Innate Immune Responses and Pulmonary Diseases

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Abstract

Innate immunity is the first defense line of the host against various infectious pathogens, environmental insults, and other stimuli causing cell damages. Upon stimulation, pattern recognition receptors (PRRs) act as sensors to activate innate immune responses, containing NF-κB signaling, IFN response, and inflammasome activation. Toll-like receptors (TLRs), retinoic acid-inducible gene I-like receptors (RLRs), NOD-like receptors (NLRs), and other nucleic acid sensors are involved in innate immune responses. The activation of innate immune responses can facilitate the host to eliminate pathogens and maintain tissue homeostasis. However, the activity of innate immune responses needs to be tightly controlled to ensure the optimal intensity and duration of activation under various contexts. Uncontrolled innate immune responses can lead to various disorders associated with aberrant inflammatory response, including pulmonary diseases such as COPD, asthma, and COVID-19. In this chapter, we will have a broad overview of how innate immune responses function and the regulation and activation of innate immune response at molecular levels as well as their contribution to various pulmonary diseases. A better understanding of such association between innate immune responses and pulmonary diseases may provide potential therapeutic strategies.

Keywords

Pattern recognition receptors · NF-κB signaling · IFN response · Inflammasome · Pulmonary diseases

Abbreviations

AHR	Airway hyperresponsiveness
AIM2	Absent in melanoma 2
ALS	Amyotrophic lateral sclerosis
AnkRs	Ankyrin repeats
ASC	Apoptosis-associated speck-like protein containing a caspase recruitment domain or CARD
ATP	Adenosine triphosphate
BAF1	Barrier-to-autointegration factor 1
BAK	BCL2 antagonist/killer
BAX	BCL2-associated X
BHR	Bronchial hyperreactivity
C/EBPε	CCAAT enhancer-binding protein epsilon

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CCDC50	Coiled-coil domain-containing protein 50
cGAMP	Cyclic GMP-AMP
cGAS	Cyclic GMP-AMP synthase
CHIKV	Chikungunya virus
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CS	Cigarette smoke
CYLD	CYLD lysine 63 deubiquitinase
DAMPs	Danger-associated molecular patterns
DDX3	DEAD (Asp-Glu-Ala-Asp)-box helicase 3
DHX15	DEAH-box helicase 15
DHX9	DExH-box helicase 9
DRAIC	Downregulated RNA in cancer, inhibitor of cell invasion and migration
eATP	Extracellular ATP
FEV1	Forced expiratory volume in 1 s
FSTL-1	Follistatin-like 1
FVC	Forced vital capacity
HCV	Hepatitis C virus
HDAC6	Histone deacetylase 6
HIV	Human immunodeficiency virus
HOPS	Hepatocyte odd protein shuttling
IFI16	Interferon-γ (IFNγ)-inducible protein 16
IFN	Interferon
IFNAR	IFN-I receptor
IFN-α	Type I interferon-alpha
IFN-β	Type I interferon-beta
IKK	IκB kinase
IL-1	Interleukin-1
IPF	Idiopathic pulmonary fibrosis
IRAKs	IL-1R-associated kinases
IRF9	IFN-regulatory factor 9
ISGF3	IFN-stimulated gene factor 3
ISGs	IFN-stimulated genes
ISREs	IFN-stimulated response elements
IκB	Inhibitor of κB
JAK1	Tyrosine kinases Janus kinase 1
JNK	Jun N-terminal kinase
LDH	Lactate dehydrogenase
LF	Lethal factor
LGP2	Laboratory of genetics and physiology 2
LPS	Lipopolysaccharide
m(6)A	N(6)-Methyladenosine
MAD5	Melanoma differentiation-associated factor 5
MAVS	Mitochondrial antiviral signaling protein
Miz1	c-Myc-interacting zinc finger protein-1
MSU	Monosodium urate
mtDNA	Mitochondrial DNA
mtROS	Mitochondrial reactive oxygen species
MyD88	Myeloid differentiation primary response 88
MYSM1	Myb-like, SWIRM, and MPN domains 1
NADPH	Nicotinamide adenine dinucleotide phosphate hydrogen
NAIPs	NLR family, apoptosis inhibitory proteins
NF-κB	Nuclear factor-κB
NLRs	NOD-like receptors
NLS	Nuclear localization sequence
NOD	Nucleotide oligomerization domain
NSP6	Nonstructural protein 6
OGT	O-GlcNAc transferase
ORF6	Open reading frame 6
OTUB1	OTU deubiquitinase, ubiquitin aldehyde binding 1
PAH	Pulmonary arterial hypertension
PAMPs	Pathogen-associated molecular patterns
PBMCs	Peripheral blood mononuclear cells
PRRs	Pattern recognition receptors
RA	Rheumatoid arthritis
RHD	Rel homology domain
RIG-I	Retinoic acid-inducible gene I
RKIP	Raf kinase inhibitor protein
RLRs	Retinoic acid-inducible gene I (RIG-I)-like receptors
ROS	Reactive oxygen species
rRNA	Ribosomal RNA
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

SPOP	Speckle-type POZ protein
STAT	Signal transducer and activator of transcription
STING	Stimulator of interferon genes
TBK1	TANK-binding kinase 1
TIRAP	TIR domain-containing adaptor protein
TLRs	Toll-like receptors
TRAF6	Tumor necrosis factor receptor-associated factor 6
TRIF	Toll/IL-1R domain-containing adaptor-inducing IFN-β
TRIKAs	TRAF6-regulated IKK activators
TRIM14	Tripartite-motif containing 14
TYK2	Tyrosine kinase 2
USP18	Ubiquitin-specific peptidase 18
USP19	Ubiquitin-specific protease 19
VEEV	Venezuelan equine encephalitis virus
WNV	West Nile virus
YFV	Yellow fever virus
YY1	Yin Yang 1
ZBP1	Z-DNA-binding protein 1
ZCCHC3	Zinc finger CCHC-type containing 3
ZNFX1	Zinc finger NFX1-type containing 1

4.1 Introduction

The innate immune system is crucial for the host to provide a protective response to infection or tissue injury. It utilizes distinct pattern recognition receptors (PRRs) to mediate diverse sets of pathogen-associated molecular pattern (PAMP) or danger-associated molecular pattern (DAMP) recognition, leading to infection removal and maintenance of tissue homeostasis. PRRs can be categorized based on their subcellular location, including Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), NOD-like receptors (NLRs), and several nucleic acid sensors that detect viral DNA or RNA. Upon stimuli recognition, PRRs activate a series of intracellular signaling molecules to initiate signal transduction pathways, including the nuclear factor-κB (NF-κB) signaling, interferon (IFN) response, and inflammasome activation.

4.2 TLRs

TLRs are the earliest discovered and the best characterized PRRs. Ten TLRs (TLR1–10) had been identified for recognizing distinct PAMPs and DAMPs in humans. TLR2 forms heterodimers with TLR1 or TLR6, sensing bacterial lipoproteins and lipopeptides [1]. TLR3, TLR7, TLR8, and TLR9 recognize viral RNA and DNA in the endosome [2, 3]. TLR4 functions as a lipopolysaccharide (LPS) sensor. TLR5 specifically detects flagellins and type IV secretion system components in various bacterial pathogens, including *Salmonella*, *Vibrio*, and *Helicobacter pylori* [4]. TLR7 recognizes the GUrich miR-Let7b, secreted from rheumatoid arthritis (RA) synovial fluid macrophages, resulting in synovitis [5]. Conversely, TLR10, the unique anti-inflammatory TLR, promotes HIV-1 infection and exerts anti-inflammatory effects [6, 7]. The mouse genome encodes 13 TLRs, although humans do not harbor the gene to encode functional TLR11, TLR12, and TLR13 [8]. TLR11 and TLR12 working as heterodimers directly bind to the profilin-like molecule from the protozoan parasite *Toxoplasma gondii* [9]. TLR13 recognizes a conserved 23S ribosomal RNA (rRNA) sequence, which is crucial for binding macrolide, lincosamide, and streptogramin group antibiotics in bacteria [10].

4.3 RLRs

RLRs are a family of RNA helicases and are described as cytoplasmic sensors responsible for viral RNA sensing. Three RLRs have been well defined including retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated factor 5 (MAD5), and laboratory of genetics and physiology 2 (LGP2). RIG-I recognizes short cytosol viral RNA derived from various virus species including influenza virus, hantavirus,

reovirus, hepatitis, and rhinovirus [11, 12]. In comparison with RIG-I, MDA5 recognizes long strands of viral dsRNA following coronavirus, picornavirus, or influenza A virus infection [13, 14]. Negative regulator for this step includes LGP2, a homolog of RIG-I and MDA5, competing with RIG-I and MDA5 to interact with viral RNA, thereby inhibiting downstream signaling activation [15].

4.4 NLRs

The NLRs represent the largest and most diverse family. It is a group of evolutionarily conserved intracellular proteins that are responsible for the host against DAMPs or PAMPs. It harbors an N-terminal effector domain, a NOD domain that mediates ATP-dependent self-oligomerization, and a C-terminal LRR domain responsible for ligand recognition [16]. According to the characteristics of N-terminus, NLRs could be divided into two subgroups: the PYD domain-containing NLRP group and the CARD-containing NLRC group [17]. Most of the NLRPs, including NLRP1, NLRP2, NLRP3, NLRP6, NLRP7, and NLRP9, assemble inflammasome. NLRP1 is the first described receptor for inflammasome activation. It recognizes the stimulation of lethal factor (LF) protease secreted by *Bacillus anthracis* and is activated via proteasome-mediated degradation [18]. NLRP2 associates with the P2X7 receptor and the pannexin 1 channel to sense adenosine triphosphate (ATP) [19]. NLRP3 is activated by various stimuli, including monosodium urate (MSU), silica, asbestos, amyloid-β, alum, ATP, apolipoprotein E, nigericin, and viral RNA [12, 20–24]. NLRP6 and NLRP7 promote host defense against bacterial by detecting lipoteichoic acid and microbial acylated lipopeptides, respectively [25, 26]. NLRP9 recognizes short dsRNA from *Rotavirus* by concerting with the RNA sensor DExH-box helicase 9 (DHX9) [27]. Besides, some other NLRPs are involved in the inflammasome-independent pathway. NLRP4 inhibits double-stranded RNA or DNA-mediated type I interferon [28]. NLRP10 has significant effects on helper T-cell-driven immune responses in response to adjuvants, including lipopolysaccharide, aluminum hydroxide, and complete Freund's adjuvant [29]. NLRP11 impairs LPS-induced NF-κB activation [30]. NLRP14 promotes fertilization by blockading cytosolic nucleic acid sensing [31]. NLRCs are involved in immune responses, and they consist of six members: nucleotide oligomerization domain 1 (NOD1), NOD2, NLRC3, NLRC4, NLRC5, and NLRX1 [32]. NOD1 and NOD2 recognize peptidoglycan (PGN) fragment produced by bacteria [33]. NLRC3 binds viral DNA and other nucleic acids through its LRR domain and licenses immune responses [34]. NLRC4 is an important gatekeeper against gram-negative bacteria including *Legionella pneumophila*, *Salmonella enterica* serovar *Typhimurium* (*Salmonella*), and *Shigella flexneri* [20, 35]. NLRC5 impairs gastric inflammation and mucosal lymphoid formation in response to *Helicobacter* infection [36]. Moreover, crystal analysis of the NLRX1 C-terminal fragment indicates a role for NLRX1 in intracellular viral RNA sensing in antiviral immunity [37].

4.5 Other Nucleic Acid Sensors

Notably, several other nucleic acid sensors have been identified recently. cGAS (cyclic GMP-AMP synthase) is known to be the most important DNA sensor that generates the second messenger cyclic GMP-AMP (cGAMP) for downstream cascade activation [38, 39]. Absent in melanoma 2 (AIM2) as well as interferon-γ (IFNγ)-inducible protein 16 (IFI16) are reported to recognize intracellular DNA. Additionally, Z-DNA-binding protein 1 (ZBP1; also known as DAI or DLM-1), DEAD (Asp-Glu-Ala-Asp)-box helicase 3 (DDX3), and zinc finger NFX1-type containing 1 (ZNFX1) are involved in RNA sensing and promoting innate immune responses [40–42]. These intracellular nucleic acid sensors are widely or ubiquitously expressed in almost all cell types and responsible for viral pathogen detection as well as endogenous nucleic acid recognition.

4.6 NF-κB Signaling

NF-κB is a collective name for a transcription factor family which consists of five different DNA-binding proteins (RelA, RelB, c-Rel, p105/p50, and p100/p52) [43]. Those five family members all contain an N-terminal Rel homology domain (RHD) responsible for dimerization and cognate DNA element binding [44]. Three of them (RelA, RelB, c-Rel) are synthesized as mature proteins and harbor C-terminal transactivation domains, which are essential for transcriptional activation [45]. The other two members (p105/p50 and p100/p52) are synthesized as large precursors (p105 and p100) and partially proteolyzed by the proteasome to yield active forms (p50 and p52) for DNA binding [46, 47]. The NF-κB family members can assemble into several homodimeric and heterodimeric dimers, and two paradigmatic dimers are p50:p65 and p52:RelB [48]. Different NF-κB dimers regulate various gene expressions, which are critical for immune responses, cell proliferation, migration, and apoptosis [49].

The activation of NF-κB dimers has sophisticated controls at multiple levels. In unstimulated cells, NF-κBs are inactive and retained in the cytoplasm by the binding of its specific inhibitors called "inhibitor of κB" (IκB) family [48]. The IκB proteins contain 5–7 tandem ankyrin repeats (AnkRs) that bind to the RHD of NF-κB, thus covering its nuclear localization sequence (NLS) [48]. Upon stimulation, IκB kinase (IKK) complex, including catalytic (IKKα and IKKβ) and regulatory (NEMO, also called IKKγ) subunits, was activated. The activated IKK complex catalyzes the phosphorylation and polyubiquitination of IκB family members, leading to degradation of IκB family members via proteasome and subsequent nuclear translocation of NF-κB family members [50]. Tumor necrosis factor receptor-associated factor 6 (TRAF6), a RING domain E3 ligase, together with two TRAF6-regulated IKK activators (TRIKAs) were identified as responsible for the IKK complex activation [51]. TRIKA1 is an E2 enzyme complex containing Ubc13 and Uev1A (or the functionally equivalent Mms2). Together with TRAF6, it mediates the K63-linked ubiquitination of NEMO and TRAF6 itself. TRIKA2 is a trimeric complex composed of the protein kinase TAK1 and two other proteins as TAB1 and TAB2 [52, 53]. TAK1 is a direct kinase in TRIKA2 to phosphorylate and activate IKK in a manner that depends on TRAF6 and Ubc13-Uev1A [51]. Of note, TAK1 also activates the Jun N-terminal kinase (JNK)-p38 kinase pathway by mediating MKK6 phosphorylation [51]. Additionally, the E3 ubiquitin-ligase TRAF2 (and/or TRAF5) and the kinase RIP1 are also reported to mediate the recruitment of the TRIKA2, contributing to the downstream cascade activation [54]. Adaptors, such as myeloid differentiation primary response 88 (MyD88), TIR domain-containing adaptor protein (TIRAP), and Toll/IL-1R domain-containing adaptor-inducing IFN-β (TRIF), are reported to engage and activate TRAFs by cytoplasmic intermediate IL-1R-associated kinases (IRAKs), such as the kinase IRAK1, IRAK2, and IRAK4 [55]. Importantly, IRAK4 acts upstream of IRAK1, and the kinase activity of IRAK4 might be required for IRAK1's modification [56]. Thus, upon stimulation, PRRs (TLR1, 2, 3, 4, 6, 7, 9) mediate PAMP or DAMP recognition and subsequently recruit adaptors for TRAF and TRIKA recruitment, leading to IKK complex activation, IκB degradation, and release of NF-κB for transcription. Those stimulations include viral and bacterial infections, necrotic cell products, DNA damage, oxidative stress, and pro-inflammatory cytokines (Fig. 4.1) [57].

The regulation of NF-κB signaling has been extensively studied. Additional regulators of NF-κB signaling include OTU deubiquitinase, ubiquitin aldehyde binding 1 (OTUB1), CYLD lysine 63 deubiquitinase (CYLD), and A20 that modulates the ubiquitination of various components [58–62]. Furthermore, phosphorylation, acetylation, methylation, and palmitoylation have also been reported to fine-tune the activity of the NF-κB signaling through multiple post-translational modifications on signal proteins. Besides, Speckle-type POZ protein (SPOP) is recruited to MyD88 to inhibit the aggregation of MyD88 and recruitment of the downstream signaling kinases IRAK4, IRAK1, and IRAK2 [63]. S100A10 interacts with TLR4 and inhibits its association with adaptor proteins including

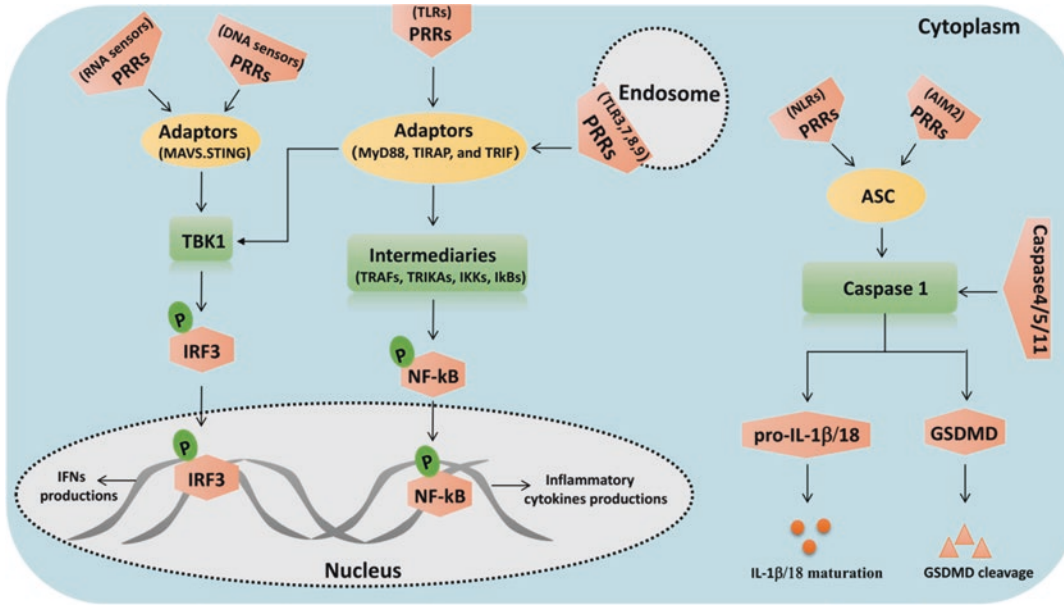

Fig. 4.1 Activation of innate immune responses. In response to distinct stimulation, different PRRs recruit various adaptors for downstream signaling cascades. In detail, cytosolic RNA or DNA sensors recruit MAVS or STING for TBK1 activation, respectively. Activated TBK1 mediates IRF3 phosphorylation, and the phosphorylated IRF3 translocates from the cytoplasm to the nucleus, promoting IFN production. TLRs on plasma or endosome membrane associate with distinct adaptors including MyD88, TIRAP, and TRIF, triggering intermediate activation and subsequent NF-κB phosphorylation. Phosphorylated NF-κBs enter into the nucleus, inducing inflammatory cytokine production. NLRs and AIM2 bind to ASC and enhance the caspase-1 activity for cleaving pro-IL-1β and pro-IL-18, leading to IL-1β/18 maturation. On the other hand, activated caspase-1 mediates the cleavage of GSDMD, and the N-terminal of GSDMD mediates membrane pore formation and pyroptosis. Also, caspase 4/5/11 directly recognize LPS and bind to caspase-1 for downstream signaling activation

MyD88 and TRIF [64]. Downregulated RNA in cancer, inhibitor of cell invasion and migration (DRAIC) impairs IKK complex assembly and inhibits the phosphorylation of IκBα and the activity of NF-κB [65]. Lamtor5 and hepatocyte odd protein shuttling (HOPS) control TRAF6 and TLR4 stability for regulating NF-κB signaling, respectively [66, 67]. A well-controlled NF-κB signaling is crucial for the maintenance of tissue homeostasis, and the dysfunction of NF-κB signaling leads to many pathological conditions such as combined immunodeficiency, type 2 diabetes, and pulmonary diseases [43, 68–70].

4.7 IFN Response

Type I interferons have long been characterized as key players in antiviral responses, inhibiting viral replication and spread by sensing PAMPs, including viral DNA and RNA [71]. Upon virus infection, PRRs promote type I interferon expression, triggering pro-inflammatory cytokine and chemokine production, as well as the expression of innate immune genes to establish an intracellular antiviral state [72]. Fourteen subtypes of type I alpha IFNs (IFN-α) in mice and thirteen in humans, and one beta (IFN-β) IFNs are engaged in that signal through the same IFN-I receptor (IFNAR) [73]. IFNAR, which is composed of IFNAR1 and IFNAR2 subunits, employs the receptor-associated protein tyrosine kinases Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) to phosphorylate cytoplasmic transcription factors signal transducer and activator of transcription 1 (STAT1) and STAT2. Subsequently, phosphorylated STAT1 and STAT2 assemble heterodimers and translocate to the nucleus, together with IFN-regulatory factor 9 (IRF9), to form a transcrip-

tionally active IFN-stimulated gene factor 3 (ISGF3) for directly activating the transcription of IFN-stimulated genes (ISGs) through binding IFN-stimulated response elements (ISREs; consensus sequence TTTCNNTTTC) [74, 75]. Several discovery-based screens demonstrate hundreds of ISGs for their ability to inhibit the replication of several important viruses including influenza A H1N1 virus, hepatitis C virus (HCV), yellow fever virus (YFV), West Nile virus (WNV), chikungunya virus (CHIKV), Venezuelan equine encephalitis virus (VEEV), and HIV-1 [76, 77].

Many types of PRRs can promote IFN-I production. These receptors mediate recognition of foreign and self-nucleic acids as well as a limited number of other non-nucleic acid PAMPs and recruit distinct adaptors for downstream TANK-binding kinase 1 (TBK1) phosphorylation. For example, RNA sensors including MDA5, RIG-I, and zinc finger NFX1-type containing 1 (ZNFX1) recruit mitochondrial antiviral signaling protein (MAVS) to activate and propagate antiviral response [42, 78–80]. Then, MAVS protein forms fibrils and behaves like prions to convert endogenous MAVS into functional aggregates to promote downstream signaling cascade [81]. Likely, DNA sensors including cyclic GMP-AMP synthase (cGAS) and IFI16 recruit stimulator of interferon genes (STING) for antiviral response. STING is an endoplasmic reticulum membrane protein. The cytoplasmic domain of STING undergoes a 180° rotation and unwinds around the crossover point between the proteins to form oligomers [82]. Oligomerized STING adopts a β-strand-like conformation and inserts into a groove between the kinase domain of one TBK1 through a conserved PLPLRT/SD motif within the C-terminal tail of STING [83, 84]. Activated TBK1 directly targets IRF3 for its phosphorylation and the phosphorylated IRF3 translocated from the cytosol to the nucleus for IFN production and subsequent ISG expression for the antiviral response [85]. Of note, MAVS and STING not only activate TBK1 but also recruit IRF3 to bind TBK1 to activate the IRF3 pathway [86]. In addition to MAVS and STING, TLR3 and TLR4 signaling activate TBK1 and IRF3 through the adaptor protein TRIF (Fig. 4.1) [87].

The dysfunction of IFNs results in multiple diseases. For example, activated variants in STING lead to a rare auto-inflammatory disease named STING-associated vasculopathy with onset in infancy via preventing the development of lymph nodes and Peyer's patches [88, 89]. Dysfunction of TDP-43- or C9orf72-induced STING activation causes amyotrophic lateral sclerosis (ALS) [90, 91]. Aberrant mitochondrial DNA (mtDNA)-induced cGAS-STING activation promotes lupus-like disease, acute kidney injury, renal Inflammation, and fibrosis [92–94]. Thus, the activation of the IFN response should be precisely controlled. Various regulators have been reported to modulate IFN signaling through distinct mechanisms. Myb-like, SWIRM, and MPN domains 1 (MYSM1), coiled-coil domain-containing protein 50 (CCDC50), USP15, MARCH8, OTUB1, and OTUB5 regulate IFN response through ubiquitination [95–100]. O-GlcNAc transferase (OGT), histone deacetylase 6 (HDAC6), and palmitoyltransferases modulate IFN production through O-GlcNAcylation, deacetylation, and palmitoylation, respectively [101–103]. N(6)-Methyladenosine (m(6)A) modification controls IFN response by dictating the fast turnover of IFNα and IFNβ mRNA [94]. G3BP1 and barrier-to-autointegration factor 1 (BAF) interfere DNA binding of cGAS for IFN regulation [104, 105]. Furthermore, zinc finger CCHC-type containing 3 (ZCCHC3) and DEAH-box helicase 15 (DHX15) are shown to facilitate RLR-mediated RNA recognition [106, 107].

4.8 Inflammasome Activation

Inflammasome is a molecular platform that mediates the processing of caspases, maturation, and secretion of interleukin-1 (IL-1) family members, and activation of inflammatory cell death called pyroptosis [20, 108]. It can be categorized into apoptosis-associated speck-like protein containing a caspase recruitment domain or CARD (ASC)-dependent or CARD (ASC)-independent

inflammasome activation. Upon stimulation, NLRP3 and absent in melanoma 2 (AIM2) interact with ASC for inflammasome assembly. However, NLRC4 and NLRP1 could directly activate caspase-1 for downstream cascade activation without binding to ASC. Of note, ASC binding for NLRC4 or NLRP1 could enhance its inflammasome activity, although it is dispensable for NLRC4 or NLRP1 inflammasome activation [20]. Caspase-4/5/11 are directly activated by LPS sensing and cleave GSDMD for pyroptosis independent of ASC [109]. Intriguingly, those inflammatory caspases also target NLRP3-dependent caspase-1 activation in an ASC-dependent manner [110].

NLRP1, NLRC4, AIM2, and NLRP3 inflammasomes are most widely reported. Over the past decade, numerous mechanisms have been demonstrated in those inflammasome activations. During the *Bacillus anthracis* infection, bacterial secreted lethal factor (LF) protease was reported to mediate the degradation of amino-terminal domains of NLRP1B, leading to the release of a carboxyl-terminal fragment and subsequently caspase-1 activation [18, 111]. NLRC4 is responsible for bacterial detection. However, it is not the direct sensor for its activator. NAIP (NLR family, apoptosis inhibitory protein)-mediated ligand recognition is required for NLRC4 inflammasome activation. During bacterial infection, mouse NAIP1 and NAIP2 act as cytosolic innate immune sensors for bacterial T3SS needle and rod protein recognition, respectively [112]. In comparison to NAIP1 and NAIP2, NAIP5 and NAIP6 bind to the bacterial protein flagellin for NLRC4 inflammasome activation [113, 114]. AIM2 is a direct sensor, binding double-stranded DNA and utilizes ASC to form a caspase-1-activating inflammasome. The HIN domain of AIM2 is responsible for recognizing sugar-phosphate backbone of various double-stranded DNA, including bacterial DNA, viral DNA, and radiation-induced damaged DNA [115, 116]. NLRP3 inflammasome is the most extensively characterized inflammasome. The activation of NLRP3 inflammasome involves sophisticated regulations. NF-κB signaling activation acts as the first step to mediate the priming process, including induction of both NLRP3 and pro-IL-1β. Subsequently, NLRP3 is activated. Three working models of NLRP3 activation have been proposed: (1) lysosomal rupture and release of the proteinase cathepsin B caused by crystal phagocytosis result in NLRP3 activation [117]; (2) mitochondrial reactive oxygen species (mtROS)-induced oxidized mtDNA conversion leads to NLRP3 activation [118]; and (3) ATP triggered the efflux of K+ contributing to NLRP3 activation [119]. Nonetheless, more details about NLRP3 activation need further investigation (Fig. 4.1).

Emerging evidence shows that sustained and uncontrolled inflammasome activation contributes to the development of many diseases, such as lung injury, vitiligo, very-early-onset inflammatory bowel disease, neutrophilic chronic rhinosinusitis with nasal polyps, adipose tissue inflammation, and auto-inflammatory diseases [12, 120–123]. Many regulators have been reported to regulate inflammasome activation through distinct mechanisms. Raf kinase inhibitor protein (RKIP) and synthetic vitamins K3 and K4 block inflammasome activation through interrupting inflammasome assembly [124, 125]. CCAAT enhancer-binding protein epsilon (C/EBPε), IRF4, and IRF8 modulate transcription level of inflammasome-associated genes for inflammasome regulation [126, 127]. Nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) and ubiquitin-specific protease 19 (USP19) regulate inflammasome activation by reactive oxygen species (ROS) [128, 129]. Besides, various post-translational modifications were implicated in inflammasome regulation, including ubiquitination, phosphorylation, S-nitrosylation, prenylation, deglutathionylation, and ADP-ribosylation. Notably, several drugs have been developed for therapy via targeting to inflammasome activation, such as rasagiline, ticagrelor, kaempferol, and metformin [130–133]. Therefore, targeting inflammasome activation by the deployment of those drugs will shed light on inflammasome-related disease therapy.

4.9 Pulmonary Diseases

4.9.1 Role of Innate Immune Responses in COPD

NF-κB signaling and COPD Chronic obstructive pulmonary disease (COPD), a common chronic inflammatory disease of the airways, the alveoli, and the microvasculature, affects millions of people worldwide. The diagnosis of COPD is based on the reduced ratio of the post-bronchodilator forced expiratory volume in 1 s to the forced vital capacity (FEV1:FVC ratio) (<0.7) [134]. It is characterized by three pathological phenotypes including small airway obstruction due to remodeling, emphysema, and chronic bronchitis [134]. Cigarette smoking and indoor or outdoor air pollution are the most important risk factors and causes for COPD [135]. Emerging evidence indicates that innate immune responses are involved in COPD pathogenesis. The severity of COPD is reported to associate with an increased epithelial expression of NF-κB by analyzing bronchial biopsies from smokers with COPD, smokers with normal lung function, and nonsmokers with normal lung function [136]. Further analysis identified that IκB-α levels in lung tissue were significantly reduced and IKK complex activity in peripheral blood mononuclear cells (PBMCs) is dramatically enhanced in patients with COPD than in control subjects [137, 138]. Consistently, in the mouse model, cigarette smoke (CS) exposure regulates RelB by IKKa in B-lymphocytes, leading to inflammatory cytokine release [139]. Of note, loss of function of Miz1 (also known as c-Myc-interacting zinc finger protein-1 and Zbtb17) in the murine lung epithelium spontaneously develops a COPD-like phenotype via inducing sustained NF-κB signaling activation [70]. In addition, follistatin-like 1 (FSTL-1) hypomorphic mice develop spontaneous emphysema by promoting NF-κB p65 phosphorylation in a Nr4a1-dependent manner [140].

Inflammasome and COPD Except for NF-κB signaling, inflammasome activation also contributes to the onset of COPD pathogenesis. The expression levels of IL-1β and IL-18, two hallmarks of inflammasome activation, are increased in COPD patients [141, 142]. Moreover, overexpression of IL-1β or IL-18 in the lungs of mice present chronic inflammatory changes similar to COPD, and lacking IL-1R or IL-18R in mice are protected against CS-induced lung inflammation [143, 144]. Likely, elevated caspase-1 activity is also observed in the lungs from both COPD patients and the CS-treated mice model [145]. Strikingly, in the mice model, acute smoke-mediated lung inflammation is blocked by z-VAD-fmk, a pan-caspase inhibitor, or z-WEHD-fmk, a caspase-1 inhibitor [146]. Notably, high levels of two inflammasome stimulators, extracellular ATP (eATP) and ROS, are observed in patients with COPD as well as in the genetic mouse models of COPD, indicating possible inflammasome activation in COPD pathogenesis [147, 148].

IFN response and COPD The role of IFN response in COPD pathogenesis needs more investigation. Deficient IFN-β expression in the lungs and reduced sputum expression of ISGs were detected in COPD patients [149, 150]. However, acute CS exposure leads to cGAS-STING-dependent IFN response by releasing self-DNA in mice model [151]. Thus, whether CS exposure induces COPD phenotype is IFN dependent or not needs to be further explored.

4.9.2 Role of Innate Immune Responses in Asthma

NF-κB signaling and asthma Asthma, one of the major chronic non-communicable diseases, affects as many as 334 million people in the world [152]. It is defined by mucus overproduction, bronchial hyperreactivity (BHR), airway wall remodeling, and airway narrowing [153]. The symptoms of asthma include repeated periods of shortness of breath, cough, wheezing, and chest tightness [154]. Genetic susceptibility and environmental exposures as well as aberrant

immune responses contribute to the onset of disease [155]. Recent studies implicated NF-κB signaling activation as a key modulator in asthma pathogenesis. Increased activation of NF-κB was observed in asthma patients [156]. Furthermore, NF-κB activation in airway epithelial is sufficient to promote allergic sensitization to an inhaled antigen [157]. In contrast, repressed NF-κB signaling activation in airway epithelial impaired inflammation, led to decreased levels of chemokines and cytokines and circulating IgE, and ameliorated mucus cell metaplasia [158]. Notably, inhibition of NF-κB by a chimeric decoy oligodeoxynucleotide transfer prevents asthma exacerbation in a mouse model [159]. Besides, ex vivo farm dust or LPS stimulation restored anti-inflammatory TNFAIP3 gene and protein levels in asthmatic patients and shifted NF-κB signaling-associated gene expression toward an anti-inflammatory state [160]. Thus, targeting NF-κB signaling may provide a novel therapeutic approach to asthma.

Inflammasome and asthma Emerging evidence showed that inflammasome activation plays a crucial role in asthma pathogenesis. In neutrophilic asthma patients, the protein level of IL-1β was significantly higher, and sputum IL-1β protein level was associated with NLRP1, NLRP3, and NLRC4 expression [161]. Similar results with increased inflammasome components including Nlrp3, Nlrc4, caspase-1, and Il-1β were observed in eosinophilic, mixed, and neutrophilic experimental asthma in mice [162]. Lacking NLRP3 inflammasome activation in mice led to ameliorated allergic airway inflammation, reduced eosinophil infiltration, and dampened Th2 lymphocyte activation in the lung [163, 164]. Strikingly, treatment with an inhibitor of caspase-1 or NLRP3 suppresses airway hyperresponsiveness (AHR) in severe, steroid-resistant asthma [165]. Most importantly, uric acid, protein serum amyloid A, apolipoprotein E, and fatty acid exposure may contribute to inflammasome activation in allergic asthma [24, 166–168].

IFN response and asthma The role of IFN response in asthma pathogenesis is more complicated and warrants more investigation. On the one hand, increased expression of IFN-β, IFN-λ1/IL-29, OAS, and viperin in neutrophilic asthmatics and high IFN-α, IFN-β, and IFN-λ1 were detected in atopic asthmatic [169, 170]. Moreover, elevated ISG expression in epithelial in asthma is related to lung inflammation and FEV1 [171]. On the other hand, reduced IFN-α/β expression level in the bronchial epithelium in asthmatic cells was also reported [172]. Thus, how IFN response activated in asthma patients needs to be further explored.

4.9.3 Role of Innate Immune Responses in COVID-19

IFN response and COVID-19 Coronavirus disease 2019 (COVID-19), an ongoing pandemic of acute respiratory disease, affects millions of people in the world since late 2019. It is caused by a highly transmissible and pathogenic coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A wide range of clinical features of COVID-19 patients were reported including fever, cough, myalgia or fatigue, sputum production, headache, hemoptysis, and diarrhea [173]. Bilateral diffused alveolar damage, hyaline membrane formation, desquamation of pneumocytes, and fibrin deposits are observed in the lungs of patients with severe COVID-19 via histopathology analyses [174]. Several hypotheses have been proposed for the mechanisms of COVID-19 including imbalanced innate immune responses promoting the pathogenesis of COVID-19 [175], in which aberrant IFN response is the key player driving the progression of COVID-19. Appropriate activation of IFN signaling controls SARS-CoV-2 infection [176]. However, overactivated IFN response amplifies inflammatory signals and induces inflammation in COVID-19 patients [177]. People genetically deficient in IFN response are more vulnerable to SARS-CoV-2 infection [178, 179]. Moreover, the mice model infected with SARS-CoV-2 demonstrates the activation of type I interferon signaling [180].

Thus, early interferon therapy is associated with reduced mortality and accelerated recovery [181, 182]. Of note, a truncated isoform of ACE2, the receptor for SARS-CoV-2, could be induced by interferon response activation [183]. On the other side, SARS-CoV-2 proteins, such as nonstructural protein 6 (nsp6), nsp13, and open reading frame 6 (ORF6), could antagonize cellular IFN response [184].

NF-κB signaling and COVID-19 IL-6, an inflammatory cytokine controlled by the activated NF-κB signaling, is commonly increased in COVID-19 patients [185, 186]. The maximal level of IL-6 and C-reactive protein level, lactate dehydrogenase (LDH) level, ferritin level, d-dimer level, neutrophil count, and neutrophil-to-lymphocyte ratio are highly predictive of the need for mechanical ventilation and mortality in COVID-19 patients [187, 188]. Strikingly, repurposing of anti-IL-6 therapeutics by tocilizumab reduces mortality and/or morbidity in severe COVID-19 from clinical trials [189, 190].

Inflammasome and COVID-19 Activation of the inflammasome was also found in COVID-19 lungs [191]. Fatal COVID-19 cases showed a higher number of ASC inflammasome specks [192, 193]. Thus, innate immune responses may represent a new target for COVID-19 therapy.

4.9.4 Role of Innate Immune Responses in Other Pulmonary Diseases

Dysfunctions of innate immune responses also lead to other pulmonary diseases, such as idiopathic pulmonary fibrosis (IPF) and pulmonary arterial hypertension (PAH). The SNPs in TOLLIP, an important regulator of innate immune responses mediated by the Toll-like receptor, are associated with IPF susceptibility [194]. Yin Yang 1 (YY1), a downstream gene of NF-κB signaling, regulates fibrogenesis by increasing α-SMA and collagen expression [195]. Statin, uric acid, and extracellular ATP enhance lung fibrosis through promoting NLRP3 inflammasome activation [196, 197]. In patients with PAH, serum IFN levels were elevated, and expression of TLR3 in lung tissue is reduced [198, 199]. IFNAR1-deficient mice were protected from PAH [198]. In contrast, Tlr3−/− mice showed a more severe PAH phenotype [199]. Besides, NLRP3 inflammasome activation may contribute to the pathogenesis of PAH, representing a possible target for PAH treatment [200].

4.10 Conclusion

In response to environmental stimulation signals, PRRs, including TLRs, NLRs, RLRs, and other nucleic acid sensors, trigger a variety of signaling pathways for defense to control and eventually eliminate such stimulation. However, aberrant immune responses lead to severe inflammatory diseases especially pulmonary diseases, such as COPD, asthma, COVID-19, IPF, and PAH. Thus, the optimal regulation and fine-tuning of innate immune responses are necessary. Distinct mechanisms have been revealed in immune response regulation. Various post-translational modifications control the intensity, duration, and timing of activated innate immune responses by manipulating protein stability, activity, and subcellular localization. Additional regulators control mRNA levels and stability to regulate innate immune responses. Discoveries of these and additional mechanisms modulating innate immune response will guide and illuminate current and future clinical trials for pulmonary diseases.

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