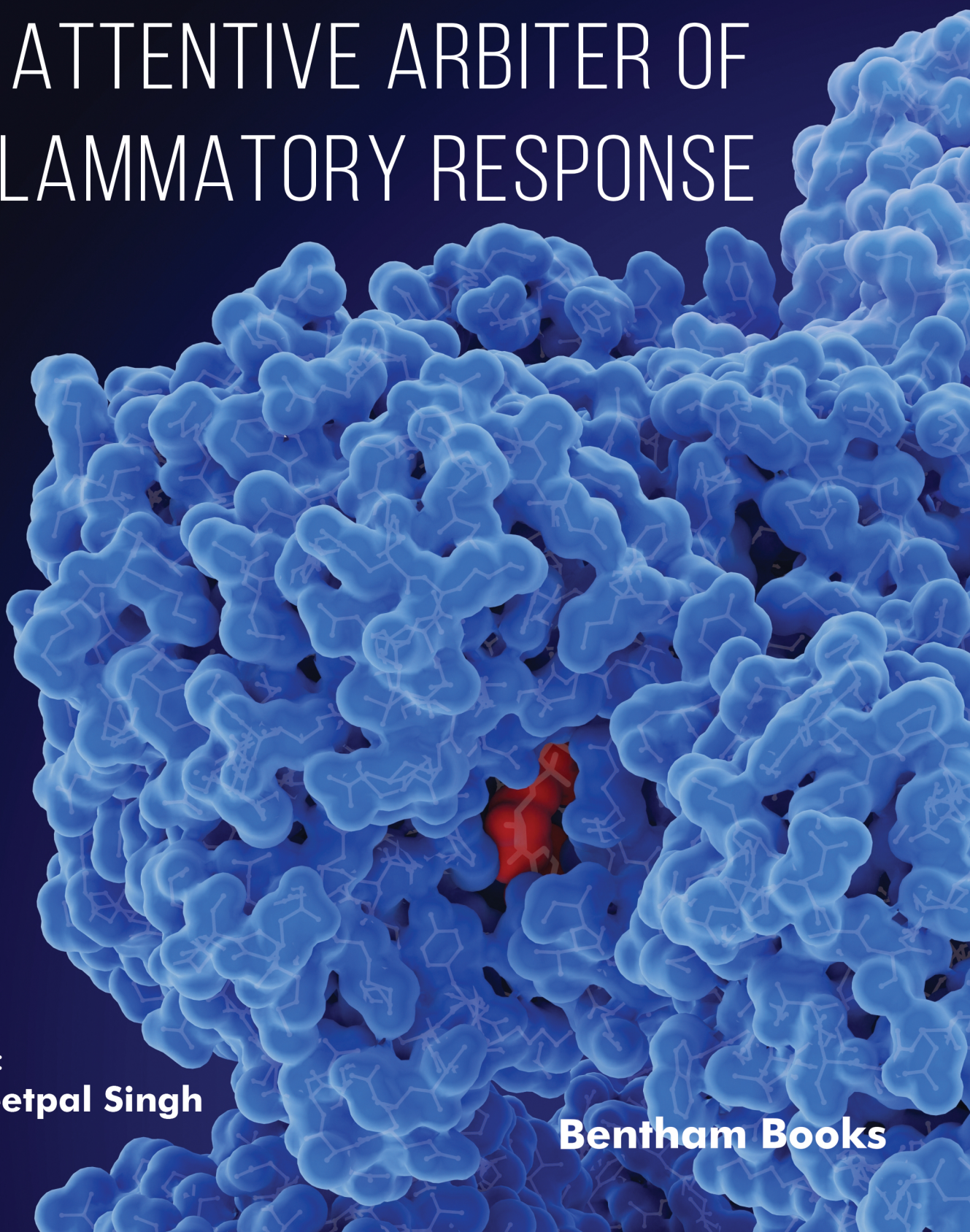
THE NLRP3 INFLAMMASOME: AN ATTENTIVE ARBITER OF INFLAMMATORY RESPONSE



Editor:
Puneetpal Singh

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The NLRP3 Inflammasome: An Attentive Arbiter of Inflammatory Response

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PREFACE

The human body is an intricate and wondrous system, constantly engaged in a delicate balance of maintaining health and combating various threats. Inflammation, a fundamental process of the immune system, plays a critical role in the body's defense against infection and injury. While inflammation is an essential mechanism for maintaining tissue homeostasis, dysregulated or chronic inflammation can lead to the development and progression of numerous diseases. Within the realm of inflammation, the NLRP3 inflammasome has emerged as a captivating protagonist in recent years. This book, "The NLRP3 Inflammasome: An Attentive Arbiter of Inflammatory Response," delves deep into the intricate workings of this molecular complex and explores its pivotal role in shaping the inflammatory landscape.

Our understanding of the NLRP3 inflammasome has undergone significant advances since its initial discovery. This enigmatic protein complex, comprised of NLRP3 (NOD-like receptor family, pyrin domain-containing 3), ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain), and pro-caspase-1, acts as a sensor of danger signals within the cell, orchestrating a cascade of events that culminate in the production and release of pro-inflammatory cytokines, particularly interleukin-1β (IL-1β) and IL-18.

"The NLRP3 Inflammasome: An Attentive Arbiter of Inflammatory Response" is a comprehensive exploration of the intricacies surrounding the NLRP3 inflammasome. Through the collaboration of esteemed scientists, researchers, and clinicians, this book seeks to shed light on the various aspects of NLRP3 biology, regulation, and its involvement in a wide array of diseases, ranging from metabolic disorders to neurodegenerative conditions.

In the first chapter, writer Dr. Rashmi Singh, along with her co-authors, has made a significant contribution to the understanding of the role of the NLRP3 inflammasome in airway inflammation and fibrosis. In their research, they have focused on elucidating the mechanisms of NLRP3 inflammasome activation and its impact on respiratory diseases such as asthma. Their work has highlighted the crucial role of NLRP3 in mediating caspase-1 activation and the secretion of proinflammatory cytokines, which contribute to the progression of asthma by promoting excessive inflammation, extracellular matrix accumulation, and airway remodeling. Moreover, they have identified endotoxin (lipopolysaccharide, LPS) as one of the activators of NLRP3, linking environmental factors to the incidence of asthma and allergic diseases. This chapter provides a comprehensive summary of their research findings, shedding light on the mechanisms underlying NLRP3 inflammasome activation and its regulation in asthmatic exacerbations.

In the second chapter, Dr. Sushweta Mahalanobish, along with co-authors Noyel Ghosh and Parames C. Sil, has made a significant contribution to the understanding of the role of NLRP3 inflammasome in pulmonary hypertension (PH). Their research focuses on the progressive pulmonary vasculopathy characterized by increased mean pulmonary arterial pressure, adverse vascular remodeling, and right ventricular failure. They explore the involvement of inflammation as a crucial factor in the onset and development of PH, specifically highlighting the NLRP3 inflammasome as a key mediator in the signaling cascade that regulates PH-associated conditions through inflammatory mechanisms. The activation of NLRP3 and the subsequent release of proinflammatory cytokines IL-1β and IL-18 contribute to adverse consequences on pulmonary vasculature and the onset of PH. The chapter delves into current PH therapies and their limitations and introduces the potential therapeutic targeting of NLRP3 inflammasomes to modulate inflammation in PH pathobiology. The authors provide a comp-

rehensive insight into the role of NLRP3 inflammasome in PH and its implications for future therapeutic interventions.

Dr. Abhinav Kanwal and his team have provided a comprehensive exploration of the modulatory mechanism of the NLRP3 inflammasome in heart diseases. Despite significant advancements in therapy, heart failure remains a leading cause of mortality worldwide. The authors highlight the crucial role of the inflammasome in the progression of various cardiovascular diseases, including heart failure, abdominal aortic aneurysm, atherosclerosis, diabetic cardiomyopathy, hypertension, dilated cardiomyopathy, cardiac remodeling, and calcific aortic valve disease. Specifically, they focus on the NLRP3 inflammasome, a multi-protein signaling platform that tightly regulates inflammatory responses and antimicrobial host defense, leading to the generation of pro-inflammatory cytokines through the activation of caspase-1 and subsequent pyroptosis. By investigating the NLRP3 inflammasome in different cardiovascular diseases, the authors aim to uncover critical disease triggers and endogenous modulators with the aimof developing new therapeutic interventions in the future. The chapter provides a summary of recent literature, emphasizing the activation mechanism of the NLRP3 inflammasome and its implications in the pathophysiology of heart failure, shedding light on this complex and intriguing aspect of heart diseases.

In the fourth chapter, Monika Joon and Manisha Yadav explore the intricate relationship between Mycobacterium tuberculosis (Mtb) and the inflammasome. Mtb is known as a highly successful human pathogen, capable of evading the host immune response through the development of robust effectors. It can survive and multiply within the host's immune system, even in the presence of immune tools meant to eliminate it. Granuloma formation, a compensatory mechanism, offers partial benefits to both the host and the pathogen. While extensive research has been conducted on various mycobacterial virulence factors, the relatively newer concept of inflammasomes requires further investigation. Insights into the inflammasome-Mtb interaction may open up new avenues for the development of host-directed therapy (HDT) strategies to combat TB. By comprehending the intricate dynamics between the inflammasome and Mtb, novel approaches for managing this disease can be explored.

The fifth chapter by Syed Ehtaishamul Haque, Aamir Khan, and Ashif Iqubal deals with an overview of the NLRP3 inflammasome's activation mechanism, its association with cardiovascular complications, and the potential of NLRP3 inhibitors as cardioprotective agents. They highlight the positive correlation between NLRP3 inflammasome activation and various cardiovascular disorders, including hypertension, angina, arrhythmia, cardiac fibrosis, myocardial infarction, and heart failure. By discussing the structural components of the NLRP3 inflammasome and its molecular activation pathway, the authors underline its crucial role in the pathogenesis of cardiovascular diseases. Furthermore, they shed light on promising outcomes from studies exploring NLRP3 inflammasome inhibitors in cardiovascular disorders. Overall, the manuscript underscores the importance of targeting the NLRP3 inflammasome as a potential therapeutic approach for managing and treating cardiovascular diseases.

In the sixth chapter, Sonal Yadav examines the role of NLRP3 in protozoan parasitic infections. They discuss the activation of the NLRP3 inflammasome by various protozoan parasites, including *Giardia duodenalis*, *Entamoeba histolytica*, *Trichomonas vaginalis*, Plasmodium species, *Trypanosoma cruzi*, *Schistosomes*, *Toxoplasma gondii*, and Leishmania species. The authors highlight the protective effects of NLRP3 against certain infections, such as Giardia, *Trypanosoma cruzi*, and *Entamoeba histolytica*, while also noting its contribution to pathology in Schistosomes and Malaria parasite infections. They emphasize the need for

further research to better understand the precise mechanisms and roles of NLRP3 in host defense and inflammatory pathology in parasitic protozoan infections, which could pave the way for the development of innovative treatment strategies.

The seventh chapter by Dr. Adekunle Babajide Rowaiye and his colleagues focuses on the NLRP3 inflammasome as a target for anti-inflammatory drugs. They highlight the crucial role of the NLRP3 inflammasome in the innate immune response and its association with various inflammation-related diseases. The authors discuss the activation of the NLRP3 inflammasome and the production of proinflammatory cytokines, emphasizing the importance of inhibitory mechanisms to decrease inflammation and inflammasome-mediated cell death. They further explore the potential of targeting signaling molecules along the NLRP3 inflammasome pathway as drug targets for effective inhibition and downregulation of proinflammatory cytokines. The chapter provides insights into the classes of NLRP3 inflammasome inhibitors, their anti-inflammatory effects, and underlying mechanisms of action.

Dr. Agnès Hamzaoui and co-authors, in the eighth chapter, investigate the potential value of sputum levels of Interleukin-38 (IL-38) and NLRP3 inflammasome in severe childhood asthma. Asthma is known to be an inflammatory airway disorder with varying expression of cytokines based on disease severity. The transition from exacerbation to remission involves a complex interplay between inflammatory and anti-inflammatory mediators. The authors focus on the expression of IL-38 and NLRP3 inflammasome in severe asthmatic children. They find that NLRP3 inflammasome is upregulated in severe asthma, while levels of IL-38 are low. The inflammatory profile of severe asthma in children is characterized by the expression of IL-17, IL-32, IL-1β, and NLRP3 inflammasome. This study sheds light on the potential role of IL-38 and NLRP3 inflammasome as biomarkers in severe childhood asthma. It contributes to a better understanding of the inflammatory mechanisms involved in the disease.

The ninth chapter by Lokesh Sharan, Anubrato Pal, Priya Saha, and Ashutosh Kumar explores the role of inflammasomes, specifically NLRP1, NLRP3, NLRC4, and AIM2, in inflammation and neuropathic pain. These inflammasomes play a crucial role in the development of autoimmune and metabolic disorders, cancer, and various inflammatory conditions. The activation of inflammasomes is triggered by molecular changes, such as mitochondrial dysfunction, neuroinflammation, lysosomal damage, oxidative stress, sensitization, and disinhibition, leading to the activation of proinflammatory pathways and subsequent development of inflammasome-related neuropathic pain. Among these inflammasomes, NLRP3 has been extensively studied and identified as a key player in neuropathy. This chapter provides an overview of the involvement of inflammasomes, particularly NLRP3, in neuropathic pain. Based on available evidence, targeting inflammasome activity is proposed as a potential cutting-edge approach for the successful treatment of neuropathic pain. The understanding of inflammasome-mediated mechanisms in neuropathic pain may pave the way for the development of novel therapeutic strategies in the future.

The chapters in this book provide in-depth analyses of the mechanisms underlying NLRP3 inflammasome activation, the signaling pathways involved, and the interplay between NLRP3 and other cellular processes. Additionally, the authors delve into the consequences of dysregulated NLRP3 activation, highlighting the implications for disease pathogenesis and potential therapeutic interventions. From the role of NLRP3 in sterile inflammation to its contribution to the pathogenesis of autoimmune disorders, each chapter offers valuable insights into this captivating field of research.

I hope that "The NLRP3 Inflammasome: An Attentive Arbiter of Inflammatory Response" serves as a valuable resource for scientists, clinicians, and students alike, fostering a deeper understanding of the NLRP3 inflammasome and its impact on human health. It is our sincere belief that by unraveling the mysteries surrounding this vigilant arbiter of inflammation, we can unlock novel therapeutic strategies that harness its potential for the betterment of patients worldwide.

I would like to express my sincere gratitude to Mr. Nitin Kumar for his invaluable assistance in the editing and refining of the book. I am also immensely thankful to Ms. Humaira Hashmi, In-charge of the eBook Department, and Ms. Asma Ahmed, Manager of the eBooks Publication Department for her support in publishing this book and Mr. Mahmood Alam, Director of Publications at Bentham Science Publishers, for their unwavering support, encouragement, and assistance. Their contributions have been instrumental in bringing this book to fruition.

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CHAPTER 1

Role of NLRP3 Inflammasome in Airway Inflammation and Fibrosis

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Abstract: The NLRP3 inflammasome is a critical component of the innate immune system that mediates caspase-1 activation and the secretion of proinflammatory cytokines IL-1β/IL-18 in response to microbial infection and cellular damage. Nucleotide-binding oligomerization domain (NOD)-like receptor family pyrin domain 3 (NLRP3), one of the members of the NLR family, consists of NLRP3, the adaptor molecule, apoptosis-associated speck-like protein containing a caspase and recruitment domain (ASC) and an inflammatory caspase-1 that causes excessive inflammasome activation in respiratory diseases like asthma and could exacerbate the progression of asthma by considerably contributing to ECM accumulation and airway remodeling. NLRP3 is closely associated with airway inflammation and asthma exacerbations as endotoxin (lipopolysaccharide, LPS) is one of its activators present in the environment. Asthma is a complex immunological and inflammatory disease characterized by the presence of airway inflammation, airway wall remodeling and bronchial hyperresponsiveness (BHR). Symptomatic attacks of asthma can be caused by a myriad of situations, including allergens, infections, and pollutants, which cause the rapid aggravation of respiratory problems. The presence of LPS in the environment is positively correlated with the incidence of asthma and allergic diseases. In this chapter, we summarize our current understanding of the mechanisms of NLRP3 inflammasome activation by multiple signaling events in asthmatic exacerbations and their regulation.

Keywords: Caspases and NLRP3 regulators, Fibrosis, Inflammation, Inflammasomes, Pyroptosis, ROS.

INTRODUCTION

The fundamental elements of the innate immune system are physical as well as chemical obstacles to infection and a number of cellular components that identify invasive pathogens and trigger antimicrobial immune responses. The mucosal surfaces with antimicrobial secretions, vascular endothelium, ciliated respiratory

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epithelium, and epidermis all serve as examples of physical and chemical defensive systems. The air, along with a mixture of gases, carries other substances, such as dust particles, smoke and biological contaminants, such as dust mites, fungi, bacteria, spores, pollen grains and viruses. Lungs remain in continuous contact with the environmental air and several stimuli; hence, the quality of breathing air has a great impact on the health of an individual (Fig. **1**). The overall risk assessment of respiratory diseases is further complicated by socioeconomic status, lifestyle, age, nutritional status, environmental exposure to pollutants and genetic factors of the individual. These factors altogether may predispose or alter the prognosis of the disease (Fig. **2**). The extent of lung damage is also determined by the toxicity, intensity, duration and route of exposure as well as the physical state, such as the size or characteristics of the inhaled substances.

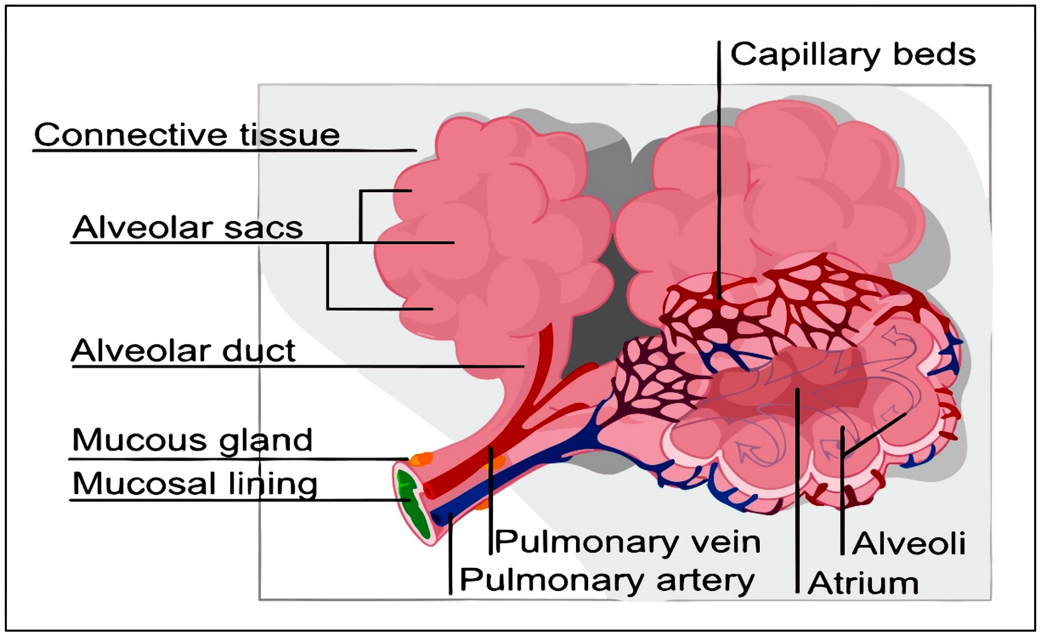


Fig. (1). Structure of lungs showing internal anatomy. Lungs are divided into smaller subunits *i.e.*, alveolar sacs confined with fine capillaries (www.wikipedia.org).

INNATE IMMUNE SYSTEM AND PATTERN RECOGNITION RECEPTORS (PPRs)

Apart from acting as the first line of protection, innate immunity is also essential for the initiation of adaptive responses, which guard against recurrent infections caused by the same pathogen [1]. The cellular elements of innate immunity also include T lymphocytes, cytotoxic natural killer (NK) cells, phagocytic

macrophages and granulocytes, and DCs that deliver antigens. By using autophagy, phagocytosis, complement activation, and immunological stimulation by several families of PRRs, the innate immune system is initially able to identify and restrict microorganisms in an infection [2]. To identify the evolutionarily conserved features of pathogens, referred to as pathogen-associated molecular patterns (PAMPs), the innate immune reactions require a small number of pattern recognition receptors (PRRs), which are encoded in the germ line [3]. In addition, PRRs identify host elements as "danger" signals if they are found in atypical biological macromolecules or on areas of either infection, inflammation or any kind of cellular stress. Several different categories of PRRs were identified by a particular pathogen *via* diverse PAMPs. Host PRRs recognize microbes with extremely diverse biochemical compositions by nearly identical mechanisms. A transmembrane protein called TLRs and cytosolic NLRs are the two PRR families with the best-described members. The induction of specific genes and the formation of a wide variety of chemicals, such as cytokines, cell adhesion molecules, chemokines, and immunoreceptors, are the final effects of PRR-induced signal transduction processes. These molecules work with each other to synchronize the initial infection-related response from the host in addition to serving as a crucial link to the adaptive immune response. The two most important PAMPs are thought to be viral RNA and bacterial endotoxins. One of the strongest PAMPs ever discovered is LPS, a bacterial endotoxin that causes inflammation.

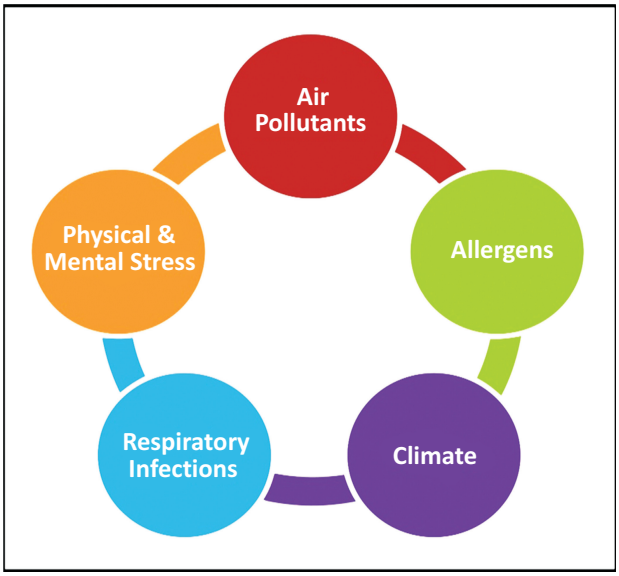


Fig. (2). Common inducers of respiratory diseases among thousands of known factors (www.wikipedia.org).

LPS INDUCED RESPIRATORY DISEASES

Endotoxin or Lipopolysaccharide (LPS) is the most ubiquitous pro-inflammatory factor present in almost all types of living environments (rural, urban or larger cities). Being a major component of bioaerosols, LPS is a common cause of airborne-associated lung diseases all over the world. It is an integral component of the outer wall of gram-negative bacteria, with potent immune stimulatory capacity due to the presence of Lipid A moiety (Fig. **3**).

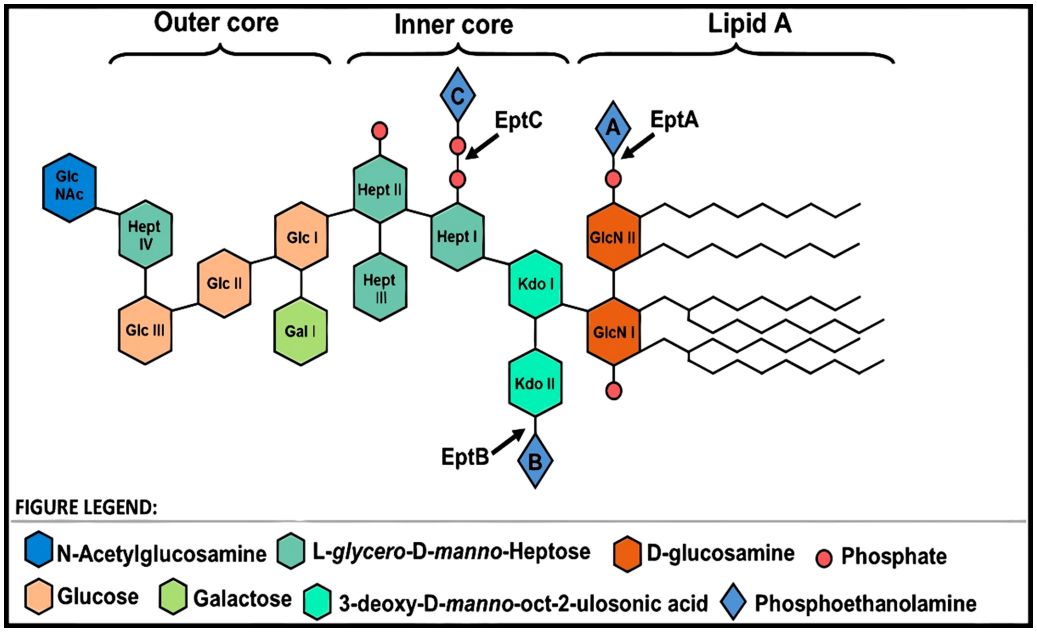


Fig. (3). Structure of Lipopolysaccharide [10].

In addition to the cytoplasmic membrane, the gram-negative bacterial cell wall also has an outer membrane made of LPS, proteins, and phospholipids as well as a thin coating of peptidoglycan. The lipid A moiety is connected to the core polysaccharide by an O-linked polysaccharide, which is what makes up LPS [4]. LPS binds to the TLR4 receptor to initiate several signaling cascades, including inflammation. LPS has a potent immunostimulatory capacity that stimulates immune cells to initiate inflammatory response characterized by proinflammatory cytokines, such as tumor necrosis factor (TNF-α), IL-1, IL-6 and interferon gamma (IFN-γ) [5]. Increasing incidences of allergic and asthmatic diseases in developing countries have been explained by the "hygiene hypothesis", where low level of endotoxin exposure at an early age is responsible for protection from allergic diseases as compared to exposure at later phases of life. Hygienic

practices also contribute to more episodes of allergic diseases in the later phases of life [6] (Strachan, 1989). On the other hand, in recent years, studies have shown that the presence of LPS in a living environment was positively correlated with the incidence of asthma and allergic diseases [7]. In another study, lower doses of LPS exposure have been found to cause asthmatic exacerbations in mice models [8]. Recent studies have linked the risk of developing asthma to skewed Th2 response to an allergen and an imbalance between Th1 and Th2 response [9].

LPS Induced Asthmatic Exacerbations

Asthma is a complex disease of the airways affecting almost all ages, genders and races worldwide. The major symptoms include wheezing, coughing and shortness of breath, leading to sleepless nights and missed school and workdays. It is associated with enormous healthcare expenditures, and despite the advances in effective therapies, the economic burden associated with disease control and morbidity continues to increase. It represents multiple phenotypes depending upon the frequency and severity of the inducer (Figs. **4** and **5**).

Airway hyperresponsiveness is a pathological hallmark of asthma, where airways become highly sensitive and responsive to inhaled constrictor agonists, such as methacholine, histamine or cold air [11]. It is defined as an ease with which the airways respond to a stimulator, such as the sensitivity and reactivity to a given stimuli. Histamine, prostaglandins and leukotriene altogether mediate the constriction and narrowing of the airway passage. They promote smooth muscle contraction, increased vascular permeability in small blood vessels and mucus secretion, and also help in further recruitment of leukocytes to airways [12].

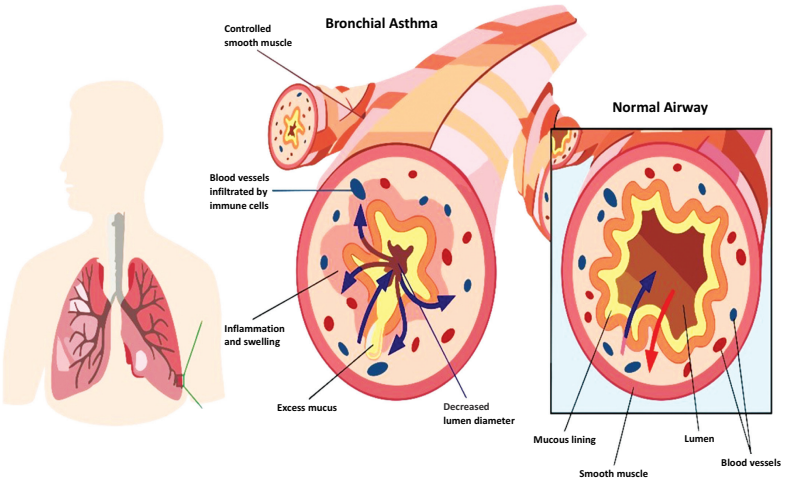


Fig. (4). Pathological changes in bronchial asthma (www.kabs.com).



Fig. (5). Factors responsible for inducing and exacerbating asthma (www.wikipedia.org).

Asthmatic inflammation is mainly driven by Th2-specific cytokines, such as IL-4, IL-5 and IL-13. IL-5 regulates the genes responsible for cell proliferation and maturation of eosinophils, whereas IL-4 promotes class switching of IgG to IgE production. Interleukin-13 mediates airway hyperresponsiveness, mucus production and sub-epithelial fibrosis [13]. Inflammation can be of two types, acute and chronic. Acute inflammation can be caused by toxic pollutants, microbial intrusion, or tissue injury. The most noticeable aspect of the remodeling of the airways is fibrosis, which is the end phase of chronic inflammatory processes, and excessive extracellular matrix (ECM) deposition is one of its defining characteristics. Structural changes in the asthmatic airways, irreversible or reversible, are referred to as airway remodeling. These changes result in airway wall thickening associated with a rapid decline in the lung function and severity of the disease. It is characterized by epithelial cell alterations, sub-epithelial fibrosis, sub-mucosal gland hyperplasia, increased airway smooth muscle mass and airway vascularization [14, 15].

Inflammasome: An Important Aspect of Innate Immune System

The word “Inflammasome” was first used in 2002 by a scientific team led, Jurg Tschopp. It is a complex consisting of multiple proteins made up of a Nod sensor that can trigger an inflammatory caspase called caspase 1 [16]. The human genome has 23 NLR genes, compared to 34 NLR genes in the mouse genome [17]. Various inflammasomes have various activation patterns, and NLRs participate in a variety of signaling pathways. Based on the commonalities in their domain topologies and the unique roles they play, these receptors are further split

into three different subfamilies. The three subfamilies are made up of the NLRPs also known as NALPs, the IPAFs (also called NLRC4,) and the NODs [18]. The biggest and most well-studied NLRP subfamily that possesses the PYRIN (PYD) domain is the NLRP3 inflammasome [19]. The nucleotide-binding domain and leucine-rich repeat protein 3 (NLRP3) inflammasome are now the most studied of the four inflammasome subtypes. NLRP3 inflammasomes are vast multiprotein complexes formed inside cells that participate in exacerbating inflammatory response in the lungs after activating pro-inflammatory cytokine IL-1β and IL-18, and a lytic form of programmed cell death. An increasing body of research has shown that pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), which are known to enhance asthmatic symptoms, trigger the activation of NLRP3 inflammasome. LPS-induced respiratory illness can be of several types, like lung inflammation, injury, disseminated Intracellular Coagulation (DIC) and oxidative damage. But all of these lead to an exacerbated response in airway disease conditions.

The most significant and researched class of PRRs is the Toll like receptor (TLR) family. TLRs were initially identified primarily due to their resemblance to the Toll protein of *Drosophila melanogaster*, which was involved in antifungal response as well as dorsoventral patterning during embryogenesis of *Drosophila* [20, 21]. TLRs are receptors that are positioned at cell or endosome membranes. They recognize PAMPs through their LRR domain and use their TIR domain to transmit signals to the intracellular space [22]. Numerous distinct signaling pathways are activated when TLR4 is engaged by particular PAMPs. TLR4 either activates the toll/interferon response factor (TRIF)-dependent signaling pathway or the myeloid differentiation factor 88 (MyD88)-dependent and independent signaling pathway to produce type I interferons (IFNs) and proinflammatory cytokines [23]. The activation of MAPK and early-phase NF-B contributes to the development of a proinflammatory reaction that is brought in by the MyD88-dependent pathway [3]. The MyD88-independent pathway leads to the induction of IFN and IFN-inducible genes. A significant number of cytosolic PRRs are responsible for TLR4-independent pathogen recognition [24].

The human cias1 gene, which has 9 coding exons and is found on chromosome 1q44, is the source of the 1016 amino acid protein NLRP3 [25]. NLRP3 inflammasome is a multimeric protein complex made up of the adapter protein ASC, the caspase-1 enzyme, and the sensor molecule NLR3 [26]. NLRP3 has a core NACHT domain, a carboxy-terminal LRR, and a PYD domain at its amino-terminal region interacting in association with the PYD domain of ASC in a homotypic manner [26].

Activation Mechanism of the NLRP3 Inflammasome

The NLRP3 inflammasome is activated by a wide range of stimuli, both pathogenic and sterile [27]. There are two categories of inflammasome effects: "conventional" and "non-conventional" impacts [28]. The first stage of the process is a reaction that involves the activation of certain cytokines or TLR4 receptors (through a PRR-mediated signal), which can increase the NF-kb mediated transcription of NLRP3, pro-IL-1 and pro-IL-18 [29]. The complex's oligomerization phase, in which the adaptor proteins ASC and inflammatory pro-caspase-1 are recruited, represents the second stage of the canonical route. The complex is then activated, and the conversion of pro-IL-1 and pro-IL-18 into their activated version takes place. Also, the subsequent caspase-1 activation causes a breakdown of Gasdermin D (GSMD), which causes pyroptosis, a sort of programmed form of cell death [30]. It is characterized by cell enlargement, accompanied by lysis and the discharge of internal contents, including proinflammatory cytokines like IL1 and IL18. The non-canonical pathway is dependent on either caspase-4/5 or caspase-11 in mice (for humans) instead of caspase-1 [28]. Ion flux, mitochondrial malfunction, and the formation of reactive oxygen species (ROS), as well as lysosomal disruption, are among the various processes reported to cause inflammasome activation. Uncertainty still exists on how these circumstances contribute to inflammasome activation. An intracellular potassium ion efflux is one activation process that seems to be conserved by numerous activators. Extracellular ATP can activate the P2X7, a purinergic receptor (ATP-gated ion channel,) causing potassium efflux, that is required for the activation of the inflammasome [19]. LPS priming causes the formation of NLRP3, which is essential for pro-inflammatory cytokine and ATP release *via* the P2X7 receptor [31].

ROS generation represents a stress-related signal, which is also a key step in NLRP3 inflammasome activation by acting on a target that is upstream of it [32]. By preventing NLRP3 activation, ROS inhibition can decrease the release of IL-1β [33]. DAMPs, such as crystalline or particulate matter, can cause lysosomal membrane damage, releasing lysosomal substances (such as cathepsin B) into the cytosol and activating NLRP3 [34]. IL-1β exerts its physiological impacts by initiating a cascade of signaling that includes p38, JNK (Jun N-terminal kinase) and NF-kB activation (Fig. **6**) [29, 35].

NLRP3 Inflammasome and Airway Inflammation

Innate immunity and inflammation appear to be significantly influenced by the inflammasome. The contribution of NLRP3 inflammasome to airway inflammation is expanding [36]. There is debate about the extent of the