; MAVS, mitochondrial antiviral signalling protein.

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Disclosure

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