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Innate immunity in allergy

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Abstract

Innate immune system quickly responds to invasion of microbes and foreign substances through the extracellular and intracellular sensing receptors, which recognize distinctive molecular and structural patterns. The recognition of innate immune receptors leads to the induction of inflammatory and adaptive immune responses by activating downstream signaling pathways. Allergy is an immune-related disease and results from a hypersensitive immune response to harmless substances in the environment. However, less is known about the activation of innate immunity during exposure to allergens. New insights into the innate immune system by sensors and their signaling cascades provide us with more important clues and a framework for understanding allergy disorders. In this review, we will focus on recent advances in the innate immune sensing system.

KEYWORDS
inflammasome, pattern recognition receptors, pyroptosis

1 | INTRODUCTION

Our body is endlessly exposed to microbial agents and environmental noxious substances. These may cause serious illness, or toxicity to the body; therefore, they must be eliminated. This is mediated by the innate immune system, which is the first line of host defense against foreign invasion. Any disruption in the physical barriers that prevent pathogens from entering the body triggers pro-inflammatory responses by activating myeloid cells and dendritic cells (DCs) that are central players of the innate immune defense. Furthermore, pro-inflammatory responses induce antigen presentation shifting from an innate immune response to an acquired immune response. B cells and T cells, in which antigen receptors are individually specialized by DNA rearrangement, mainly mediate acquired immune responses. One of the main features making the innate immune system highly specialized is the germline-encoded receptors distinguishing between self and nonself. This discrimination is mediated by membrane-bound or cytoplasmic pattern recognition receptors (PRRs).[1] The membrane-bound receptors are Toll-like receptors (TLRs) and C-type lectin receptors (CLRs). The cytoplasmic-type receptors are retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) and nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs). These receptors directly sense various components from pathogens and distinguish conserved microbial structural features, called pathogen-associated molecular patterns (PAMPs).[2] The recognition of PAMPs leads to robust innate immune responses through the activation of these downstream signaling pathways. PRRs also recognize self-components released from the damaged cells, called damage/danger-associated molecular patterns (DAMPs), and can thus be associated with the pathogenesis of many diseases.

Allergy is an increasing problem in the health sector, with a soaring number of patients in recent years. Accumulating evidence suggests the importance of the innate immune system in the development of allergy susceptibility. Therefore, in this review, we will summarize recent advances in the involvement of PRRs in allergic diseases, and improvements to current allergy treatment modalities.

2 | T-HELPER 2 RESPONSE AND ALLERGY

In recent years, although highly criticized, the *hygiene hypothesis* has been proposed to explain the increase in frequency of patients with allergy worldwide.[3] It suggests that a cleaner environment may lead to development of allergic diseases, highlighting that early exposure to microbes and parasites during childhood is essential to reduce development of susceptibility.[4] As evidence in favor of the hygiene hypothesis, it is demonstrated that maternal intranasal exposure to the nonpathogenic microbe *Acinetobacter* protected against the development of experimental asthma in the progeny.[5]

Allergy is characterized by a T-helper 2 (Th2) hypersensitivity response with a significant increase in immunoglobulin (Ig) E. Type 2 immune responses are characterized by the expression of type 2 cytokines, such as interleukin (IL)-4, IL-5, IL-9, and IL-13. Contact with bacteria during early development may be protective by inducing T-helper 1 (Th1) cell differentiation. Intestinal microbiota also plays an important role in the prevention of allergies.[6,7] Although oral administration of ovalbumin (OVA) abrogates both Th1 and Th2 responses in specific pathogen-free mice, only Th1 responses are reduced in germ-free mice.[8] The reconstitution of the intestinal microbiota of germ-free mice suppressed the susceptibility of the Th2 responses in neonates,[9] suggesting the importance of exposure to intestinal microbiota at the neonatal stage for prevention of allergies.

A high dose of lipopolysaccharide (LPS) promotes Th1 immune responses and prevents allergic disease in an OVA-induced allergic asthma model.[10] Conversely, a low amount of LPS skews the immune response to Th2 type and induces allergic airway inflammation in a thymic stromal lymphopoietin (TSLP)-dependent manner.[11] TSLP is an epithelial cell-derived cytokine expressed in the thymus, lung, skin, and gut. The release of TSLP,[12,13] IL-25,[14,15] IL-33,[16] and granulocyte-macrophage colony-stimulating factor (GM-CSF)[17] from nonlymphoid cells is important for the initiation of Th2 immune responses. Furthermore, epithelial cells in the damaged barriers may also cooperate in the initiation of Th2 immune responses to repair the tissue injury. Activation of group 2 innate lymphoid cells (ILC2s) by epithelium-derived cytokines such as TSLP, IL-7, IL-25, IL-33, and also IL-4 induces the production of type 2 cytokines including IL-5, IL-9, IL-13, and epidermal growth factor receptor (EGFR) ligand amphiregulin (AREG) for leading innate type 2 immunity.[18-20] In this context, the intensity of activation of downstream signaling molecules
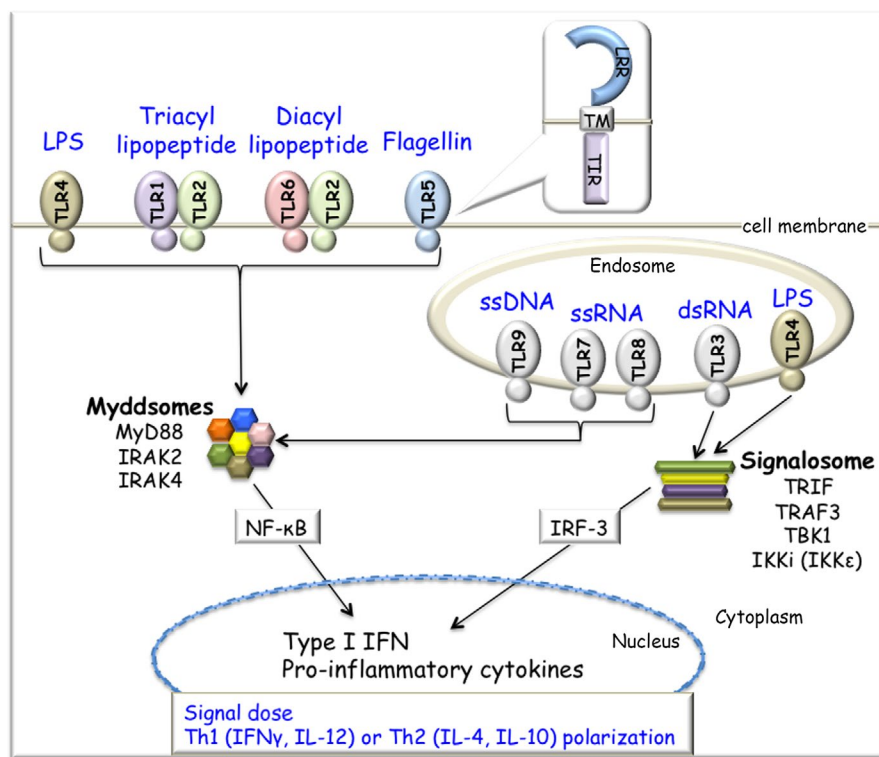

FIGURE 1 TLR-mediated signaling pathway. All TLR proteins have LRR and TIR domains (in the balloon). Individual TLRs recognize different ligands, such as LPS, triacyl lipopeptide, diacyl lipopeptides, bacterial flagellin, DNA, and RNA. TLRs localize at the cell surface or in endosomes. TLRs recruit two adaptor proteins, MyD88 and TRIF. The ligand engagement of TLRs induces the formation of the Myddosome (MyD88 and IRAKs) and activates the NF-κB pathway. TLR3 and TLR4 also induce the formation of a signalosome (TRIF, TRAF3, TBK1, and IKKi [IKKε]). Activated IRF-3 induces type I IFN production. Th1/Th2 polarization into either a Th1 immune response or Th2 immune response is dependent on the signal dose through TLRs. IKKi, inducible inhibitor of NF-κB (IκB) kinase; IRAK, IL-1 receptor-associated kinase; IRF-3, IFN regulatory factor 3; LPS, lipopolysaccharide; LRR, leucine-rich repeat; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor-kappa B; TBK1, TRAF-associated NF-κB activator (TANK)-binding kinase 1; Th1, T-helper 1; Th2, T-helper 2; TIR, Toll/interleukin-1 receptor; TLR, Toll-like receptor; TM, transmembrane; TRAF3, TNF receptor-associated factor 3; TRIF, TIR-domain-containing adaptor inducing interferon (IFN)-β

and pathways may be strongly associated with the development of allergy.

3 | TOLL-LIKE RECEPTORS

The TLRs were the first discovered PRR and are mammalian homologues of *Drosophila* Toll protein involved in innate immune response.[21,22] Studies over the past two decades have revealed important roles of TLRs in a variety of biological phenomena including inflammation, the bridging between innate and acquired immune responses, and cancer cell proliferation and survival.

3.1 | TLR family

Toll-like receptors include 10 and 13 family member proteins in humans and mice, respectively. The TLR family is evolutionarily conserved and contains the ligand-binding domains via leucine-rich repeat (LRR) motifs at the N-terminus and intracellular Toll/IL-1 receptor (TIR) domain at the C-terminus (Figure 1). TLRs act as the *gatekeepers* of host defense to various pathogens through structure- and sequence-dependent immune recognition (Figure 1).[23-26] Most TLRs in humans and mice recognize similar PAMPs with some exceptions. TLR11, TLR12, and TLR13 have been lost in the human genome, and the *Tlr10* gene is disrupted in the mouse genome. TLR1 through to TLR9 are conserved in both species. TLR4 recognizes bacterial LPS. Triacyl and diacyl lipopeptides are recognized by dimerization of TLR2 with TLR1 and TLR6, respectively. TLR5 recognizes bacterial flagellin derived from flagella. TLR9 is a deoxyribonucleic acid (DNA) sensor and recognizes nonmethylated cytosine-phosphate-guanine (CpG) DNA. TLR3 recognizes double-stranded RNAs (dsRNAs), and both TLR7 and TLR8 detect unmodified uridine-rich single-stranded RNAs (ssRNAs). TLRs localize either on the cell surface (TLR1, TLR2, TLR4, TLR5, and TLR6) or in endosomes (TLR3, TLR7, TLR8, and TLR9) through the transmembrane (TM) domain (Figure 1).

3.2 | TLR signaling

Once activated by their ligands, individual TLRs recruit two major TIR-containing adaptor molecules, myeloid differentiation primary response 88 (MyD88) and TIR-domain-containing adaptor inducing interferon-β (IFN-β) (TRIF) (Figure 1). The engagement of all TLRs except for TLR3 induces the signaling complex, named the Myddosome, which consists of MyD88 and IL-1 receptor-associated kinases (IRAKs), leading to activation of NF-κB.[27] The ligand engagement to TLR3 or TLR4 recruits TRIF, which results in activation of IFN regulatory factor 3 (IRF-3) through a signalosome complex (TNF receptor-associated factor 3 [TRAF3], TRAF-associated NF-κB activator [TANK]-binding kinase 1 [TBK1], and inducible inhibitor of nuclear factor [NF]-κB [IκB] kinase [IKKi], also known as IKKε, *IKBKE*). Phosphorylated IRF-3 translocates into the nucleus and eventually induces the production of type I IFN.

3.3 | TLR and allergy

Allergic development is believed to result from genetic backgrounds and environmental factors. Mutations in *TLR* family genes have been investigated using single nucleotide polymorphism (SNP) analysis and meta-genome-wide association studies (GWAS). Indeed, SNPs in the *TLR4* gene are a risk factor for asthma,[28,29] indicating that genetic variations of *TLR* family genes are related to susceptibility to allergic diseases.

Toll-like receptor family proteins are differentially expressed in all cells types including macrophages, DCs, B cells, regulatory T (Treg) cells, and epithelial cells. They are directly capable of interacting with pathogens or foreign particles in the epithelial barrier and influence host immune cell responses with environmental factors. Barrier epithelial cells function as an origin of allergic response to external signals from the mucous membranes of the respiratory tract, intestinal tract, or skin. Tight junction barriers are extremely sensitive to detergents.[30] LPS also increases tight junction permeability in a TLR4-dependent manner.[31] The dysregulation of the epithelial barrier may increase uptake of allergens in the pathogenesis of allergy.

Microbial-treated TLR2/3/4/7/9 knockout mother mice are no longer protected from the development of asthma in their offspring,[5] suggesting that maternal TLR signaling plays a pivotal role in the transfer of protective effects. However, the precise roles of TLRs in the development of allergic diseases are greatly influenced by many factors, such as cell types, expression level, and the nature of antigens. Indeed, TLR4 signaling leads to allergic responses.[32-34] This TLR4-mediated allergic reaction develops only by intranasal sensitization but not by subcutaneous or intraperitoneal sensitization, suggesting that TLR-mediated reactions influence the dose of immune-stimulatory components, as well as the route of administration and the timing of exposure. Treg cells have also been implicated in allergy development.[35] Manipulation of Th1/Th2 balance or Treg cell function by administrating TLR agonists may be promising for the treatment of allergic diseases.[36]

3.4 | Allergen-specific immunotherapy for TLRs

Different TLR agonists have been assayed in clinical trials as adjuvants.[37] These were further developed in the context of allergen-specific immunotherapy (AIT) with different outcomes. Oral administration of TLR9 agonists displayed a significant benefit in the treatment of asthma and food allergy in mice.[38] Several kinds of TLR agonists have now been applied to asthmatic or allergic patients in clinical trials.[37,39] In the case of TLR9 agonists, CpG-containing nucleotides (Amb a 1-CpG vaccine)[40,41] and bacteriophage-derived virion-like particles (VLPs) packaging A-type CpG motif[42] have been shown to be effective in treating rhinitis and allergic asthma. Intranasal administration of a TLR7 agonist (AZD8848) and TLR8 (VTX-1463) has also reduced nasal symptoms in patients with allergic rhinitis.[43] TLR4 agonist monophosphoryl A (MPL) promotes Th1 and Treg cell responses in cooperation with switching from IgE to IgG blocking antibody production.[39]
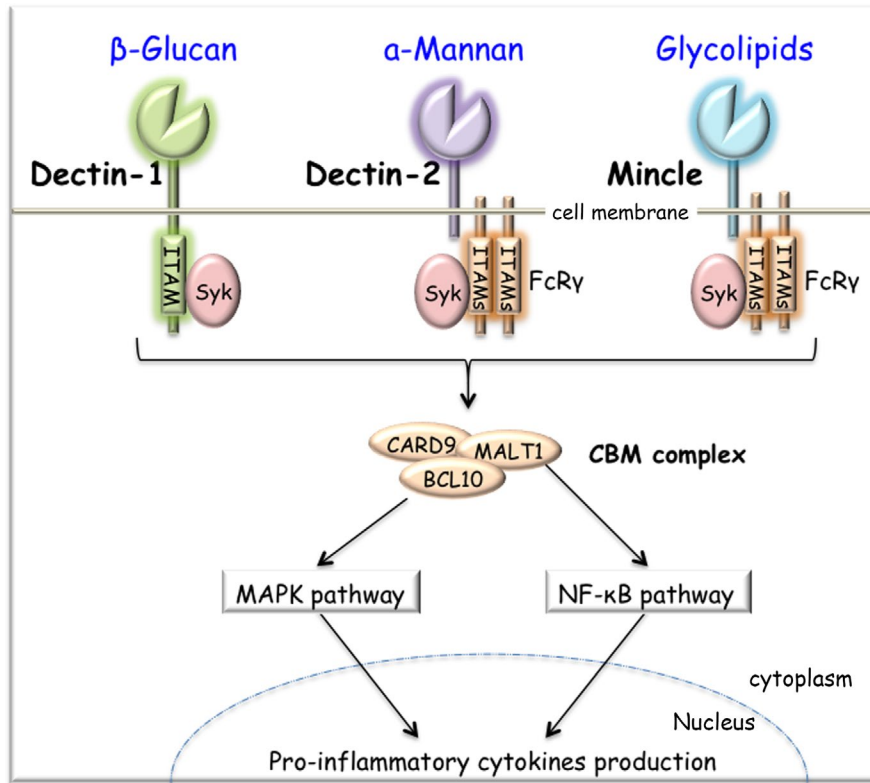
FIGURE 2 Type II transmembrane CLR. Type II transmembrane CLR proteins possess a single CRD. Dectin-1 (*CLEC7A*) recognizes fungal wall-derived β-glucans. Dectin-2 (*CLEC6A*) recognizes the structure of α-mannans. Mincle (*CLEC4E*) recognizes diverse glycolipids including TDM, Glc-DAG, and MGDG. Dectin-1 transduces the signal through its ITAM-like motif. Both Dectin-2 and Mincle associate with FcRγ for signaling. Ligand-bound CLRs result in the Syk-dependent formation of the CBM (CARD9-BCL10-MALT1) complex. The CBM complex activates the pathways of MAPK and NF-κB, leading to pro-inflammatory cytokine production. BCL10, B-cell CLL/lymphoma 10; CARD9, caspase-recruitment domain 9; CLR, C-type lectin receptor; CRD, carbohydrate recognition domain; Dectin-1, dendritic cell (DC)-associated C-type lectin-1; Dectin-2, DC-associated C-type lectin-2; FcRγ, Fc receptor common gamma chain; Glc-DAG, glucosyl diacylglycerol; ITAM, immunoreceptor tyrosine-based activation motif; MALT1, mucosa-associated lymphoid tissue protein 1; MAPK, mitogen-activated protein kinase; MGDG, monoglucosyldiacylglycerol; Mincle, macrophage-inducible C-type lectin; NF-κB, nuclear factor-kappa B; Syk, spleen tyrosine kinase; TDM, trehalose-6,6′-dimycolate

4 | C-TYPE LECTIN RECEPTORS

CLRs recognize a diverse range of nonself PAMPs derived from microbes, especially fungi and house dust mites.[44-46] Most cells, including DCs and macrophages, express CLRs. CLRs belong to the C-type lectin-like domain (CTLD) superfamily, which carries the carbohydrate recognition domain (CRD). CLRs contain one or more conserved CTLD.[47] Type II transmembrane CLRs, which possess a single CRD, have been most extensively studied among CLRs (Figure 2). This subfamily includes DC-associated C-type lectin-1 (Dectin-1, *CLEX7A*), Dectin-2 (*CLEC6A*), macrophage-inducible C-type lectin (Mincle, *CLEC4E*), DC-specific intracellular adhesion molecule 3 (ICAM3)-grabbing nonintegrin (DC-SIGN, *CD209*), and DC NK lectin group receptor-1 (DNGR-1, *CLEC9A*).

4.1 | Dectin-1, Dectin-2, and Mincle

Dectin-1 and Dectin-2 recognize fungal wall-derived β-glucan and α-mannan structure, respectively[48] (Figure 2). Both are organized

in the gene cluster in the human and mouse genomes.[49,50] Mincle, a member of the Dectin-2 family, recognizes various glycolipids (Figure 2), such as trehalose-6,6′-dimycolate (TDM) in the cell wall of *Mycobacterium tuberculosis*,[51] glucosyl diacylglycerol (Glc-DAG) of *Streptococcus pneumoniae*,[52] monoglucosyldiacylglycerol (MGDG) produced by Group A *Streptococcus*,[53] and others derived from self and nonself.[54]

4.2 | CLR signaling

Dectin-1 directly transduces the signal through its immunoreceptor tyrosine-based activation motif (ITAM)-like motif in the cytoplasmic domain. Dectin-2 and Mincle are required for the ITAM-containing adaptor protein Fc receptor common gamma chain (FcRγ, *FCER1G*) (Figure 2). Once ligands are bound to CLRs in a calcium-dependent manner, spleen tyrosine kinase (Syk) is recruited to phosphorylated ITAM motifs, leading to cellular activation. In this signaling cascade, caspase-recruitment domain (CARD)-containing adaptor proteins, CARD9 and B-cell CLL/lymphoma 10 (BCL10), form a complex with

caspase-like cysteine protease mucosa-associated lymphoid tissue protein 1 (MALT1). CARD9-BCL10-MALT1 (CBM) complex activates NF-κB and mitogen-activated protein kinase (MAPK) pathways, resulting in the production of pro-inflammatory cytokines (Figure 2).

4.3 | CLRs and allergy

Dectin-1 is involved in fungal-mediated allergic inflammation mediating T-helper 17 (Th17) cell differentiation.[55,56] Genetic polymorphisms of Dectin-1, TLR3, and TLR9 are significantly associated with susceptibility to severe asthma with fungal sensitization.[57] Dectin-2 has been implicated in allergic inflammation to house dust mites with Th2 polarization.[58-60] A recent study shows that Mincle recognizes not only glycolipids but also self-derived cholesterol sulfate in skin epithelial cells and is involved in the induction of allergic skin inflammatory response.[61]

4.4 | Allergen-specific immunotherapy for CLRs

Recent findings have shown that allergoids conjugated to nonoxidized mannan from *Saccharomyces cerevisiae* are next-generation vaccines targeting DCs through CLRs. These vaccines are candidates for AIT of allergic diseases as they promote the generation of Treg cells by mechanisms partially depending on programmed death-ligand 1 (PD-1) and IL-10 in both humans and mice.[62,63] Phase II clinical trials for grass-pollen and house dust mite allergens are currently ongoing.[64]

5 | RIG-I-LIKE RECEPTORS

5.1 | RLR family

Tlr3 -deficient cells showed normal type I IFN production toward viral infection,[65] suggesting that additional mechanisms were hidden in the RNA sensing. As the cytosolic dsRNA sensor sensing both RNA helicases, RIG-I (*DDX58*)[66] and melanoma differentiation-associated gene 5 (MDA5, *IFIH1*)[67] were identified.[68] The RLR family proteins possess the DExHD motif containing the helicase domain for dsRNA recognition and have the two CARD domains at the N-terminus (Figure 3).[69] Laboratory of genetics and physiology 2 (LGP2, *DHX58*) lacks a CARD domain and, therefore, has no intrinsic signaling activity.
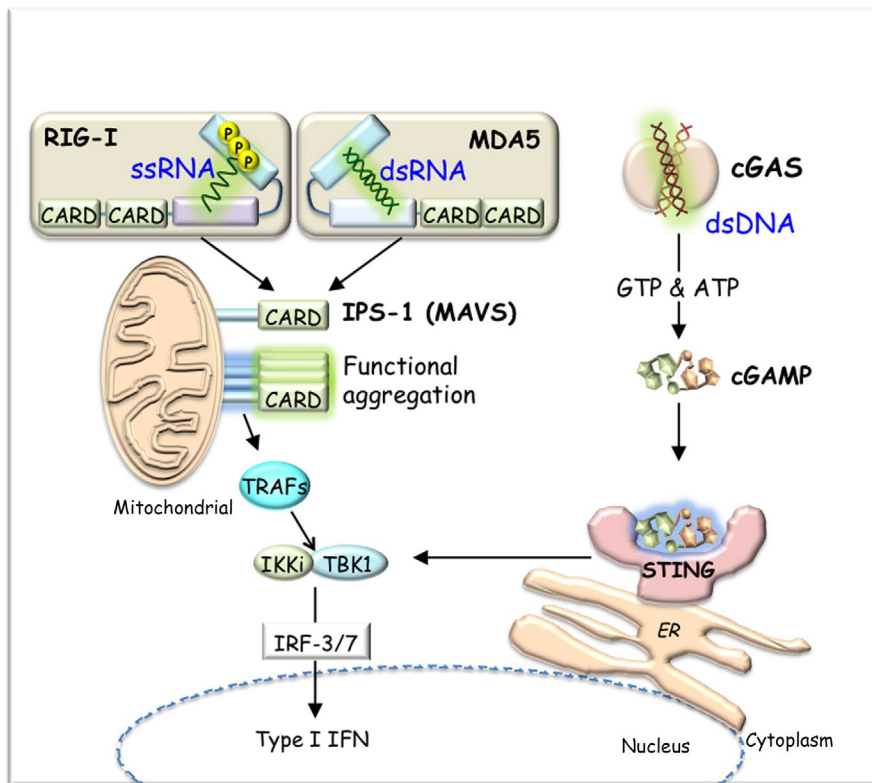

FIGURE 3 Nucleic acid sensors. RIG-I and MDA5 have two CARD domains at the N-terminus and a helicase domain at the center. Both RIG-I and MDA5 bind viral RNAs bearing 5'-triphosphate or 5'-diphosphate distinct from the mammalian RNA with 5' cap structure. After viral RNA recognition, RIG-I and MDA5 interact with IPS-1 (MAVS) through CARD-CARD interactions. IPS-1 (MAVS) is localized on the mitochondrial outer membrane. Aggregated IPS-1 (MAVS) activates TBK1 and IKKi (IKKε) through TRAFs, leading to induction of type I IFN via phosphorylation of IRF-3/7. cGAS binds dsDNA and produces a second messenger, cGAMP, from ATP and GTP. cGAMP binds to STING localized on the ER membrane and induces type I IFN production via the TBK1/IRF-3 pathway. CARD, caspase-recruitment domain; cGAMP, cyclic GMP-AMP; cGAS, cyclic GMP-AMP synthase; ER, endoplasmic reticulum; IKKi, inducible inhibitor of NF-κB (IκB) kinase; IPS-1, *IFN-β* promoter stimulator 1; IRF, IFN regulatory factor; MDA5, melanoma differentiation-associated gene 5; RIG-I, retinoic acid-inducible gene I; STING, stimulator of IFN genes; TBK1, TRAF-associated NF-κB activator (TANK)-binding kinase 1; TRAF, TNF receptor-associated factor

5.2 | RLR recognition and signaling

Retinoic acid-inducible gene I and MDA5 have different roles in the recognition of RNA viruses.[70] RIG-I recognizes relatively short viral RNA blunt ends bearing 5′-di-/triphosphate distinct from the host cellular RNA with 5′ cap structure.[71-73] RIG-I detects many RNA viruses, such as rhinovirus, Sendai virus, vesicular stomatitis virus, and influenza virus. RIG-I-mediated RNA recognition mechanisms are viral replication-independent.[71] MDA5 responds to longer (over 1k bp) dsRNA,[74] such as polyinosinic-polycytidylic acid [poly(I:C)], as well as dsRNA generated after infection of picornaviruses including encephalomyocarditis virus (EMCV), Mengo virus, and Theiler's virus. After viral RNA recognition, RIG-I and MDA5 interact with the downstream CARD-containing adaptor protein, IFN-β promoter stimulator 1 (IPS-1, MAVS), through CARD-CARD interactions[75-78] (Figure 3). IPS-1 localizes on the mitochondrial outer membrane, which triggers prion-like aggregation of IPS-1[79] (Figure 3). The aggregated IPS-1 recruits IRF-3 kinase and activates the IRF-3-TBK1-IKKi (IKKε)-IRF-3/7-IFN-dependent signaling pathway through TRAFs.

5.3 | RLRs and allergy

Early viral infections in children are associated with further allergic sensitization and asthma persistence. Similarly, viral infections in asthma patients (both allergic and nonallergic) are also associated with asthma exacerbations. In the development of respiratory disease, innate immune mechanisms are involved in virus-infected airway epithelial cells.[80] Loss-of-function mutations in the IFIH1 gene increase susceptibility to severe respiratory infection caused by human rhinovirus in children.[81,82] A meta-phenome-wide association study also revealed a novel association of an IFIH1 allele mutation to increased risk for asthma.[83] In an experimental model, poly(I:C) and rhinovirus-derived dsRNA exacerbated asthma.[84-86] Taken together, RLRs play a nonredundant and critical role in the development and progression of asthma.

5.4 | cGAS—DNA sensor

Recent studies have revealed the existence of a new intracellular DNA sensing system. Cyclic GMP-AMP synthase (cGAS), a member of nucleotidyltransferase family, binds dsDNA in a sequence-independent manner but is activated in a length-dependent manner (longer than 94-bp DNA).[87] cGAS undergoes a conformational change of its catalytic center and then produces the cyclic GMP-AMP (cGAMP) from ATP and GTP (Figure 3).[88-90] cGAMP acts as second messenger,[91,92] binds to the stimulator of IFN genes (STING),[93-95] localizes on the endoplasmic reticulum (ER) membrane, and induces type I
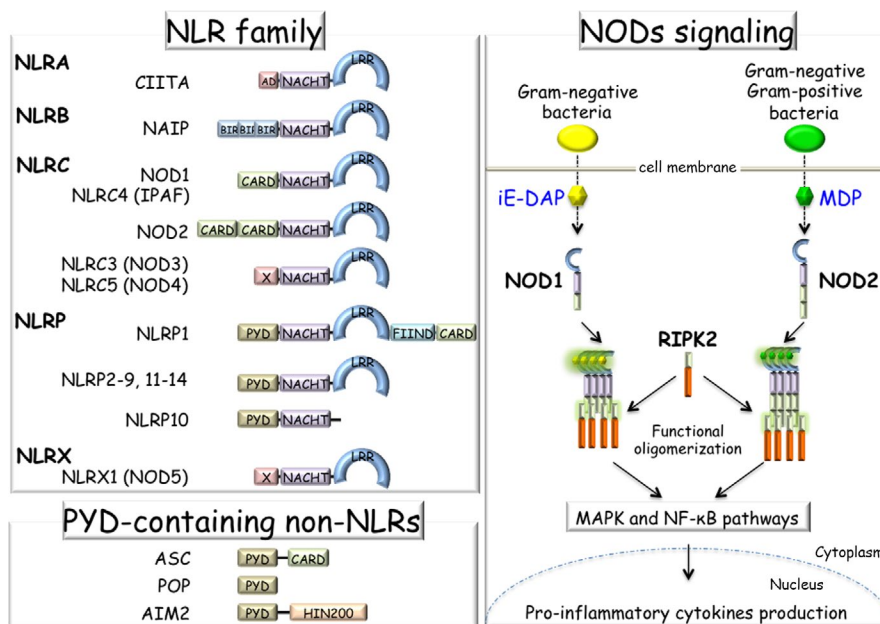

FIGURE 4 NLR family, PYD-containing non-NLR proteins, and NOD signaling. In the NLR family, there are five major subfamilies based on the unique N-terminal domain structure: NLRA (AD-type), NLRB (BIR-type), NLRC (CARD-type), NLRP (PYD-type) and NLRX (X-type). All family proteins have a NACHT domain in the central region. NOD2 senses bacterial cell wall-derived peptidoglycan derivative MDP; however, NOD1 only senses Gram-negative bacteria-derived iE-DAP. After sensing ligands, NODs oligomerize and interact with RIPK2 through the CARD domain. RIPK2 further activates downstream cascades and MAPK and NF-κB pathways, leading to cytokine production. AD, transactivation domain; BIR, baculoviral inhibitor of apoptosis repeat; CARD, caspase-recruitment domain; FIIND, function-to-find domain; HIN200, hematopoietic interferon-inducible nuclear antigens with 200 amino acid repeats; iE-DAP, γ-D-glutamyl-meso-diaminopimelic acid; LRR, leucine-rich repeat; MAPK, mitogen-activated protein kinase; MDP, muramyl dipeptide; NACHT, NAIP, CIIA, HeT-E, and TEP1; NF-κB, nuclear factor-kappa B; NOD1, nucleotide-binding oligomerization domain-containing protein 1; NOD2, nucleotide-binding oligomerization domain-containing protein 2; PYD, Pyrin domain; RIPK2, receptor-interacting serine/threonine-protein kinase 2

IFN production via the TBK1/IRF-3 pathway (Figure 3).[96,97] cGAMP senses viral-derived DNA as well as host-derived DNA.[98,99] cGAS is involved in DNA damage-induced inflammatory signaling in cancer cells.[100,101] The cGAS-STING-mediated DNA sensing system also contributes to the induction of apoptosis, control of ER stress response, and autophagy.

6 | NOD-LIKE RECEPTORS

A third group of PRRs are NLRs.[102] NLRs are localized in the cytosol and recognize PAMPs and DAMPs. NLRs carry three unique structural properties (Figure 4); the central region is named NOD or nucleotide-binding domain (NACHT), which consists of conserved motifs including ATP/GTPase-specific phosphate-binding loop and magnesium-binding site; the C-terminal region contains LRRs, which respond to ligand specificity similar to TLRs; the N-terminal region is different among NLRs (Figure 4). Based on the name, NLRs are divided into five major subgroups (NLRA, NLRB, NLRC, NLRP, and NLRX) (Figure 4). So far, twenty-five NLR family genes have been identified in the human genome.

6.1 | NOD1 and NOD2

NOD1 (*CARD4*) and NOD2 (*CARD15*) are founding members of NLR family[103] and belong to the NLRC subfamily. NOD1 has a single CARD domain and NOD2 has two CARD domains at the N-terminus (Figure 4). Both NOD1 and NOD2 sense bacterial cell wall-derived peptidoglycan derivative γ-D-glutamyl-meso-diaminopimelic acid (iE-DAP) and muramyl dipeptide (MDP) structures, respectively (Figure 4). iE-DAP is derived from Gram-negative bacteria, whereas MDP is derived both from Gram-positive and Gram-negative strains.

6.2 | NOD signaling

Upon recognition, NODs oligomerize and interact with CARD-containing receptor-interacting serine/threonine-protein kinase 2 (RIPK2) through the CARD domain, and then activate transforming growth factor (TGF)-β-activated kinase 1 (TAK1, *MAP3K7*) and IKK complex for leading to MAPK and NF-κB activation[104] (Figure 4). NOD1 is widely expressed by a variety of cell types, whereas NOD2 expression is limited to certain cell types such as hematopoietic cells[105] and Paneth cells in the intestine.[106]

6.3 | NODs and allergy

NOD1 and NOD2 promote Th1 and Th17 adaptive immunity by inducing the secretion of TNF and IL-1[107,108] in addition to Th2 immune response,[109] suggesting that signaling through these receptors may be central to susceptibility and exacerbation of allergies. Although inhalation of NOD1 and NOD2 ligands induces Th2 response, NOD2 appears to have more potent activity than NOD1 in Th2-driven allergic

inflammation. It is shown that NOD2 displays this function by promoting the expression of TSLP, OX40 ligand (OX40L/CD252, *TNFSF4*), and IL-25.[110] NOD2-induced suppression of Treg cell development and induction of early IL-4-secreting cells are completely dependent on TSLP. NOD1 cannot induce strong TSLP expression. However, intranasal infusion of high doses of NOD2 ligands did not break tolerance nor lead to asthma susceptibility, indicating a dose-dependent effect of NOD2 in allergy development.

Polymorphisms of NOD1 and NOD2 are highly associated with inflammation development in the respiratory airways,[111] childhood asthma,[112] and atopic diseases.[113-115] It has been thought that these phenotypes arise from a defect in NOD sensing fragments of bacterial peptidoglycan. However, a recent study shows that NODs also participate in sensing infection with viruses and parasites by inducing ER stress-induced inflammation,[116] and further research is needed to elucidate the role of NODs in allergic diseases.

6.4 | PYD-containing non-NLRs

The NLRP family has the Pyrin domain (PYD) at the N-terminal region. Similarly to the CARD domain, PYD prefers to assemble together; thus, PYD-containing proteins give rise to a complex. The complex formation of NLRs is important for signaling and inflammation. The overall composition of NLRs is not well characterized yet, but it is important to uncover the role of NLRs, especially in the inflammasome (Section 7). Studies on additional small molecules, such as PYD-only proteins (POPs) family (Figure 4) and CARD-only proteins (COPs) family, may provide a more detailed mechanism.[117-119]

7 | INFLAMMASOME

NLRP family proteins, a subgroup of NLR family, and absent in melanoma 2 (AIM2) form a complex with apoptosis-associated speck-like protein containing a CARD (ASC, *PYCARD*) through their PYD domains and recruit the CARD domain of pro-caspase-1, forming the inflammasome[120] (Figure 5). Inflammasomes are cytosolic multimeric protein complexes sensing and responding to pathogenic microbes and cellular damage.[121] To date, various inflammasomes including NLR subfamily proteins (NLRP1 [*CARD7*], NLRP2, NLRP3, NLRP4, NLRP6, and NLRC4 [*CARD12*]) and PYD-containing non-NLR proteins (AIM2, pyrin (*MEFV*), and IFN-γ-inducible protein (IFI) 16) have been identified. Based on the activation mechanism, the inflammasomes are categorized as canonical or noncanonical.

7.1 | Canonical inflammasome

Caspases are a group of cysteine-aspartic acid proteases, of which 12 and 10 family members have been identified in humans and mice, respectively. Caspases play an essential role in programmed cell death and are involved in either apoptosis or inflammation along with pyroptosis[122] (Section 8). In the steady state, the caspase family is present in inactive
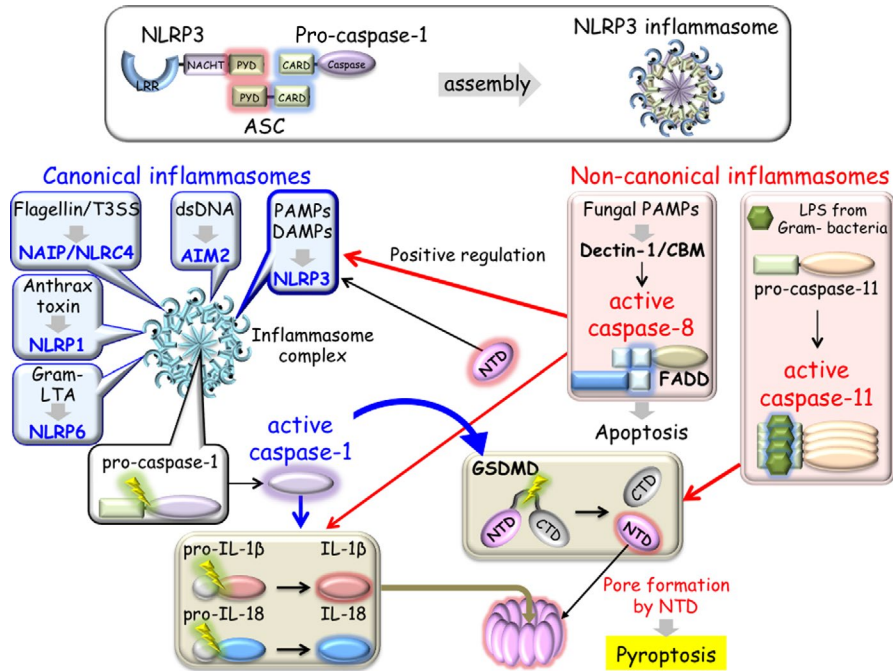
FIGURE 5 Inflammasome. NLRP3 forms a complex with ASC through their PYD binding each other and recruiting the CARD domain of pro-caspase-1. After assembly, this multimeric complex is called the inflammasome (upper box). In the canonical inflammasome assembly, ligand-sensing NLRs (NLRP1, NLRP3, NLRP6, NAIP/NLRC4, and AIM2) (blue balloons) form multisubunit disk-like structures comprising an inner ring and outer ring. Pro-caspase-1 is located in the central portion (black balloon). Activated caspase-1 processes IL-1β/IL-18 and triggers proteolytic cleavage of GSDMD (brown boxes). In the noncanonical inflammasomes, caspase-11 and caspase-8 participate in the cytoplasmic LPS sensing pathway and Dectin-1-CBM signaling pathway, respectively (pink boxes). Activated caspase-11 cleaves GSDMD similarly to caspase-1 (red arrow). GSDMD-derived NTD induces pore formation for pyroptosis and stimulates the NLRP3 inflammasome pathway (black arrows). Activated caspase-8 with FADD is capable of cleaving pro-IL-1β/pro-IL-18 (red arrow). Caspase-8 may positively regulate NLRP3 inflammasome pathway (red arrow). AIM2, absent in melanoma 2; ASC, apoptosis-associated speck-like protein containing a CARD; CARD, caspase-recruitment domain; CBM, CARD9-BCL10-MALT1; Dectin-1, lipopolysaccharide; GSDMD, gasdermin D; LPS, lipopolysaccharide; LTA, lipoteichoic acid; NAIP, NLR family apoptosis inhibitory protein; NLRC4, NLR family CARD domain containing 4; NLRP1, NLR family Pyrin domain containing 3; NLRP3, NLR family Pyrin domain containing 3; NLRP6, NLR family Pyrin domain containing 6; NTD, N-terminal domain; PYD, Pyrin domain

forms called zymogens, which require activation. Inflammasome mediates the activation of caspase-1 through CARD-CARD interactions. Caspase-1, caspase-4 (human only), caspase-5 (human only), caspase-11 (mouse only), and caspase-12 are known to be involved in the inflammatory pathway, and those inflammatory caspase genes are clustered in the human and mouse genome.[123] Inflammasomes activate caspase-1, resulting in production of pro-inflammatory cytokines IL-1β and IL-18 upon activation by various signals[124] (Figure 5). Thus, "canonical" inflammasome relies on the activation of caspase-1.

7.1.1 | NLRP3 inflammasome

NLRP3 inflammasomes can respond to a variety of substances including crystals such as urate, cholesterol, asbestos, silica, aggregated amyloid-β, and islet amyloid polypeptide.[125] As a direct interaction of NLRP3 with these substances has not been detected, NLRP3 inflammasome activation is considered to occur via mitochondrial and lysosomal damage. Reactive oxygen species (ROS) also trigger NLRP3 inflammasomes priming.[126] Extracellular ATPs released from activated or necrotic cells activate P2X purinoceptor 7 (P2X7, *P2RX7*)

receptor[127] and induce caspase-1 activation, leading to IL-1β production via formation of an NLRP3 inflammasome.[128] IL-1β is critically involved in Th17 cell differentiation, production of Th17-associated cytokines, and neutrophilic inflammation.[129] In addition to the Th2 response, a Th17 response is associated with asthma, notably severe glucocorticoid-resistant asthma.[130] From various studies of human diseases and mouse models, the elevation of IL-1β and IL-18 is associated with the development of allergic diseases, such as asthma, dermatitis, rhinitis, and conjunctivitis.[131] All these events are connected with inflammasome activation and suggest participation of the inflammasome in the development and progression of asthma. Th2 and Th17 inflammatory pathways are mutually regulated in asthmatic patient samples.[132] Type II cytokine suppression promotes Th17 responses, indicating that combined therapy targeting both Th2 and Th17 responses may benefit asthmatic patients.

7.1.2 | AIM2 inflammasome

Cytoplasmic dsDNA sensor AIM2 is a member of IFI20X/IFI16 family.[133] In normal conditions, the N-terminal PYD of AIM2

maintains an autoinhibitory state through interaction with C-terminal hematopoietic IFN-inducible nuclear proteins with a 200-amino acid repeat (HIN-200) domain, which directly binds to the sugar-phosphate backbone of dsDNA in a sequence-independent manner.[134,135] The ligand binding to the HIN-200 domain triggers the activation of the AIM2 inflammasomes, leading to pyroptosis and the production of IL-1β and IL-18.[136-139] The AIM2 inflammasomes play an important role in infection, cancer, and autoimmunity [140] by sensing of virus/bacteria-derived dsDNA and tumor-derived DNA.[141,142] A recent study shows that AIM2 is dispensable for inflammasome activation in some primary human myeloid cells, where STING-dependent cell death can trigger NLRP3 inflammasome activation by inducing potassium efflux.[143] This result implicates the presence of a cell-type-specific alternative pathway in the dsDNA sensing system. Inflammasome-derived caspase-1 binds to cGAS and restricts its downstream STING-TBK1-IRF-3/7-IFN-dependent signaling pathway by cutting out cGAS,[142] implicating a crosstalk between type I IFN production and the inflammasome. cGAMP also functions in the priming and activation of AIM2 and NLRP3 inflammasomes.[144]

7.1.3 | Other inflammasomes

NLRC4 inflammasomes are activated by NLR family apoptosis inhibitory protein (NAIP) harboring three baculoviral inhibitor of apoptosis repeat (BIR) domains at N-terminus.[145,146] NAIP family proteins detect monomeric flagellin or the needle/rod regions of type III secretion system (T3SS),[147-150] leading to the activation of downstream NAIP/NLRC4 inflammasome responses. The transcription of *Naips* is regulated by the transcription factor IRF-8.[151] NLRC4 is implicated in the exacerbation of psoriatic lesions,[152] and NLRP4 mutation is associated with exacerbation of asthma in smoking adults.[153] Polymorphisms of NACHT-LRR in NLRP12 and the promoter regions of NLRC4 and NLRP1 are associated with atopic dermatitis.[113] The elusive other inflammasomes remain of outstanding interest.

7.2 | Noncanonical inflammasome

Caspase-11 senses cytosolic LPS with noncanonical function[154-158] (Figure 5). This intracellular LPS sensing can trigger caspase-11-mediated pyroptosis under a TLR4-independent mechanism.[159-161] In this caspase-1-independent pathway, murine caspase-11 (caspase-4 and caspase-5 in humans) directly senses LPS through its CARD domain.[162] Thus, "noncanonical" inflammasomes can lead to the activation of caspase-11. The NLRP3 inflammasome is involved in both canonical and noncanonical activation. Interestingly, the NLRP6 inflammasome senses Gram-positive bacteria-derived lipoteichoic acid (LTA) (Figure 5).[163] In this activation mechanism, NLRP6 recruits both caspase-1 and caspase-11. The processed caspase-11 induces caspase-1 activation, resulting in the production of IL-1β and IL-18.

7.2.1 | Caspase-8

Caspase-8 is known to play a central role in apoptosis as initiator and apical activator. Caspase-8 has two death effecter domains (DEDs) in its N-terminus and is structurally different to CARD-containing inflammatory caspases. Interestingly, caspase-8 has been shown to form a noncanonical inflammasome in response to fungal and mycobacterial infection by Dectin-1.[164] Fungal PAMPs activate Dectin-1 signaling to induce a noncanonical caspase-8-ASC with CBM complex in a caspase-1-independent manner.[165] Caspase-8 assumes its inflammatory roles by inducing IL-1β activation[165,166] (Figure 5). Furthermore, caspase-8 mediates both canonical and noncanonical NLRP3 inflammasome priming and activation with a death domain (DD)-containing adaptor protein Fas-associated protein with DD (FADD).[167] Caspase-8-mediated IL-1 signaling promotes Th2 responses in allergic airway inflammation,[168] implicating its therapeutic potential for asthma.

7.3 | Inhibition of inflammasome activation

Inflammasomes are multiple protein complexes; therefore, abnormal assembly causes hyperinflammatory conditions, as in the case of skin inflammation in NLRP1 germline mutation.[169] Some pathogens are able to selectively inhibit the activation of the caspase-11-mediated noncanonical NLRP3 inflammasome.[170] However, the regulatory mechanisms of inflammasomes are not fully understood and need further characterization. Interestingly, a recent study shows that TAK1 restricts the NLRP3 inflammasome to regulate cell homeostasis and death in myeloid cells.[171] *TAK* deficiency promotes spontaneous NLRP3 inflammasome activation. TAK1 inhibits the activation of DD-containing receptor-interacting serine/threonine-protein kinase 1 (RIPK1). Activated RIPK1 induces the caspase-8-FADD pathway. TAK1 inactivation induces RIPK1 activation, leading to the caspase-8-dependent pathway,[172] indicating that RIPK1 plays a role upstream of caspase-8. This machinery is also associated with neuroinflammation, aging, and infection.[173] Hence, the mechanism requires further investigation to understand the implications of inhibiting inflammasome activation.

8 | PYROPTOSIS

8.1 | Pyroptosis

Pyroptosis is one form of cell death and is morphologically different to apoptosis and necrosis. Apoptosis is an immunologically silent death mode while necrosis and pyroptosis are pro-inflammatory death modes tightly associated with inflammation.[174] Caspase-1 is a key player of pyroptosis in cell death (canonical inflammasome). As described above, caspase-11 also contributes to the central mechanism of pyroptosis (Figure 5).[155] Pyroptotic cells release their entire cellular contents including nuclear and mitochondrial DNA. Pyroptosis preferentially occurs in macrophages, monocytes, and DCs. Neutrophil cell death is called NETosis (neutrophil extracellular traps) and releases chromatin components to the extracellular

space.[175,176] It is found that NETosis-derived dsDNA mediates allergic asthma exacerbations during rhinovirus infection,[177,178] suggesting dsDNA acts as an adjuvant to boost type II-mediated allergic inflammation.

8.2 | Gasdermin

The gasdermin (GSDM) family consists of six member proteins (GSDMA, GSDMB, GSDMC, GSDMD, GSDME, and Pejvakin).[179] The molecular mechanisms underlying pyroptosis and GSDM family functions have been elucidated.[161,180-186] Activated caspases directly cleave GSDMD into two fragments, the N-terminal domain (NTD) and C-terminal domain (CTD). The NTD of GSDMD oligomerizes to form a pore on the cell membrane. This formation perforates the plasma membrane and initiates pyroptosis, leading to inflammasome-mediated secretion of mature IL-1β and IL-18 (Figure 5). Recent studies show that GSDMD is involved not only in pyroptosis but also in NETosis.[187-189]

8.3 | GSDMB and allergy

Importantly, the genome locus of GSDMB and orosomucoid 1-like 3 (ORMDL3) on chromosome 17q21 is strongly associated with childhood-onset asthma.[190,191] GSDMB is highly expressed in airway epithelial cells.[192] GSDMB-mediated pyroptosis in epithelial cells may be involved in the pathogenesis of asthma. Furthermore, GSDMB transgenic mice assume asthma symptoms in the absence of airway inflammation,[192] implicating that the induction of GSDMB triggers asthma.

9 | ALPK1-TIFA-NF-κB AXIS

Besides LPS itself, ADP-β-D-manno-heptose (ADP-Hep) and D-glycero-β-D-manno-heptose 1,7-bisphosphate (HBP),[193-195] intermediate products of the LPS biosynthetic pathway, activate the NF-κB signaling pathway (Figure 6). ADP-Hep is more potent than HBP. TRAF-interacting protein with forkhead-associated domain (TIFA) was originally identified as a TRAF2-binding protein that is involved in the NF-κB pathway.[196] Both ADP-Hep and HBP sensing trigger TIFA oligomerization.[193] Recent studies have shown that TIFA oligomerization can be induced by ADP-Hep or ADP-heptose 7-P that is converted from HBP by host adenylyltransferase enzymes of the nicotinamide mononucleotide adenylyltransferase (NMNAT) family (Figure 6).[197] Alpha-kinase 1 (ALPK1), a member of the atypical kinase family alpha kinases, is necessary for phosphorylation-dependent formation of TIFA oligomerization.[194,195] These sugar molecules directly bind the N-terminal domain of ALPK1, stimulating its kinase domain to phosphorylate and activate TIFA. The role of ADP-Hep as a PAMP was further confirmed on comparison with synthetic HBP.[198] This ADP-heptose sensing system stimulates host innate immune responses.
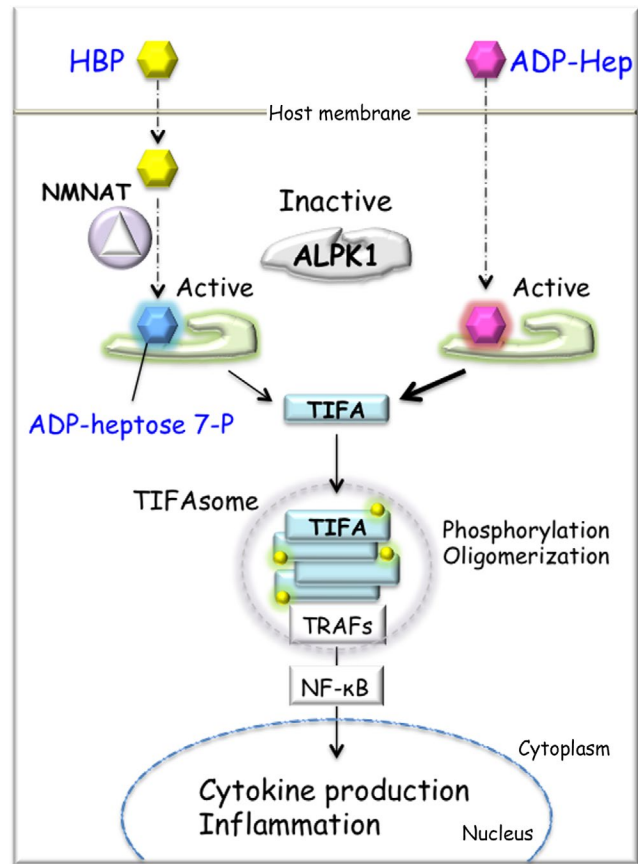

FIGURE 6 ALPK1-TIFA-NF-κB axis. Once HBP and ADP-Hep, bacterial products of the LPS biosynthetic pathway, are transported into the host cell, both types of sugars activate NF-κB signaling pathway. ADP-heptose 7-P, which is converted from HBP by host enzyme NMNAT, interacts to N-terminus of ALPK1. Activated ALPK1 phosphorylates TIFA and induces the TIFA oligomerization with TRAFs, named TIFAsome. ADP-Hep can also interact with ALPK1 in the same fashion, leading to the activation of NF-κB and inflammation. ADP-Hep has much more potent NF-κB activator than HBP. ADP-Hep, ADP-β-D-manno-heptose; ALPK1, alpha-kinase 1; HBP, D-glycero-β-D-manno-heptose 1,7-bisphosphate; LPS, lipopolysaccharide; NMNAT, nicotinamide mononucleotide adenylyltransferase; TIFA, TRAF-interacting protein with forkhead-associated domain; TRAF, TNF receptor-associated factor

10 | CONCLUSION

Over 20 years, we have witnessed a remarkable advance in understanding the mechanism of pathogen recognition by the innate immune system. New players involved in the innate immune system continue to be reported. However, despite enormous efforts, our knowledge of how the innate immune system is involved in the development of allergic diseases is still limited, and feasible target molecules or pathways are yet to be discovered. It is necessary to determine how pathogen recognition molecules and subsequent signaling pathways are involved in the development of allergic diseases.

CONFLICTS OF INTEREST

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