Postprint: Research Advances in Pattern Recognition Receptors of Innate Immunity

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Abstract

Innate immunity serves as the first line of defense in the body' s immune system against microbial infections. Pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), and retinoic acid-inducible gene I-like receptors (RLRs), recognize distinct or overlapping microbial components, triggering corresponding signal transduction to generate immune responses. In recent years, research on PRRs related to innate immunity has achieved considerable progress, providing therapeutic insights for immune-related diseases. This review summarizes the characteristics of innate immunity-related PRRs and the interactions among signaling pathways of different PRRs.

Full Text

Advances in Pattern Recognition Receptors of Innate Immunity

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Abstract: Innate immunity constitutes the first line of defense against microbial infection. Pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), and RIG-I-like receptors (RLRs) recognize distinct yet overlapping microbial components, triggering corresponding signal transduction pathways to generate immune responses. Recent research on innate immunity-related PRRs has achieved significant advancement, providing new insights for treating immune-related diseases. This review summarizes the characteristics of PRRs and the interplay among different PRR signaling pathways.

Keywords: innate immunity; pattern recognition receptors; signaling pathway

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Innate immunity refers to the non-specific natural immune defense function present at birth, also known as non-specific immunity. It serves as the first line of defense for the immune system to distinguish self from foreign substances and resist microbial infection. The host mounts extensive immune responses to block, limit, or clear invading microorganisms, which is predicated on the recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs) of the innate immune system. This receptor-ligand interaction induces production of cytokines such as interleukins (IL), tumor necrosis factor (TNF), and interferons (IFN) to mediate anti-pathogen effects. Janeway [1] first proposed the pattern recognition function of PRRs and clarified the important biological significance of innate immunity. PRRs are expressed on antigen-presenting cells, particularly dendritic cells (DCs), leading to activation of adaptive immune responses through effector signals. Currently, several classes of PRRs have been identified with distinct characteristics, including Toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), RIG-I-like receptors (RLRs), C-type lectin receptors (CLRs), and absent in melanoma 2-like receptors (ALRs).

PRRs recognize complex microbial structures including polysaccharides, glycolipids, lipoproteins, nucleotides, and nucleic acids. Through specific ligand recognition domains—leucine-rich repeats, C-type lectin domains, and various nucleic acid-binding domains—PRRs detect microbial target structures (Table 1) [2]. In addition to their structural and specific characteristics, PRRs exhibit tissue-specific expression and localization to different cellular compartments such as the plasma membrane, endosomes, lysosomes, and cytoplasm [3]. These differential expression patterns relate to two conventional recognition modes of the innate immune system: intracellular recognition mediated by cytoplasmic sensors in infected cells, where all cell types can express corresponding sensors upon pathogen infection (e.g., viral nucleic acid sensors), and extracellular recognition that does not require infected cells to express PRRs but rather relies on their expression on the surface of specific pathogen surveillance cells such as epithelial cells and myeloid cells [4].

Table 1 PRRs and PAMPs

Pattern Recognition Receptor	Adapter Molecules	Ligand (Structure)	Pathogen-Associated Molecular Pattern
TLR1-TLR2	MyD88, TIRAP	Triacyl lipopeptide	Bacterial lipoproteins
TLR2-TLR6	MyD88, TIRAP	Diacyl lipopeptide	Mycoplasma lipoproteins

Pattern Recognition Receptor	Adapter Molecules	Ligand (Structure)	Pathogen-Associated Molecular Pattern
TLR2 (with TLR1/6)	MyD88, TIRAP	Lipoteichoic acid, GPI-mucin, HA protein	Gram-positive bacteria
TLR3	TRIF, TRAM	dsRNA	Respiratory syncytial virus
hTLR8	MyD88	ssRNA	RNA viruses
mTLR11	MyD88	Profilin-like molecule	Uropathogenic *E. coli*, *Toxoplasma gondii*
NOD-1/NLRC1	RICK, CARD9	iE-DAP	Gram-negative bacteria
NOD-2/NLRC2	RICK, CARD9	MDP	Bacteria
NALP3/NLRP3	CARDINAL	Uric acid, calcium pyrophosphate dihydrate, β-amyloid	Bacteria, viruses, host
RIG-I	IPS-1 (CARD)	5' - triphosphate ssRNA, short dsRNA	RNA viruses
MDA5	IPS-1	poly I:C, long dsRNA	Viruses
Dectin-1		β-glucan	Fungi

NOD: nucleotide-binding oligomerization domain; RIG-I: retinoic acid-inducible gene I; MDA5: melanoma differentiation-associated gene 5; LGP2: laboratory of genetics and physiology 2; Dectin-1: dendritic cell-associated C-type lectin-1; MyD88: myeloid differentiation factor 88; TIRAP: TIR domain-containing adapter protein; TRIF: TIR domain-containing adapter molecule inducing IFN-β; TRAM: TRIF-related adapter molecule; RICK: RIP-like interacting CLARP kinase; CARD: caspase recruitment domain; ASC: apoptosis-associated speck-like protein; IPS-1: interferon-β promoter stimulator 1; Cardinal: an adapter protein; LPS: lipopolysaccharide; CpG DNA: cytosine-phosphate-guanine motif; poly I:C: polyinosinic-polycytidylic acid.

1.1 TLRs in Innate Immune Recognition

Research on TLRs initially involved the interleukin-1 receptor (IL-1R). IL-1 is a pleiotropic pro-inflammatory cytokine that in the 1980s was reported to

participate in T cell activation, pyrogenicity, cartilage tissue degradation, and acute phase response activation [5]. In 1988, IL-1R was cloned through gene editing, but since its cytoplasmic region lacked recognizable motifs, the signal transduction mechanism remained elusive. In 1991, this domain was found to be homologous to the *Drosophila* cytoplasmic protein Toll [6]. Toll determines the dorsal-ventral axis development in *Drosophila* embryos. Subsequent studies revealed that highly similar Toll and IL-1R share amino acid sequences essential for NF- B signaling and are associated with antimicrobial peptide production, thus initiating research on Toll-like receptors as innate immune receptors [7].

Lipopolysaccharide (LPS), a major component of endotoxin, has been extensively studied as a Gram-negative pathogen component that causes bacterial sepsis. Poltorak et al. [8] cloned the LPSd gene, work that later earned the Nobel Prize in Physiology, while Qureshi et al. [9] confirmed that LPSd was actually TLR4. Hoshino et al. [10] found that TLR4 knockout mice were unresponsive to LPS, further confirming TLR4 as the LPS signaling receptor. Following TLR4 involvement in LPS recognition, other microbial components were tested as potential TLR ligands. Ten human TLR genes and twelve mouse TLR genes were identified, with knockout mouse models determining specific ligands for various TLRs [11]. TLR2 recognizes bacterial lipopeptide structures, forming heterodimers with TLR1 or TLR6 to recognize triacyl lipopeptides and diacyl lipopeptides, respectively [12]. TLR5 recognizes flagellin from flagellated bacteria [13], with further research demonstrating that TLR5 regulates both innate and adaptive immune responses in the intestine [14]. Mouse TLR11 was found to detect components of urinary tract infection bacteria [15] and, together with TLR12, binds *Toxoplasma gondii* profilin-like molecules [16]. TLR13 also recognizes bacterial rRNA [17].

TLRs recognize diverse ligands from bacteria, parasites, and viruses. TLR3 recognizes viral double-stranded RNA, mediating activation of NF- B and type I IFN signaling pathways [18]. TLR9 functions as a receptor for unmethylated CpG DNA motifs, with subsequent studies revealing that plasmacytoid dendritic cell TLR9 also recognizes herpes virus DNA [19]. TLR7 senses the antiviral chemical imiquimod and, along with TLR8, recognizes viral single-stranded RNA [20]. Thus, the TLR receptor family can initiate innate immune and inflammatory responses upon sensing danger signals such as microbial infection or tissue damage.

The Toll/IL-1 receptor homologous region (TIR) is the initiation point for TLR signaling, capable of binding with IL-1R to activate NF- B signaling pathways. Myeloid differentiation factor 88 (MyD88) was the first identified TLR adapter molecule containing a TIR domain. The TIR domain interacts with TIR-containing receptors to participate in MyD88 signal transduction. Additionally, MyD88 contains a death domain (DD) that recruits DD-containing interleukin-1 receptor-associated kinases (IRAKs) through homotypic interactions. IRAKs interact with TNF receptor-associated factor 6 (TRAF6), forming a complex with TAB-3, TAB-2, and TAK-1 to activate mitogen-activated pro-

tein kinase kinase (MKK) or inhibitor of NF- B kinase (IKK) α/IKKβ/IKKγ, triggering the mitogen-activated protein kinase (MAPK) c-Jun N-terminal kinase (JUN) and p38 MAPK pathways as well as the NF- B pathway, thereby inducing pro-inflammatory cytokine production. In endosomes, this primarily generates interferon-regulatory factors (IRFs) that induce type I IFN production [21].

The second identified TIR adapter is MyD88-like adapter protein (MAL, also known as TIRAP). Kawai et al. [22] stimulated MyD88 knockout mice with LPS and found that type I IFN was induced through IRF3, with delayed NF- B activation downstream of TLR4, indicating MyD88-independent signaling could activate TLR downstream signals. However, studies showed that MAL cannot independently conduct MyD88-independent signal transduction but rather serves as a bridge connecting MyD88 with TLR4 or TLR2 [23]. Oshiumi et al. [24] demonstrated that TIR domain-containing adapter inducing IFN-β (TRIF or TICAM1) could induce TLR3 pathways in MyD88 knockout mice, also indicating the existence of MyD88-independent pathways and the role of TRIF as a third class of TIR adapter molecule. Additionally, research identified TRIF-related adapter molecule (TRAM or TICAM2) as a linker between TRIF and TLR4 in the TLR4 pathway. In the phagosomal TLR4 signaling pathway, TRAM connects TRIF with TLR4 to form a complex that transmits signals to TRAF3 or TRAF6 precursor signalosomes to generate IRF3 or NF- B, thereby regulating transcriptional expression.

With ongoing research, TLRs are now widely applied in disease treatment, such as TLR7 ligands for genital warts, vaccine formulations targeting TLR2 and TLR4 pathways for tuberculosis, TLR7 and TLR9 inhibitors for potential systemic lupus erythematosus treatment, and TLR2-blocking antibodies to effectively limit ischemia-reperfusion injury.

1.2 NLRs in Innate Immune Recognition

The NLR family proteins are cytoplasmic PRRs that detect PAMPs and endogenous molecules in the cytoplasm, playing important functions in innate immunity. Structurally, NLRs consist of three domains: an N-terminal protein interaction domain such as a caspase activation and recruitment domain (CARD), pyrin domain (PYD), or baculovirus IAP repeats domain (BIR); a central nucleotide-binding oligomerization domain (NOD); and a C-terminal leucine-rich repeat domain (LRR). NLRs can be divided into five subfamilies based on their N-terminal structure: NLRA, NLRB, NLRC, NLRP, and NLRX. Currently, 23 human NLR genes and 34 murine NLR genes have been reported, though the physiological functions of most NLRs require further investigation [25]. The most representative NLR family proteins are NOD1 and NOD2, which recognize peptidoglycan (PGN) structures. NOD1 exists in Gram-negative bacteria and some Gram-positive bacteria, recognizing the PGN product meso-diaminopimelic acid (iE-DAP); NOD2 exists in all Gram-positive and Gram-negative bacteria, recognizing the PGN component muramyl dipeptide (MDP).

NOD1 participates in recognizing various intracellular pathogenic microorganisms such as *Escherichia coli*, *Shigella flexneri*, *Pseudomonas*, *Chlamydia*, *Haemophilus influenzae*, and *Helicobacter pylori*; NOD2 participates in recognizing *Streptococcus pneumoniae* and *Mycobacterium tuberculosis* [26]; *Listeria monocytogenes* can activate both NOD1 and NOD2. When the C-terminal LRR of NLRs recognizes PAMPs or danger-associated molecular patterns, conformational reorganization triggers NOD oligomerization, exposing the N-terminal effector domain. Through homotypic interactions, the effector domains CARD or PYD recruit corresponding effector molecules, bringing them into proximity for activation and participation in multiple signaling pathways. For example, NLR family proteins NOD1 and NOD2 interact with receptor-interacting protein kinase 2 (RIPK2) to induce NF- B and MAPK signals. Additionally, NOD1 and NOD2 can induce autophagy by recruiting the autophagy-related protein ATG16L1 to the plasma membrane [27]. During viral infection, NOD2 can bind mitochondrial antiviral signaling protein (MAVS) to induce type I IFN production [28]. NLR family members NLRP1, NLRP3, and NLRC4 can assemble large protein complexes to form inflammasomes that activate inflammatory caspase-1 to produce IL-1β and IL-18. For example, NLRP3 recruits the adapter protein apoptosis-associated speck-like protein containing CARD (ASC) through homotypic PYD interactions; ASC then binds pro-caspase-1 through homotypic CARD interactions, leading to caspase-1 activation and production of pro-inflammatory cytokines IL-1β and IL-18, which amplify antiviral innate immune responses. To maintain homeostasis mediated by NLR family signaling, NLRX1 and NLRC5 proteins play important regulatory roles, with studies showing they can inhibit NF- B and type I IFN-mediated signaling pathways [29]. The primary biological function of the NLR family is to enhance the immune system' s ability to detect microbial infections and mediate production of pro-inflammatory cytokines such as IL-1β to regulate immune responses and inflammatory reactions.

1.3 RLRs in Innate Immune Recognition

Viral invasion of the cytoplasm during dsRNA production activates antiviral signaling pathways. This response exists in the cytoplasm of all immune and non-immune cells and, apart from some TLR family proteins, involves the RLR protein family. RLRs have three members that recognize viral RNA in the cytoplasm: retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated gene 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2) [30]. RIG-I, the typical RLR representative, has an N-terminal CARD that interacts with other CARDs, a central RNA helicase domain, and a C-terminal repressor domain (RD) that binds RNA. In resting cells, RIG-I exists in a self-inhibited state; upon viral infection, RNA binding triggers conformational changes that activate RIG-I, relieving self-inhibition and promoting CARD recruitment of downstream signaling molecules. MDA5 also contains a CARD and helicase domain, though whether it has RD function at the C-terminus remains uncertain. LGP2 contains a helicase domain and RD but lacks a CARD. Stud-

ies indicate that LGP2 negatively regulates virus-induced responses by binding RIG-I through its RD to interfere with conformational association and inhibit immune signaling [31].

In the cytoplasm, RIG-I primarily recognizes various ssRNA viruses including paramyxoviruses, influenza A virus, vesicular stomatitis virus, and Japanese encephalitis virus; MDA5 participates in recognizing other RNA viruses such as picornavirus encephalomyocarditis virus and also recognizes polyinosinic-polycytidylic acid (poly I:C). Upon viral invasion, RIG-I and MDA5 initially interact with MAVS, activating signaling cascades through stimulator of interferon genes (STING) and TANK-binding kinase 1 (TBK1) to induce type I IFN expression. Additionally, MAVS signaling can activate activator protein 1 (AP-1) through RIPK1 to generate innate immune responses [31]. Due to this specific recognition, specific viral RNA ligands can be identified by infecting mice with RIG-I or MDA5 knockout or double knockout [32]. RIG-I is activated by in vitro transcribed RNA, while MDA5 is activated by synthetic poly I:C, confirming that RIG-I recognizes the 5' -triphosphate moiety of ssRNA. Furthermore, RIG-I recognizes 21-27 nucleotide dsRNA, while MDA5 recognizes long-chain dsRNA. Although LGP2 acts as a negative regulator, LGP2 knockout mice show different response levels to different RNA viruses: type I IFN levels increase after poly I:C and vesicular stomatitis virus infection but decrease after encephalomyocarditis virus infection [33].

1.4 Other PRRs in Innate Immune Recognition

Currently, CLRs are a popular class of PRRs that recognize many different microorganisms. All CLRs contain a C-type lectin-like domain (CTLD), initially identified as a double-loop domain that binds calcium and carbohydrates, though later studies found CTLD-linked proteins could bind other ligand types. Based on different structures, the CLR protein family can be divided into 17 subgroups [34], with dendritic cell-associated C-type lectin-1 (Dectin-1) and Dectin-2 as typical representatives. Dectin-1 is expressed on DCs, macrophages, neutrophils, and monocytes as a transmembrane protein containing an extracellular irregular CTLD domain and an intracellular modified immunoreceptor tyrosine-based activation motif (ITAM). Dectin-1 primarily recognizes fungal β-1,3-glucans; upon ligand binding, Dectin-1 promotes ligand uptake through phagocytosis and initiates signaling cascades that regulate gene expression and cytokine production, participating in defense against fungal infection. Additionally, Dectin-1 can recognize secretory IgA, mucins, and other microbial β-1,3-glucans [35]. Dectin-2, which connects to the ITAM-bearing molecule Fc receptor γ (FcRγ) for signal transduction, lacks signaling function in its intracellular portion—this represents a difference in ITAM usage between Dectin-1 and Dectin-2, though downstream signal transmission is essentially similar. Dectin-2 primarily recognizes fungal cell wall α-mannans [36] as well as *Schistosoma mansoni* and *Mycobacterium tuberculosis* [35].

ALRs are a class of PRRs that recognize intracellular DNA, containing a pyrin

and HIN domain-containing protein (PYHIN) interaction domain and a DNA-binding HIN200 domain. Upon detection of intracellular DNA invasion, the receptor absent in melanoma 2 (AIM2) interacts with the adapter ASC to promote inflammasome formation, initiating innate immune responses that secrete pro-inflammatory cytokines IL-1β and IL-18 and rapidly trigger apoptosis with inflammatory symptoms [37]. Interferon-inducible protein 16 (IFI16), another ALR family member, can recognize herpes simplex virus (HSV), cytomegalovirus, Kaposi' s sarcoma herpesvirus (KSHV), and human immunodeficiency virus (HIV). IFI16 functions as a cytoplasmic sensor that, like other DNA receptors, can activate STING or inflammasomes. Since viral DNA replication occurs in the nucleus, receptor recognition also occurs there. For example, HSV and KSHV recognition occurs in the nucleus, but signals are ultimately activated through cytoplasmic inflammasomes or STING; thus, ligand-induced IFI16 translocation to cytoplasmic signaling sites is required to initiate herpesvirus defense [38]. IFI16 plays an important role in recognizing foreign DNA in both cytoplasmic and nuclear compartments; however, how IFI16 distinguishes self from foreign DNA in the nucleus requires further scientific investigation.

2 Interplay Among Different PRR Signaling Pathways

TLRs, NLRs, and RLRs interact closely during signal transduction to activate innate immune defenses against pathogens (Figure 1 [Figure 1: see original paper]). During inflammation, PRRs exhibit partial overlap and mutual compensation in recognizing PAMPs across different species, tissues, cells, and organelles. While Gram-negative bacterial LPS is critical for TLR4 activation, studies have also found that cytoplasmic caspase-4/5/11 can recognize LPS and initiate innate immune signals [39]. Inhibitory phenomena exist between RLR and TLR pathways: virus-stimulated IRF3 signaling induced by RLRs can inhibit bacteria-stimulated IRF5 signaling induced by TLRs through competitive occupation of the IL-12b promoter, which molecularly explains the mechanism of bacterial superinfection following viral infection [40]. TLR7 small molecule agonists inhibit nucleic acid-mediated TLR3, TLR9, and RIG-I-dependent type I IFN signaling by suppressing phosphorylation of signal transducer and activator of transcription (p-STAT1/2) and IRF9 complexes [41]. Additionally, RIG-I plays a positive role in inflammasome formation and IL-1β secretion: upon RNA virus stimulation, RIG-I interacts with adapter ASC to trigger caspase-1-dependent inflammasome activation and IL-1β maturation [42]. Conversely, NLRs regulate RLR-mediated type I IFN responses by targeting RIG-I and MDA5 through NLRC5 to inhibit signaling molecules, or by disrupting RLR-MAVS connections through NLRX1-MAVS interactions; NLRC3 can interfere with STING-TBK1 interactions, and NLRP4 causes TBK1 degradation [31]. TLRs and NOD proteins are crucial for bacterial defense and also interact: NOD1 and NOD2 agonists can synergize with TLR2, TLR3, TLR4, and TLR9 agonists to promote dendritic cell and basophil maturation, while NLRs also regulate TLR signaling through NLRX1 and NLRC3 interference with the TRAF6-

NF- B pathway, NLRC5 disruption of IKKα and IKKβ phosphorylation, and NLRP6 and NLRP12 targeting of MAPK and NF- B activation [43]. These synergistic and antagonistic interactions among PRRs create complex cross-talk in PRR signaling pathways, enabling more precise and rapid responses to microbial invasion.

Figure 1 Interplay across TLRs, RLRs and NLRs signaling pathways

MyD88: myeloid differentiation factor 88; MAPK: mitogen-activated protein kinase; LGP2: laboratory of genetics and physiology 2; RIG-I: retinoic acid-inducible gene I; MDA5: melanoma differentiation-associated gene 5; MAVS: mitochondrial antiviral signaling protein; STING: stimulator of interferon genes; TBK1: TANK-binding kinase 1; TRIF: TIR domain-containing adapter molecule inducing IFN-β; TRAF3/6: TNF receptor-associated factor 3/6; IRF: interferon regulatory factor; AP-1: activator protein 1; TIRAP: TIR domain-containing adapter protein; IKK: inhibitor of NF- B kinase; RIP2: receptor-interacting protein 2; ASC: apoptosis-associated speck-like protein; Caspase-1: cysteine-aspartic acid protease 1; Cytoplasm: cell cytoplasm; Nucleus: cell nucleus.

The innate immune system employs multiple recognition mechanisms in different cell types and subcellular structures. Each PRR signaling pathway plays an indispensable role in pathogen elimination and immune tolerance maintenance, as mutations in PRRs or their signaling molecules are closely associated with many inflammatory diseases, immunodeficiencies, and autoimmune disorders. A single PAMP can trigger recognition by multiple different PRRs under certain circumstances, cooperatively inducing inflammatory responses and adaptive immunity. Therefore, better understanding of the complex interactions among PRRs and the coordinated control between innate and adaptive immunity is crucial for developing effective and quantitative therapeutic drugs for immune-related diseases. These issues will also promote the development and theoretical framework improvement of immunology.

References

[1] JANEWAY C J. Approaching the asymptote? Evolution and revolution in immunology[J]. Cold Spring Harbor Symposia on Quantitative Biology, 1989, 54: 1-13.

[2] AKIRA S, TAKEUCHI O. Pathogen recognition and innate immunity[J]. Cell, 2006, 124(4): 783-801.

[3] BARTON G M, KAGAN J C. A cell biological view of Toll-like receptor function: regulation through compartmentalization[J]. Nature Reviews Immunology, 2009, 9(8): 535-542.

[4] IWASAKI A, MEDZHITOV R. Control of adaptive immunity by the innate immune system[J]. Nature Immunology, 2015, 16(4): 343-353.

[5] DINARELLO C A. Inflammatory cytokines: interleukin-1 and tumor necrosis factor as effector molecules in autoimmune diseases[J]. Current Opinion in Immunology, 1991, 3(6): 941-948.

[6] GAY N J, KEITH F J. Drosophila Toll and IL-1 receptor[J]. Nature, 1991, 351(6325): 355-356.

[7] HEGUY A, BALDARI C T, MACCHIA G, et al. Amino acids conserved in interleukin-1 receptors (IL-1Rs) and toll proteins are essential for IL-1R signal transduction[J]. Journal of Biological Chemistry, 1992, 267(4): 2605-2609.

[8] POLTORAK A, HE X, SMIRNOVA I, et al. Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene[J]. Science, 1998, 282(5396): 2085-2088.

[9] QURESHI S T, LARIVIERE L, LEVEQUE G, et al. Endotoxin-tolerant mice have mutations in Toll-like receptor 4 (Tlr4)[J]. Journal of Experimental Medicine, 1999, 189(4): 615-625.

[10] HOSHINO K, TAKEUCHI O, KAWAI T, et al. Cutting edge: Toll-like receptor 4 (TLR4)-deficient mice are hyporesponsive to lipopolysaccharide: evidence for TLR4 as the Lps gene product[J]. Journal of Immunology, 1999, 162(7): 3749-3752.

[11] KAWAI T, AKIRA S. The roles of TLRs, RLRs and NLRs in pathogen recognition[J]. International Immunology, 2009, 21(4): 317-337.

[12] JIN M S, KIM S E, HEO J Y, et al. Crystal structure of the TLR1-TLR2 heterodimer induced by binding of a tri-acylated lipopeptide[J]. Cell, 2007, 130(6): 1071-1082.

[13] HAYASHI F, SMITH K D, OZINSKY A, et al. The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5[J]. Nature, 2001, 410(6832): 1099-1103.

[14] UEMATSU S, FUJIMOTO K, JANG M H, et al. Regulation of humoral and cellular gut immunity by lamina propria dendritic cells expressing Toll-like receptor 5[J]. Nature Immunology, 2008, 9(7): 769-776.

[15] ZHANG D, ZHANG G, HAYDEN M S, et al. A Toll-like receptor that prevents infection by uropathogenic bacteria[J]. Science, 2004, 303(5663): 1522-1526.

[16] ANDRADE W A, SOUZA M C, RAMOS-MARTINEZ E, et al. Combined action of nucleic acid-sensing Toll-like receptors and TLR11/TLR12 heterodimers imparts resistance to *Toxoplasma gondii* in mice[J]. Cell Host & Microbe, 2013, 13(1): 42-53.

[17] OLDENBURG M, KRUGER A, FERSTL R, et al. TLR13 recognizes bacterial 23S rRNA devoid of erythromycin resistance-forming modification[J]. Science, 2012, 337(6098): 1111-1115.

[18] ALEXOPOULOU L, HOLT A C, MEDZHITOV R, et al. Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3[J]. Nature, 2001, 413(6857): 732-738.

[19] LUND J, SATO A, AKIRA S, et al. Toll-like receptor 9-mediated recognition of Herpes simplex virus-2 by plasmacytoid dendritic cells[J]. Journal of Experimental Medicine, 2003, 198(3): 513-520.

[20] VOLLMER J, TLUK S, SCHMITZ C, et al. Immune stimulation mediated by autoantigen binding sites within small nuclear RNAs involves Toll-like receptors 7 and 8[J]. Journal of Experimental Medicine, 2005, 202(11): 1575-1585.

[21] FLANNERY S, BOWIE A G. The interleukin-1 receptor-associated kinases: critical regulators of innate immune signalling[J]. Biochemical Pharmacology, 2010, 80(12): 1981-1991.

[22] KAWAI T, TAKEUCHI O, FUJITA T, et al. Lipopolysaccharide stimulates the MyD88-independent pathway and results in activation of IFN-regulatory factor 3 and the expression of a subset of lipopolysaccharide-inducible genes[J]. Journal of Immunology, 2001, 167(10): 5887-5894.

[23] HORNG T, BARTON G M, FLAVELL R A, et al. The adaptor molecule TIRAP provides signaling specificity for Toll-like receptors[J]. Nature, 2002, 420(6913): 329-333.

[24] OSHIUMI H, SASAI M, SHIDA K, et al. TIR-containing adapter molecule (TICAM)-2, a bridging adapter recruiting to toll-like receptor 4 TICAM-1 that induces interferon-beta[J]. Journal of Biological Chemistry, 2003, 278(50): 49751-49762.

[25] TING J P, LOVERING R C, ALNEMRI E S, et al. The NLR gene family: a standard nomenclature[J]. Immunity, 2008, 28(3): 285-287.

[26] KANNEGANTI T D, LAMKANFI M, NUNEZ G. Intracellular NOD-like receptors in host defense and disease[J]. Immunity, 2007, 27(4): 549-559.

[27] TRAVASSOS L H, CARNEIRO L A, RAMJEET M, et al. Nod1 and Nod2 direct autophagy by recruiting ATG16L1 to the plasma membrane at the site of bacterial entry[J]. Nature Immunology, 2010, 11(1): 55-62.

[28] SABBAH A, CHANG T H, HARNACK R, et al. Activation of innate immune antiviral responses by Nod2[J]. Nature Immunology, 2009, 10(10): 1073-1080.

[29] ARNOULT D, SOARES F, TATTOLI I, et al. An N-terminal addressing sequence targets NLRX1 to the mitochondrial matrix[J]. Journal of Cell Science, 2009, 122(17): 3161-3168.

[30] BRUBAKER S W, BONHAM K S, ZANONI I, et al. Innate immune pattern recognition: a cell biological perspective[J]. Annual Review of Immunology, 2015, 33: 257-290.

[31] CAO X. Self-regulation and cross-regulation of pattern-recognition receptor signalling in health and disease[J]. Nature Reviews Immunology, 2015, 16(1): 35-50.

[32] KATO H, TAKEUCHI O, SATO S, et al. Differential roles of MDA5 and RIG-I helicases in the recognition of RNA viruses[J]. Nature, 2006, 441(7089): 101-105.

[33] VENKATARAMAN T, VALDES M, ELSBY R, et al. Loss of DExD/H box RNA helicase LGP2 manifests disparate antiviral responses[J]. Journal of Immunology, 2007, 178(10): 6444-6455.

[34] ZELENSKY A N, GREADY J E. The C-type lectin-like domain superfamily[J]. Federation of European Biochemical Societies Journal, 2005, 272(24): 6179-6217.

[35] HOVING J C, WILSON G J, BROWN G D. Signalling C-type lectin receptors, microbial recognition and immunity[J]. Cellular Microbiology, 2014, 16(2): 185-194.

[36] SAIJO S, IKEDA S, YAMABE K, et al. Dectin-2 recognition of alpha-mannans and induction of Th17 cell differentiation[J]. Immunity, 2010, 32(5): 681-691.

[37] HENAO-MEJIA J, ELINAV E, STROWIG T, et al. Inflammasomes: far beyond inflammation[J]. Nature Immunology, 2012, 13(4): 321-324.

[38] LI T, DINER B A, CHEN J, et al. Acetylation modulates cellular distribution and DNA sensing ability of interferon-inducible protein IFI16[J]. Proceedings of the National Academy of Sciences, 2012, 109(26): 10558-10563.

[39] SHI J, ZHAO Y, WANG Y, et al. Inflammatory caspases are innate immune receptors for intracellular LPS[J]. Nature, 2014, 514(7521): 187-192.

[40] NEGISHI H, YANAI H, NAKAJIMA A, et al. Cross-interference of RLR and TLR signaling pathways modulates antibacterial T cell responses[J]. Nature Immunology, 2012, 13(7): 659-666.

[41] FORSBACH A, MULLER C, MONTINO C, et al. Negative regulation of the type I interferon signaling pathway by synthetic Toll-like receptor 7 ligands[J]. Journal of Interferon and Cytokine Research, 2012, 32(6): 254-268.

[42] HENAO-MEJIA J, ELINAV E, STROWIG T, et al. Inflammasomes: far beyond inflammation[J]. Nature Immunology, 2012, 13(4): 321-324.

[43] LIU J, CAO X. Cellular and molecular regulation of innate inflammatory responses[J]. Cellular and Molecular Immunology, 2016, 13(6): 711-721.

Note: Figure translations are in progress. See original paper for figures.