Current Trends in Immunology
Vol. 24, 2023

Review

Crosstalk between pattern recognition receptors tailors immune responses to pathogens

Emma Frank[1,2,#], Killian E. Vlaming[1,2,#], Danny M. Cohn[3], Godelieve J. de Bree[2,3] and Teunis B. Geijtenbeek[1,2,*]

[1]Amsterdam UMC location AMC, Department of Experimental Immunology, Meibergdreef 9, 1105AZ, Amsterdam, The Netherlands; [2]Amsterdam Institute for Immunology and Infectious Diseases, 1105AZ, Amsterdam, The Netherlands; [3]Amsterdam UMC location University of Amsterdam, Department of Internal Medicine, Meibergdreef 9, 1105AZ, Amsterdam, The Netherlands.

ABSTRACT

The intricate dialogue between the human immune system and diverse pathogens paints a vivid picture of a dynamic and ever-evolving battle for survival. This review explores the multifaceted interplay in the context of viruses, bacteria, parasites, and fungi, unveiling the underlying mechanisms that define their complex dance. The immune response is driven by an array of pattern recognition receptors, encompassing Toll-like receptors (TLRs), NOD-like receptors (NLRs), AIM2-like receptors (ALRs), RIG-I-like receptors (RLRs), and C-type lectin receptors (CLRs), each contributing to the orchestration of complex immune reactions. Crosstalk among these receptors emerges as a pivotal mechanism that shapes immune responses, by enhancing or modulating inflammation, or by providing a tolerogenic environment limiting excessive tissue damage. Through detailed examinations of various infectious agents, this review highlights the nuanced interplay between immune recognition and responses, inspiring to provide a better understanding of immunity and host defence capacity.

*Corresponding author
t.b.geijtenbeek@amsterdamumc.nl

#These authors contributed equally to this work.

KEYWORDS: PRR signalling, innate immunity, crosstalk.

Introduction

The human immune system consists of an intricate network of receptors and signalling pathways, orchestrating coordinated responses to a vast array of pathogens. A vital component of early defence mechanisms is a subset of receptors, called pattern recognition receptors (PRRs). They serve as protein-sentinels to detect the presence of pathogens. Expressed by various cell-subsets and located on the surface, in endosomal compartments or in the cytoplasm, PRRs recognize conserved, specific molecular structures known as pathogen-associated molecular patterns (PAMPs) found on viruses, bacteria, and other microorganisms. These receptors can be classified into different families, including TLRs, NLRs, ALRs, RLRs, and CLRs. Each family recognizes different types of PAMPs and has distinct structural characteristics resulting in the activation of particular signalling pathways. This separation allows the immune system to refine its response based on the specific pathogen encountered. However, emerging research suggests that, beyond their individual functions, crosstalk between receptor families is paramount to tailor the immune responses. By interacting and collaborating with each other, PRRs create pathogen-specific responses that are both nuanced and targeted.

Here, we provide a comprehensive overview of the different receptor families themselves, followed by a discussion of the currently known forms of crosstalk. We discuss the underlying mechanisms that allow the immune system to coordinate its defences against the plethora of existing pathogens. Next, we elucidate on how crosstalk leads to synergistic or antagonistic signalling cascades, thereby influencing the hosts' defences and infection outcomes. By dissecting the intricacies of receptor identification, crosstalk, and their combined influence on pathogen-specific responses, this review aims to shed light on the complex interplay between immune recognition and responses.

Pattern recognition receptors

The human immune system consists of innate and adaptive immunity. Innate immunity is rapidly activated upon an infection, acting as the body's first line of defence, while the adaptive response generates highly tailored responses to a specific infectious agent via generation of antigen-specific immune cells [1, 2]. PRR activation via ligand binding triggers intracellular signalling pathways that activate key transcription factors, like nuclear factor-kappa B (NFKB).

Different pathogens necessitate tailored immune responses to effectively combat infections. Each family of receptors enacts a different signalling pathway following activation, likely associated with the type of infectious agent found at specific cellular locations. NRLs induce inflammasome priming and caspase-1 activation through recruitment of the adaptor molecule apoptosis associated speck-like protein containing a caspase activation and recruitment domain (CARD) (ASC), leading to the production and release of Interleukin (IL)-1ß and IL-18 [1, 3, 4]. CLRs signal through multiple adaptor proteins, including Syk-mediated activation of caspase-recruitment domain protein 9 (CARD9), B cell lymphoma/leukaemia 10 (Bcl-10) and mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1), as well as the Raf-1 signalosome or inhibitory phosphatases like the Src homology region 2 domain-containing phosphatase 1 (SHP1) or SHP [3, 5-7]. Different ligands induce various forms of activation to generate different responses, encompassing a wide array of cyto- and chemokines including tumor necrosis factor-α (TNF-α), IL-6, IL-8, IL-10, IL-12. Importantly, induction of type I interferons (IFNs) enables tailoring by regulating cytokines, inducing interferon stimulated genes (ISGs) and modulating T-cell proliferation.

RLRs, located within the cytosol, signal through the mitochondrial antiviral signalling (MAVS) adaptor protein to activate TANK-binding kinase 1 (TBK1) and IKKe kinases, which phosphorylate interferon regulatory factor 3 (IRF3) and IRF7, resulting in the generation of type I IFNs [1, 3, 8-11]. TLRs activate the immune system mainly through the Myeloid differentiation primary response 88 (MyD88) dependent pathway, where recruitment of Interleukin-1 receptor-associated kinases (IRAKs) and TNF receptor associated factor 6 (TRAF6) leads to the activation of the NFKB complex and therefore the production of associated, pro-inflammatory cytokines TNF-α, IL-6, IL-8, IL-1ß and IL-12 [1, 3, 12].

The balance of the various cytokines produced in response to different pathogens through distinct PRRs shapes the subsequent immune response. The numerous cytokines produced during the initial innate immune reaction following the recognition of an infectious agent can generate an abundance of cellular responses. Some of the most common cytokines are displayed in Table 1.

T-helper responses following PRR stimulation

Immune responses can be classified into different types of cell-mediated innate and adaptive reactions. Intracellular pathogens, such as bacteria or viruses, elicit a type 1 response. Activated antigen-presenting cells secrete IL-12, which leads to the differentiation of naïve CD4+ T-cells into TH1 cells that secrete IFN-γ, the key effector molecule. IFN-γ enhances the phagocytic abilities of macrophages and promotes the differentiation of CD8+ cytotoxic T-cells with enhanced cytolytic potential for better intracellular killing. IL-2 and TNF-α amplify the type 1 response. While vital for the clearance of intracellular pathogens, excessive TH1 signalling can cause tissue damage and autoimmune diseases. A type 2 response mainly protects against parasitic infections and is characterized by IL-4, IL-5 and

Table 1. Common cytokines produced after activation of PRRs. Specific cytokines, which cell types mainly produce them, which cell type respond to them (effector) and their functions.

Cytokine	Main producer	Effector	Function	Reference
Chemokines (IL-8, CCL2)	Macrophages, dendritic cells, endothelial cells, epithelial cells, T cells, fibroblasts.	Neutrophils, monocytes, lymphocytes	Immune cell recruitment to site of infection	[26, 47]
IL-12	Monocytes, macrophages, dendritic cells	T-cells, NK-cells	Stimulates TH1 cell differentiation and natural killer (NK) cell activation via STAT4.	[25]
IL-18	Monocytes, macrophages, dendritic cells, epithelial cells	T-cells, NK-cells	Enhance IFN-y production together with IL-12 and promotes TH1 responses	[25, 62]
IL-1β	Monocytes/ Macrophages, Dendritic cells, neutrophils, epithelial cells	Endothelial cells, immune cells (e.g., T cells, B cells), various tissues.	Promotes inflammation via TH17 cell differentiation; induces other cytokines, enhances vasodilation; increases vascular permeability.	[2, 26]
IL-6	Monocytes/ Macrophages, dendritic cells, T-cells, fibroblasts	Hepatocytes (acute phase response), T and B cells (differentiation), and the hypothalamus (fever).	Induces acute phase proteins, supports B and T cell differentiation, contributes to fever.	[26]
TNF-α	Monocytes, Macrophages, dendritic cells	Endothelial cells, immune cells	Promotes inflammation by inducing vasodilation and increased vascular permeability via NFKB and MAPK pathways	[26]
Type 1 IFN	Dendritic cells, monocytes, macrophages, infected cells	Neighbouring cells, NK-cells	Induce an antiviral state through the JAK-STAT pathway, activating genes that inhibit viral replication	[9]

IL-13 producing CD4+ TH2 lymphocytes, which activate eosinophils and basophils along with class switching of B cells to Immunoglubulin E (IgE) producing plasma cells. While finely tuned to expulse parasites and regenerate tissue damage caused by the invading pathogens, overactivation can result in chronic asthma and allergies (Figure 1).

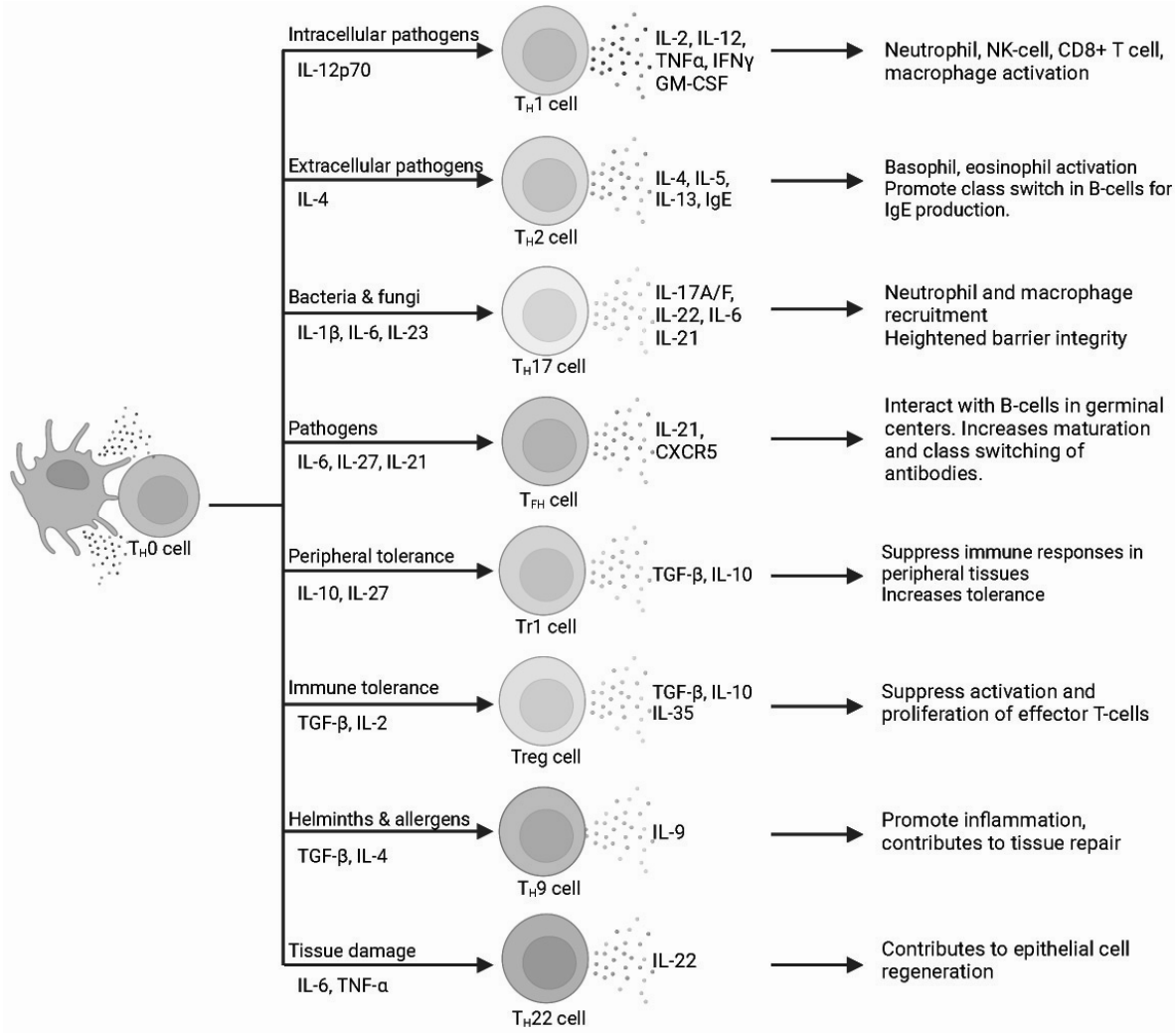

Figure 1. Types of immunity and Th effector types.

Intracellular pathogens, such as bacteria or viruses, induce a pro-inflammatory type 1 immune reaction. IL-12p70 signalling leads to the differentiation of Th1 lymphocytes which produce IL-2, IL-12p70, TNF-α, IFN-γ and GM-CSF. Parasites meanwhile, stimulate a Th2-dominant response. IL-4 stimulates differentiation of IL-4, IL-5, IL-13-producing cells which mediate an anti-inflammatory environment as well as the switching of B-cells to IgE-producing plasma cells. Type 3 immunity mainly protects barriers against extracellular pathogens like bacteria or fungi via the IL-1β and IL-6-mediated induction of Th17 cells resulting in the release of pro-inflammatory cytokines such as IL-17A, IL-17F and IL-22. Tolerance is maintained by the induction of Tr1 and Treg cells, via secretion of IL-10, IL-27 and TGF-β, IL-2. These cells suppress immune responses and maintain tolerance via the secretion of TGF-β, IL-10 and IL-35. Helminth and allergens induce Th9 responses via TGF-β and IL-4, which lead to a Th2-like response, with the secretion of IL-9, attraction of mast-cells and strengthening of mucosal immunity. Involved in homeostasis and tissue repair are Th22 cells, induced by IL-6 and TNF-α following inflammation, and they contibute to epithelial cell regeneration via secretion of IL-22.

Extracellular pathogens, both fungi or bacteria, induce a type 3 response, primarily charged with protecting barrier structures and the mucosal equilibrium. IL-1ß and IL-6 stimulation of TH17 lymphocytes leads to the production of IL-17A, IL-17F and IL-22, resulting in the activation of immune and nonimmune cells to protect epithelial recovery, production of antimicrobial peptides as well as the recruitment of neutrophils to effectively combat the infection (Figure 2) [2, 9-11]. T follicular helper (Tfh) cells play a pivotal role in orchestrating the adaptive immune response by facilitating the formation of germinal centers and aiding in the development of long-lasting antibody responses. The differentiation of naïve CD4+ T cells into Tfh cells is initiated by interactions with dendritic cells (DCs) and subsequent recognition of antigens presented by B cells. Cytokines such as IL-6 and IL-21 are instrumental in guiding this differentiation process [13, 14] (Figure 1).

Type 1 regulatory T cells (Tr1) and Regulatory T cells (Tregs) are subsets that play distinct roles in maintaining immune tolerance and preventing autoimmunity. Tr1 cells are induced in the periphery and are characterized by the secretion of high levels of IL-10 and low levels of IL-4, IL-5, and IL-2. These cells exert their suppressive function mainly through the secretion of IL-10 and TGF-β, inhibiting the function of effector T cells and reducing inflammation. Moreover, Tregs, which can either develop in the thymus (tTregs) or be induced in the periphery (iTregs) from naïve CD4+ T cells, are crucial for maintaining immune homeostasis. The transcription factor Foxp3 is a master regulator for Treg development and function, and TGF-β is a crucial cytokine for the induction of Foxp3 and the differentiation of iTregs [15] (Figure 1).

Additionally, Th9 cells, characterized by the production of IL-9, emerge under the influence of TGF-β and IL-4. These cells have been implicated in immune responses against parasitic infections and in allergic inflammation. Th22 cells, another subset of CD4+ T cells, predominantly produce IL-22 and are promoted by IL-6 and TNF-α. Th22 cells are involved in tissue repair and host defence at barrier surfaces, particularly the skin [15] (Figure 1).

Thus, the adaptive immune response is highly versatile, with different T-helper subsets tailored to combat various pathogens while maintaining

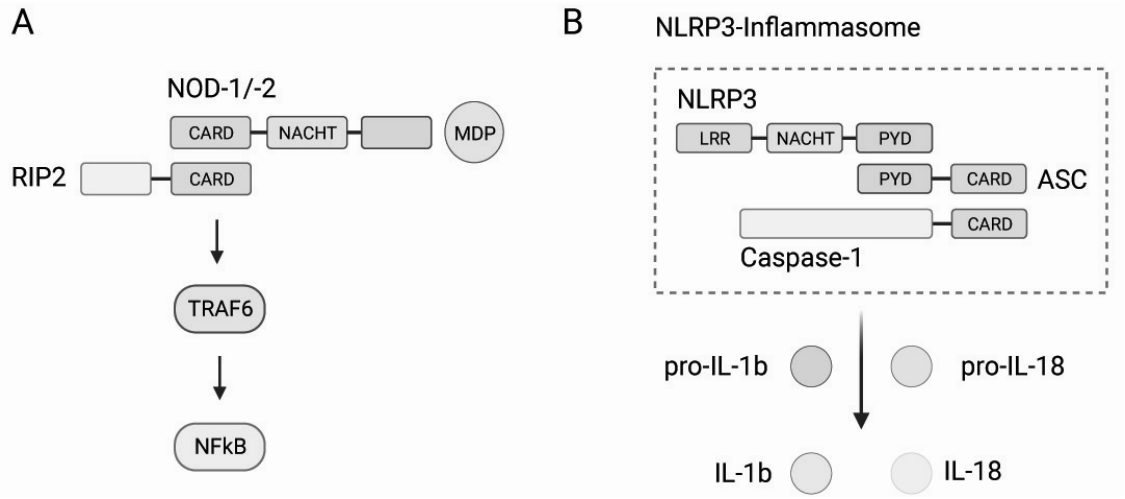

Figure 2. Graphical abstract of NLR signalling pathways.

NOD1 and NOD2 can recruit the adaptor molecule RIP2 via CARD-CARD domain interactions. RIP2 further recruits TRAF6, thereby initiating pro-inflammatory gene expression via the NFkB signaling pathway (A). NLRP3 recruits ASC via their PYD, which further recruits caspase-1 via CARD-CARD domain interaction thereby forming the NLRP3-inflammasome. The inflammasome mediates the release of the pro-inflammatory cytokines IL-1ß and IL-18 in a caspase-1 dependent-manner which initiates the cleavage of inactive pro-IL-1ß and pro-IL-18 (B).

immune tolerance and homeostasis. The proliferation and differentiation of these subsets are guided by specific cytokines and transcription factors, ensuring a coordinated and effective immune response (Figure 1).

AIM2-like receptors

Aim2-like receptors, or ALRs, are a group of cytosolic pattern recognition receptors that detect intracellular double-stranded DNA, particularly from pathogens such as bacteria or viruses or stemming from cellular damage. Ligand recognition via their C-terminus HIN-200 domain triggers the formation of caspase-1-activating pyroptosome resulting in the maturation of the pro-inflammatory cytokines IL-1ß and IL-18 as well as pyroptotic cell death, thereby thwarting intracellular attack. They contain an N-terminal pyrin domain (PYD) used to recruit the adaptor molecule ASC upon ligand binding. ASC then acts as a scaffolding complex and recruits and activates caspase-1 through homotypic CARD-CARD interactions to form an inflammasome which promotes the release of pro-inflammatory IL-1ß and IL-18 [1, 4].

NOD-like receptors

NLRs are a cytoplasmatic receptor family composed of a leucine-rich repeat (LRR) containing C-terminal domain involved in ligand recognition, a nucleotide-binding and oligomerization domain (NACHT) as well as an N-terminal effector domain involved in the interaction with further signalling molecules. The protein binding motif can differ based on the different NLR members. Several NLRs, like NOD1 and NOD2, harbour CARD domains and activate a signalling cascade cumulating in the activation of the NFκB pathway upon ligand binding (Table 2; Figure 2A). Similar to ALRs, others contain an N-terminal pyrin domain that binds and recruits ASC to initiate inflammasome complex formation (Figure 2B) [1, 3].

C-type lectin receptors

C-type lectin receptors are a family of transmembrane phagocytic PRRs characterized by their calcium-dependent carbohydrate-binding C-type lectin domain (CTLD). CLRs are mainly expressed on the surface of innate immune cells and bind to carbohydrates present on the surface of pathogens [1, 3, 5]. Ligand binding leads to the internalization of the pathogen and often to the degradation via lysosomes or autophagy, depending on the specific CLR and cell type [5]. The human CLR family consists of many members with each receptor recognizing specific carbohydrate moieties. Table 3 depicts some of the CLRs involved in PRR crosstalk. Antigens taken up by CLRs on APCs are loaded onto major histocompatibility complex (MHC) II molecules after degradation and presented to CD4+ T cells, thereby stimulating an adaptive immune response. Signalling pathways initiated by CLRs are diverse and receptor-dependent. Dectin-1, Dectin-2, and Mincle are crucial in inducing downstream signaling by recruiting the kinase Syk. However, Dectin-1 is distinguished by its inherent potency and unique mechanism of activation. Unlike Dectin-2 and Mincle, which rely on Immunoreceptor Tyrosine-based Activation Motif (ITAM)-containing adaptor molecules for signal transduction, Dectin-1 contains an ITAM domain directly within its structure. This direct incorporation of an ITAM domain endows Dectin-1 with a more robust signaling capacity, especially since it recognizes β-glucan structures as danger signals. Upon recognizing β-glucan structures, Dectin-1 triggers various downstream pathways leading to cytokine production (TNF-α, IL-1β, IL-8, IL-10,

Table 2. Common NOD-like receptors and their ligands.

NOD-like receptor	PAMP	Pathogen	Reference
NOD1	iE-DAP (γ-D-glu-meso-diaminopimelic acid)	Gram-negative bacteria	[1, 4]
NOD2	MDP (muramyl dipeptide)	Bacteria	[1, 4]

Table 3. C-type lectin receptors. Common CLRs and their respective ligands as well as their downstream signalling pathways.

C-type lectin receptor	PAMP	Pathogen	Signalling pathway	Reference
DC-SIGN	High-mannose glycans, Fucosylated glycans	Bacteria, Virus, Fungi	Raf-1, TBK1/IKKε	[7, 8]
DCIR	Carbohydrate structures	Bacteria, Virus	SHP1/-2	[8, 63]
DECTIN-1	ß-glucan	Fungi	Syk, Raf-1	[1, 5, 8]
DECTIN-2	α-Mannan	Fungi	Syk	[1, 5, 8]
MINCLE	α-mannosyl structures	Bacteria, Fungi, Parasites	Syk	[8, 12]

IL-12, CXCL2) and induces phagocytosis and respiratory burst through ROS production. This potent signaling mechanism underscores Dectin-1's pivotal role in modulating immune responses, particularly in orchestrating a more pronounced activation of adaptive immunity through its direct ITAM-mediated pathway. It influences adaptive immunity by affecting CD4+ T cell differentiation towards Th1 or Th17 phenotypes and activating CD8+ T cells. Dectin-1 is able to independently signal via Syk and CARD9, resulting in DC activation and cytokine production. Additionally, crosstalk with Raf-1 can also occur, resulting in IL-27 production as well as Th17 responses. Dectin-2 primarily induces Th17 responses and cytokines (IL-1, IL-6, IL-23) essential for antifungal defences. Lacking the ITAM motif of Dectin-1, it signals through the FcRγ chain, activating distinct downstream signalling pathways. Dectin-2's role in protective immunity against certain fungal pathogens underscores its unique contribution to immune responses [11, 16, 17] (Figure 3).

DC-SIGN is a polyfunctional receptor and associates with the adaptor protein LSP1 and signals via the Raf-1 signalosome, consisting of Raf-1, Connector enhancer of KSR (CNK) and kinase suppressor of Ras 1 (KSR1), in a carbohydrate ligand-specific manner. Raf-1 kinase signalling leads to the phosphorylation and acetylation of the NFKB subunit p65, thereby enhancing pro-inflammatory responses. However, this enhancing requires previous engagement of another receptor, thereby allowing for modification of another signal. Inhibitory CLRs, like Dendritic cell immunoreceptor (DCIR), recruit phosphatases such as SHP1 and SHP2 to suppress inflammatory pathways induced by the Bcl-10-CARD9-MALT1 complex (Figure 4) [3, 5, 6] (Figure 3).

RIG-I like receptors

The RIG-I like receptor family are intracellular PRRs composed of RIG-I, melanoma differentiation-associated gene 5 (MDA5) and Laboratory of Genetics and Physiology 2 (LGP2) (Table 4). They are composed of N-terminal caspase activation and recruitment domains, a central helicase and ATPase domain and a C-terminal domain (CTD). They recognize viral nucleic acid and induce antiviral immune responses via pro-inflammatory cytokine and type I IFN production. The CTD of RIG-I recognizes short 5`triphosphate dsRNA while MDA5 senses long-chain dsRNA (>1000 base pairs). Upon ligand binding, RLRs undergo conformational changes to expose their CARD domain which interacts with the CARD domain of the adaptor molecule MAVS to further recruit and activate signalling molecules resulting in the activation and translocation of NF-κB and IRFs to the nucleus to drive the transcription of pro-inflammatory cytokines and type I interferon genes, thereby inducing an antiviral state in

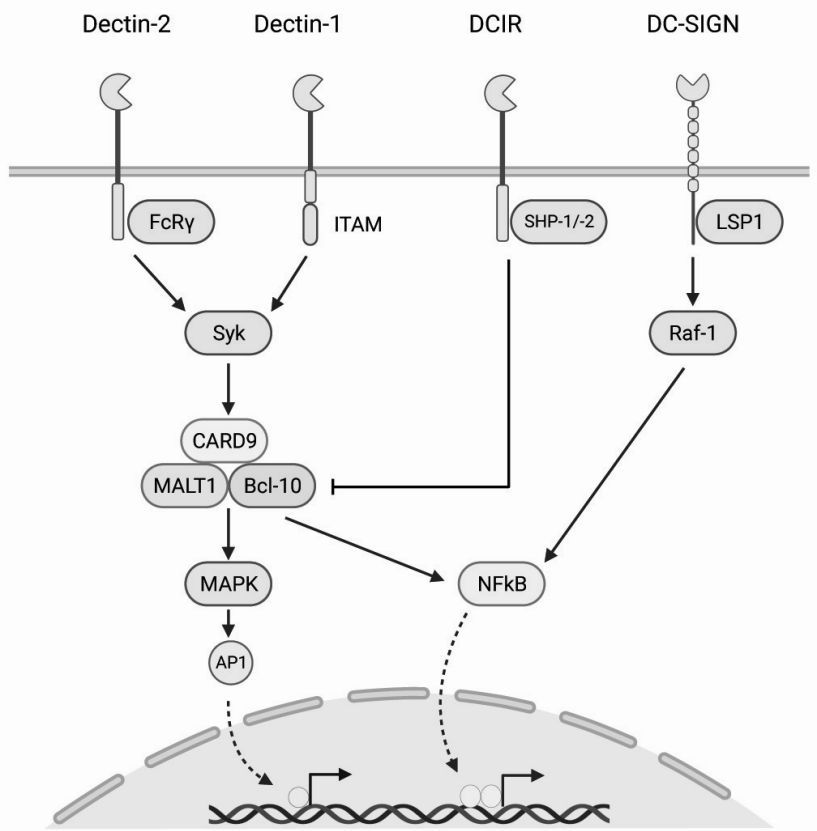

Figure 3. Graphical abstract of C-type lectin receptor signaling pathways.

CLR activation can result in multiple signaling cascades. The kinase Syk, recruited either via ITAM-containing receptors themselves or ITAM-containing adaptor molecules, initiates the complex formation of CARD9, MALT1, and BCL-10. This complex signals via the NFkB or MAPK pathway to induce the expression of pro-inflammatory cytokines. DC-SIGN associates with the adaptor molecule LSP1 to recruit the kinase RAF-1. RAF-1 signaling enhances NFkB signaling. Inhibitory CLRs, such as DCIR, signal via phosphatases, SHP-1 or SHP-2, to suppress inflammatory pathways.

infected and neighbouring cells [1, 3]. IRF3 mainly facilitates IFN-ß production which in turn enhances IRF7 and therefore IFN-α production. These type I IFNs signal through IFN receptors (IFNAR), which are expressed on all nucleated cell types. Receptor activation leads to the activation of Janus kinase 1 (JAK1) and Non-receptor tyrosine-protein kinase 2 (TYK2), which further recruit and activate signal transducer and activator of transcription (STAT) family members (Figure 4).

At this point, crosstalk can occur, with different activation pathways possible. Most commonly, STAT1 homodimers translocate to the nucleus, where they preferentially bind to Gamma-Activated Sites (GAS) in the DNA. This binding initiates the transcription of a distinct set of interferon-responsive genes, different from those activated by the ISGF3 complex. This STAT1-STAT1 homodimer pathway represents a crucial immediate-early response in IFN signalling, leading to the rapid activation of specific genes involved in the antiviral response. Another pathway follows the formation of the trimeric IFN-stimulated gene factor 3 (ISGF3) complex, where IRF9, STAT1 and STAT2 merge to assemble ISGF3 which binds to IFN-stimulated response elements (ISRE) within the nucleus resulting in the expression of numerous interferon stimulated genes (ISGs) (Figure 4) [8]. This itself already presents a form of synergistic crosstalk between STAT within the RIG-I family of receptors.

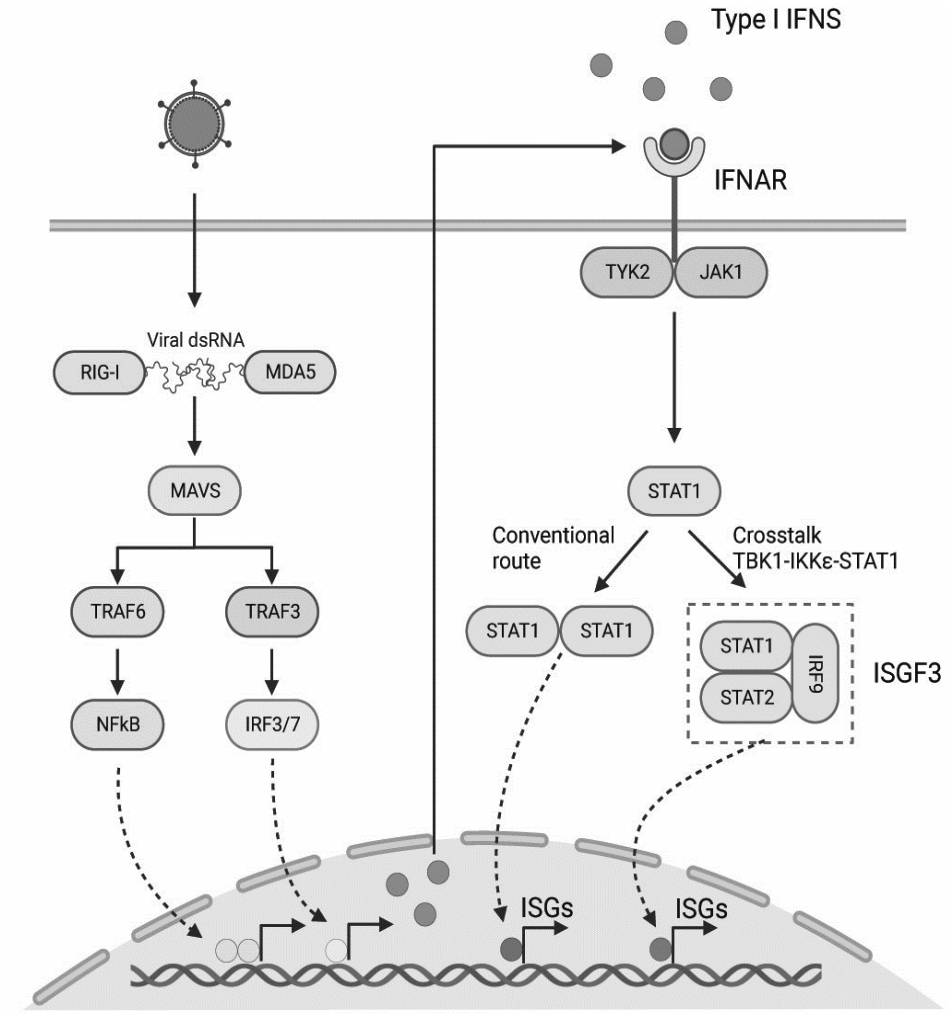

Figure 4. Graphical abstract of RIG-I like receptor signaling pathways.
Activation of RLRs via viral dsRNA recruits the adaptor protein MAVS, which signals via further downstream proteins. It can activate both TRAF6, thereby initiating the NFkB-mediated transcription pathway, as well as TRAF3. TRAF3 activates IRFs, which act as transcription factors and induce the expression of type I IFNs, IF-α and IF-β. Type I IFNs signal via their receptor on either the cell which produces them or surrounding cells. IFNAR activation activates the kinases JAK1 and TYK2, which recruit and activate STATs resulting in the induction of ISGF3. The trimeric complex translocates into the nucleus to stimulate the expression of interferon-stimulated genes, thereby inducing an anti-viral state in the cell.

Table 4. RIG-I like receptors and their ligands.

RIG-I like receptor	PAMP	Pathogen	Reference
RIG-I	Short 5'triphosphated dsRNA	Virus	[1, 4]
MDA5	Long dsRNA, poly I:C	Virus	[1, 4]
LGP2	dsRNA	Virus	[1, 4]

LGP2 itself does not contain a CARD and therefore is unable to interact with other CARD-containing adaptor molecules. Instead, it regulates the viral ligand recognition of RIG-I and MDA5, both positively and negatively [1, 3].

Toll-like receptors

The human Toll-like receptor family consists of ten members, TLR1-TLR10, that are expressed differentially among cell types and respond to different stimuli. The type I transmembrane proteins consist of three domains: an N-terminal ectodomain (NTD) that recognizes and binds to specific ligands, a transmembrane domain, and a cytosolic CTD that interacts with adaptor molecules to initiate downstream signalling pathways. TLRs can be categorized based on their cellular location: TLR1, 2, 4, 5, and 6 are expressed on the cell surface while TLR3, 7, 8, and 9 are expressed intracellularly on the membrane of cell organelles [12, 18]. TLRs can recognize a wide array of PAMPs, and their ligand specificity is conferred by LRR motifs within their ectodomain (Table 5) [18].

Upon ligand binding, TLRs initiate a signalling cascade by recruiting adaptor molecules to their CTD. Two distinct signalling pathways can be distinguished based on the recruitment of either MyD88 or TRIF (TIR-domain-containing adaptor-inducing interferon-β) for downstream signalling. The MyD88-dependant pathway is utilized by all TLRs apart from TLR3. Ligand-bound TLRs recruit MyD88 which next recruits Interleukin-1 receptor-associated kinases. Activated and phosphorylated IRAKs interact with TRAF6 to trigger further signalling cascades to ultimately

Table 5. Toll-like receptors. TLRs and their respective ligands, cellular localization, as well as downstream adaptor molecule for signalling processes.

Toll-like receptor	PAMP	Pathogen	Localization	Adaptor molecule	Reference
TLR1	Triacyl lipopeptides	Bacteria	Plasma membrane	MyD88	[1, 64]
TLR2	Lipoproteins, zymosan, porin, peptidoglycan	Bacteria, Fungi, Parasites, Virus	Plasma membrane	MyD88	[64]
TLR3	dsRNA	Virus	Endolysosomal	TRIF	[1, 4]
TLR4	Lipopolysaccharides (LPS)	Gram-negative bacteria	Plasma membrane	MyD88, TRIF	[1, 4]
TLR5	Flagellin	Bacteria	Plasma membrane	MyD88	[1, 4]
TLR6	Diacyl lipopeptides	Bacteria, Virus	Plasma membrane	MyD88	[64]
TLR7	ssRNA	Virus	Endolysosomal	MyD88	[1, 4]
TLR8	ssRNA	Virus	Endolysosomal	MyD88	[1, 4]
TLR9	Non-methylated CpG DNA	Virus	Endolysosomal	MyD88	[1, 4]
TLR10	dsRNA	Virus	Endolysosomal	MyD88	[1, 4]

lead to the activation of the transcription factors (TFs) NFKB and MAPKs and the subsequent transcription of pro-inflammatory cytokines. NFKB signalling pathway plays a pivotal role in various cellular processes, including inflammation and immune responses. Activation by PRRs leads to the canonical pathway which depends on the inducible degradation of inhibitor of kB (IkB) by IkB kinases (IKKs). This results in the rapid translocation of NFKB dimers to the nucleus where they bind to their target DNA sequences and promote the gene expression of their target genes [19]. TLR3 and TLR4 can activate the TRIF-dependant pathway, initiating a signalling cascade, which ultimately leads to the expression of type I interferons (Figure 5) [12, 18].

Crosstalk between PRRs affects immune responses

No signalling pathway operates in a vacuum, completely on its own. Pathogens, based on their unique molecular structures, stimulate multiple receptors at a time, thereby inducing complexity and interplay between the systems, which we will from now on refer to as crosstalk.

Crosstalk between PRRs plays a crucial role in orchestrating tailored immune responses to various pathogens. As each receptor recognizes distinct conserved PAMPs, the interplay of the induced responses allows the immune system to adjust its reaction to specific pathogens. Crosstalk between various receptors allows them to modulate

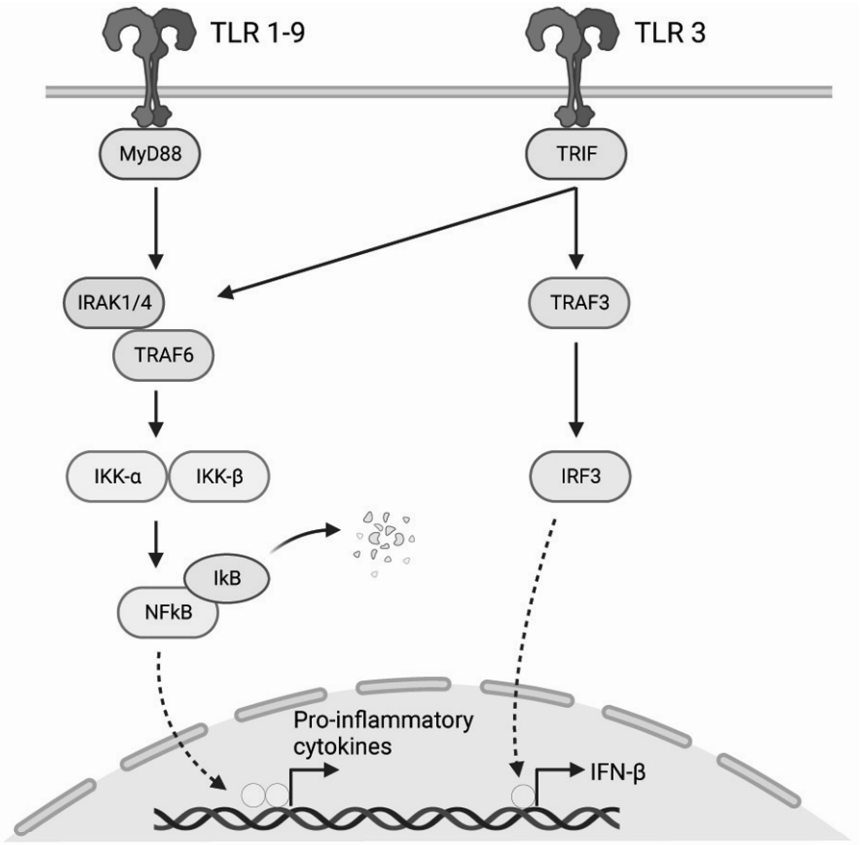

Figure 5. Graphical abstract of Toll-like receptor signalling pathways.

After activation, TLRs signal through either MyD88 or TRIF. MyD88 recruits, activates and phosphorylates IRAKs, which further recruit TRAF6. This complex activates IKKs which target the inhibitor IκB for proteasomal degradation. This releases the NFκB dimers and allows for translocation to the nucleus where they activate the transcription of pro-inflammatory genes. TRIF-dependent signaling utilises TRAF3, resulting in the recruitment of IRFs and subsequently the production of type I IFNs.

each other's signalling pathways, thereby enhancing the efficiency and specificity of the elicited immune reaction. In this section, we will explore various forms of known crosstalk between immune sensors and their implications for pathogen recognition, immune activation, and downstream modulatory effects.

TLR crosstalk

TLR-RLR

Known crosstalk between TLR and RLR receptors centralizes around enhancing antiviral immune responses. So far, interplay between TLR7, TLR8 or TLR9 with RIG-I like sensors has been demonstrated [7, 19-21]. Their respective cellular locations, endosomal in the case of the relevant TLRs and cytosolic for RLRs, suggest they play a role against intracellular infections.

Two forms of crosstalk between these receptors have been reported. Interplay between TLR8 and RIG-I leads to a synergistic pro-inflammatory reaction. Co-stimulation of DCs with TLR8 and RIG-I agonists modulates immune responses and induces potent cytokine production in terms of IL-12, IL-27 and type I IFNs [19]. This suggests interplay of MyD88-mediated NFKB as well as MAVS-directed signaling. Both IL-12 and IL-27 are key players in regulating antiviral adaptive immune responses by inducing differentiation of naïve CD4+ T cells into TH1 cells and activating cytotoxic T cells (CTLs) and NK cells, while type I IFNs are indispensable in fighting viral infections. Interferons can induce both innate and adaptive antiviral responses by leading to the expression of restriction factors, such as MxA, and the differentiation of TH1 cells, CTLs, NK cells and follicular T helper cells [8]. As TLR8-RIG-I crosstalk enhances IFN-ß expression, it thereby affects downstream ISG expression. One of the upregulated proteins, ISG15, effectively inhibits viral replication and enhances type I IFN signalling by stabilizing IRF3 [8, 20]. Additionally to its synergetic effect on pro-inflammatory cytokine production, TLR8 and RIG-I crosstalk also mediates a reduction in IL-6 production [20].

Crosstalk of either TLR7 or TLR9 with RLRs upregulates TLR-mediated Rig-I like receptor expression, therefore enhancing the type I IFN pathway and protecting against viral infections [7, 21]. Stimulation of plasmacytoid dendritic cells (pDCs) by TLR7 agonists leads to an upregulation of RIG-I expression 20. In humans, IFN-I-producing pDCs play an essential role in antiviral immunity. To detect viral PAMPs, pDCs express TLR7 and TLR9 [22]. As these PRRs are endosomal, they require prior internalization of viruses, or their components, to become activated, allowing them to mount antiviral responses. RLRs meanwhile, due to their cytosolic localization, are able to recognize replicating viral RNA intermediates [1]. A study by Szabo *et al*. showed that although the expression of RIG-I in unstimulated pDCs was undetectable, pre-treatment with either TLR7 or TLR9 agonists leads to an increase in RIG-I expression and could therefore potentially boost antiviral responses. However, co-stimulation of pDCs by both TLR7 and TLR9 agonists concurrently lead to a lower expression of RIG-I than either agonist alone [21]. A similar phenomenon has also been shown in other studies, where virus-activated pDCs increased the expression of RLRs in human monocyte-derived DCs (moDCs), thereby also demonstrating an effect on surrounding cells. The supernatant of TLR9-activated pDCs leads to an increase of RIG-I and MDA5 expression in moDCs and completely blocked the replication of the enterovirus Echovirus 9 Hill after a subsequent viral infection. The same effect was seen when activating pDCs directly by infection with a picornaviridae strain, suggesting that viral infections can directly modulate innate immune responses by enhancing RLR-mediated signaling pathways [7].

TLR-NLR

Crosstalk between TLRs and NLRs mainly strengthens anti-bacterial defences in humans. Currently, most known interactions center around TLR-mediated NLRP3 inflammasome priming and crosstalk between NOD1 or NOD2 and TLR2 or TLR4. NOD-like receptors are located within the cytosol and recognize conserved bacterial structures while both TLR2 and TLR4 are present on the plasma membrane of cells and detect peptidoglycan or LPS, respectively, a collaborative role in fighting off intracellular and extracellular bacterial infections is plausible.

The crosstalk of TLR8 or TLR4 and NLRP3 seems to positively affect antibacterial immune responses through TLR-mediated inflammasome priming. The NLR-mediated inflammasome enhances pro-inflammatory immune responses by mediating the cleavage process and subsequent release of active IL-1ß and IL-18. Both cytokines play an important role in inducing a type 1 immunity, which effectively targets intracellular pathogens such as bacteria or viruses. TLR8 can sense the RNA of *Methanosphaera stadtmanae*, the second most abundant archaeon in the human intestine, and induces strong innate and adaptive proinflammatory responses including the secretion of TNF-α, IL-1ß, as well as type I IFNs. The secretion of IL-1ß depends on caspase-1 activation within the NLRP3 inflammasome. The induction of this inflammasome requires prior *M. stadtmanae*-mediated TLR signalling, demonstrating a synergistic relationship between these two receptor families [23].

Besides inflammasome priming, crosstalk between TLRs and NLRs also enhances anti-bacterial immune responses by upregulating the expression of anti-microbial pro-inflammatory cytokines, such as TNF-α, IL-6, IL-12, and IL-8. Both IL-12 and TNF-α are strongly involved in activating and amplifying TH1 responses, thereby enhancing the killing potential of Cytotoxic T cells and natural killer cells, as well as activating macrophages to help clear infections [24]. The chemokine IL-8 plays a key role in the activation and recruitment of neutrophils to the site of an infection, where they remove pathogens via phagocytosis. IL-6 is an indicator of early bacterial infections, produced during the acute phase [25]. The combinational activation of the bacteria-recognizing receptors NOD1 and TLR4 in macrophages results in an enhanced antimicrobial cytokine expression. This synergy induces an increase in both primary response genes, such as *TNF*, as well as secondary response genes like *IL1B*, *IL6* or *IL12B*. Macrophage supernatant studies showed that the synergistic effect of TLR4-NOD1 crosstalk sets in relatively late. TNF-α and IL-6 levels show strong enhancement 24 hours post receptor activation due to late synergy in mRNA expression, which increases between one and four hours post agonist treatment [26]. The interactions between TLR2 and NOD2 especially are not fully understood as they can result in upregulation or downregulation of inflammatory responses [27]. Incubation of cells with *A. fumigatus* leads to an increase in expression of NOD2 in a TLR2-dependant manner as well as a synergistic effect of the two PRRs in triggering inflammatory responses in response to the fungal infection [27]. Meanwhile, other studies have shown a negative regulatory role of NOD2 on TLR2-induced inflammatory production. Pre-treatment of cells by the NOD2 ligand MDP leads to downregulation of TLR2 induced pro-inflammatory cytokines [28-30]. It therefore seems that TLR2 positively regulates NOD2-mediated inflammatory responses, while NOD2 has a negative regulatory effect on TLR2. However, further research is required to fully understand the mechanism behind this receptor crosstalk pairing.

Lastly, NLR and TLR crosstalk also enhances adaptive immune responses by stimulating B cell responses. Toll-like receptors, predominantly TLR1/2, TLR7 and TLR9, are able to induce B cell proliferation, which is enhanced by simultaneous stimulation of NOD1 or NOD2 receptors [31].

TLR-CLR

The effects of crosstalk between CLRs and TLRs on downstream immune responses are multifactorial and receptor dependent. While Toll-like receptors are generally thought to be activators of the immune system, by directly inducing transcriptional pathways, C-type lectin receptors have also the ability to modulate immune responses.

The interactions of Dectin-1 and Dectin-2 with TLR family members synergize during the production of pro-inflammatory cytokines. Potent activators on their own, Dectin-1 and Dectin-2 are pivotal CLRs in antifungal immunity, each with distinct signalling pathways and roles, as discussed before. Fungi such as *C. albicans* or *A. fumigatus* can activate Dectin-1, which in turn is able to induce protective antifungal immunity through SYK and RAF-1, resulting in Th1 and Th17 responses [32]. The crosstalk with TLR receptors is complex and involves both pathways.

SYK induces REL and RELB, NFκB subunits, to increase IL-23p19 and decrease IL-12p40. RAF-1 counteracts this RELB activation by sequestering it into an inactive state and concomitantly acetylates p65, modulating TLR2 and TLR4. This crosstalk results in heightened cytokine release, such as IL-6, IL-10 and IL-12p35 [32, 33].

Dectin-2 and TLR4 crosstalk synergistically boosts TNF-α and IL-10 production. Dectin-2 has specificity for α-linked mannose structures, which includes the mannosylated O-antigen found in Hafnia alvei. This leads to higher TNF-α and IL-10 production in human monocytes expressing both TLR4 and Dectin-2 in response to mannosylated-LPS compared to galactosylated-LPS [34].

These cytokines can play pivotal roles in both type 1 and type 3 immune responses, as CLRs recognize both bacterial and fungal structures; this suggests that this type of crosstalk might strengthen defences against extracellular as well as intracellular infections. Dectin-1 and Dectin-2 have been shown to modulate immune responses towards pathogens through crosstalk with TLRs, with alternating modulatory effects on downstream immune signalling. While the interactions between TLRs and Dectin-1 promote enhanced pro-inflammatory cytokine production during secondary infections, crosstalk between Dectin-2 and TLR4 induces a synergistic increase in the production of TNF-α and IL-10 [3, 5, 32, 34-36]. Dectin-2 recognizes α-linked mannose structures as ligands and contains an ITAM domain which activates Syk after activation, while TLR4 recognizes the conserved Lipid A region of LPS from gram negative bacteria [1, 5, 11, 16, 17, 34]. LPS also contains a core oligosaccharide and a variable O-antigen polysaccharide region. It has been shown that Dectin-2 is activated by the mannosylated O-antigen of the human pathogen *Hafnia alvei*. Human monocytes, which express both TLR4 as well as Dectin-2, produced higher levels of the pro-inflammatory cytokines TNF-α and IL-10 in response to mannosylated-LPS compared to galactosylated-LPS, indicating a synergistic crosstalk between these two receptors [34]. Another synergistic relationship between CLRs and TLRs was observed in human monocytes during studies of the commensal fungus *Saccharomyces cerevisiae*. *S. cerevisae* was able to induce the so called 'trained immunity', characterized by increased responsiveness to a secondary infection by the innate immune system, resulting in monocytes with enhanced killing capacities against fungal and bacterial pathogens. The effect is driven by chitin, which is recognized by Dectin-1 as well as DC-SIGN [36, 37]. Pre-exposure of monocytes to *S. cerevisae,* or chitin directly, resulted in enhanced IL-6 and TNF-α cytokine production upon secondary TLR engagement [36].

The specific carbohydrate composition of the ligand plays a pivotal role in determining which signalling pathways are activated. The carbohydrate moiety composition of DC-SIGN ligands shapes the signalosome composition and thereby tailors the immune response to different pathogens through TLR-induced cytokine production. DC-SIGN recognizes mannosylated and fucosylated glycans from pathogens which induce distinct signalling pathways. The C-type lectin receptor is constitutively associated with a scaffolding complex, consisting of a triad of LSP1, KSR1 and CNK, required to recruit the kinase Raf-1 and together form the signalosome. Binding of high mannose-expressing pathogens, such as HIV-1 or *Mycobacterium tuberculosis*, to DC-SIGN induces the recruitment of Raf-1 effector molecules, the activation of Raf-1 and the enhanced expression of IL-10, IL-12, and IL-6. The upregulation of these pro-inflammatory cytokines is mediated by the phosphorylation and acetylation of the NFKB subunit p65 to enhance the pathways transcriptional activity, therefore relying upon the TLR-mediated activation of NFKB, favouring immune activation. Meanwhile, fucose-expressing pathogens, like the gram-negative bacteria *Heliobacter pylori*, actively dissociates the Raf-1-CNK-KSR1 triad from the signalosome complex, leading to the downregulation of both IL-12 and IL-6 and the upregulation of the anti-inflammatory cytokine IL-10, favouring immune regulation over activation. Fucose-induced DC-SIGN signalling is thus able to inhibit TH1 and promote TH2 polarization due to the repressing nature of IL-10; however, this pattern is subtle and liable to be affected by other receptors and cytokines at play, affecting TH polarization [38].

In a similar manner, it has been shown that the mixed immune response towards the parasite *Schistosoma mansoni,* characterized by an early TH1-dominant response followed by a shift to an anti-inflammatory TH2 response at the point of egg-laying in the *Schistosoma* life cycle, is due to TLR4 and DC-SIGN crosstalk mediated by the parasitic glycolipids. The adult worms are recognized by both DC-SIGN and TLR4. This induces the production of IL-12 and TNF-α, as well as the skewing towards IFN-γ producing TH1 cells. Meanwhile, *S. mansoni* eggs, as well as the soluble antigens produced by them, contain fucosylated glycans which are recognized by DC-SIGN resulting in an anti-inflammatory TH2-polarized immune response [39]. Another example of crosstalk between DC-SIGN and TLR-mediated immune tolerance has been observed during the studies of another parasite, *Trichinella spiralis*. The cooperation of TLR2, TLR4 and DC-SIGN in response to *T. spiralis* larvae secretory products induces stable human tolerogenic DCs (tolDCs) and shifts the immune response towards TH2 cells as well as regulatory T cells (Tregs). Tregs are key regulators in maintaining immune tolerance by producing the cytokines IL-10 and TGF-ß which both suppress excessive immune responses [40]. The intracellular pathogen *Porphyromonas gingivalis* also uses DC-SIGNs' immunosuppressive nature to evade autophagy and therefore killing by myeloid dendritic cells. Its glycoprotein Mfa-1 engages DC-SIGN, which leads to internalization and routing into vesicles that escape autophagosomal routing, therefore evading lysosome fusion, resulting in pathogen persistence and survival within DCs. However, *P. gingivalis* also express a TLR2 ligand, the fimbriae FirmA. TLR2 signalling promotes autophagosome maturation and pathogen clearance. As the TLR2-mediated pathway dominates the DC-SIGN response when both are triggered, the intracellular fate of this bacterium depends on Mfa-1 and FirmA expression patterns as well as DC-SIGN-TLR2 crosstalk [41].

Inhibitory signalling crosstalk has also been shown between dendritic cell immunoreceptor and TLR8 or TLR9. Expressed on antigen-presenting cells, DCIR signals intracellularly via an Immunoreceptor Tyrosine-based Inhibition Motif (ITIM) containing domain to mediate inhibitory signals via SHP1 and SHP2. After ligand binding, the receptor is endocytosed and processed for antigen presentation to induce further innate and adaptive immune responses [5]. Triggering of DCIR selectively has been shown to inhibit TLR8-mediated IL-12 and TNF-α production on moDCs as well as TLR9-mediated IFN-α and TNF-α production by pDCs [42].

TLR-TLR

Besides crosstalk with members of other PRR families, Toll-like receptors have also been shown to modulate immune responses via intra-family signalling. Known interactions center around the endosomal-located receptors involved in recognizing nucleic acids, TLR9 and TLR8, and the bacteria sensing TLR5 or TLR4 receptors, located on the plasma membrane. Crosstalk between them mainly downregulates their pro-inflammatory effects and limits chemotaxis of other immune cells, potentially helping to mitigate an overactive immune reaction and chronic inflammation [43-45].

The dual engagement of TLR5 and TLR9 tailors the immune reaction by changing the balance between TH1 and TH2. TLR5 recognizes bacterial flagellin, the main protein component of flagella, and favours a TH2 response by inducing high levels of IL-10 and moderate IL-12 levels. TLR9 on the other hand, induces a more TH1-like reaction in response to prokaryotic DNA, characterized by high IFN-α levels. The combinational activation of both receptors increases TLR5-induced IL-10 levels and inhibits TLR9-mediated IFN-α production [43]. Another study has shown that the treatment of monocytes with the TLR8 agonist R484 in combination with the TLR4 ligand LPS results in a downregulation of the chemokines CCL1 and CCL2. Both of them are involved in activating and recruiting immune cells, such as T cells or monocytes, to sites of infection to help clear pathogens via phagocytosis, killing and the release of pro-inflammatory proteins [46]. *In vitro* experiments revealed a reduction of immune cell migration as well as phagocytosis, measured via ovalbumin uptake, after dual receptor stimulation [44].

Inhibitory immune response modulation after TLR8 activation, particularly when combined with TLR7, has been observed during viral infections [45]. Both TLR7 and TLR8 recognize single-stranded RNA (ssRNA) and initiate signaling through MyD88, leading to the induction of pro-inflammatory cytokines, chemokines, and type I interferons (IFNs). This signaling cascade results in the recruitment of immune cells, creating an inflammatory environment and establishing an antiviral state in both infected and neighbouring cells [8]. Specifically, the antiviral cytokine IL-27, upon stimulating myeloid cells, enhances the activation of NF-κB and boosts intracellular expression of cytokines and chemokines, including IL-6, TNF-α, IL-8, and CCL5, in response to TLR7 and TLR8 ligands.

However, when TLR7 is stimulated, it introduces a regulatory checkpoint that inhibits the IL-27/ TLR8-mediated pro-inflammatory response in monocytes and macrophages. This results in the downregulation of IL-6 and TNF-α, whereas the levels of IL-8 and CCL5 remain unaffected. This mechanism underscores a nuanced layer of immune regulation, where TLR7 activation can temper the inflammatory response initiated by TLR8 and IL-27, illustrating the intricate balancing act within the immune system to modulate its response to pathogens [45].

CLR crosstalk

CLR-RLR

As previously described, CLRs have been negatively implicated in inducing potent antiviral immune responses during crosstalk with TLRs. Their immunomodulatory abilities to modify the signalling of other PRRs might play an important role in tailoring immune responses to specific pathogens; however this same characteristic might be used by certain viruses to subvert the immune system. Crosstalk with RLRs, receptors specifically involved in binding to viral RNA, negatively impacts the type I IFN pathway [5].

Measle virus (MV) has developed various strategies to subvert type I IFN responses, as they effectively control the virus's replication. RIG-I interacts with MV ssRNA to trigger the MAVS-mediated signalling cascade resulting in the expression of IFN-ß, which signals via IFNAR to induce the transcription of ISGs and therefore implement an antiviral state in infected and neighbouring cells. RLR signalling is tightly regulated as an overactive inflammatory response and can have negative effects on overall health and survival. Therefore, RLR-mediated type I IFN production first requires dephosphorylation by Protein phosphatase 1 (PP1). MV can subvert RLR-mediated antiviral responses due to its interaction with DC-SIGN on DCs in the lung, resulting in enhanced infections and subsequent viral transmission. DC-SIGN signalling activates the kinase Raf-1, which induces the complex formation of the inhibitor I-1 with the regulatory subunit of PP1 GADD34-P1 holoenzyme, thereby inhibiting its dephosphorylation activities [47].

CLR-NLR

Not only TLRs have been shown to collaborate with NLRs, but also C-type lectin receptors, resulting in an upregulation of pro-inflammatory cytokines. So far, known crosstalk has been demonstrated between Dectin-1 or Mincle and NOD1 or NOD2 [48]. While NLRs are located within the cytoplasm, CLRs are transmembrane receptors. The two NOD-like receptors both recognize bacterial cell wall components, while Dectin-1 and Mincle recognize carbohydrate structures from not only bacteria but also fungi. It is plausible to hypothesize, that the synergistic relationship between these pattern recognition receptors strengthens defences against both extra- and intracellular pathogens. Dectin-1 and Mincle were found to synergistically interact with NOD1/2. The dual stimulation enhances both the key pro-inflammatory transcription factors NFKB and AP-1 (activated protein 1) as well as the production of IL-8 and IL-6. The synergy between these pattern recognition receptors depended on downstream signalling of the kinases RIP2 and Syk [48].

Discussion

Crosstalk between pattern recognition receptors is a complex but crucial aspect of immune responses. It allows the immune system to respond more precisely and efficiently to infections by tailoring its responses based on the

specific pathogen encountered. The adaptive ability of the immune system to adjust its response depending on the specific threat is fundamental to its effectiveness. As previously discussed, PRRs are omnipresent on and within the cell. Their location is directive for their purpose, as different PAMPs will be encountered at different cellular locations, creating a fingerprint unique to each pathogen. Sensors able to locate bacteria-derived structures, such as LPS, can be found on cellular surface, while RNA sensors are primarily located within endosomes or the cellular cytosol. Observed crosstalk between these sensors follows a comparable logic, sensing similar structures and reinforcing responses against specific pathogens following tandem triggering of receptors.

Fungi are multi-cellular and a widely diverse group of organisms. In the case of humans, the vast majority of them are opportunistic pathogens, only leading to disease in immunocompromised hosts. However, invasive species, such as aspergillus or candida, can lead to serious infections resulting in more than 1.5 million annual deaths [49]. Being multicellular, therefore existing outside the cell, surface receptors are primarily used to sense them. Dectin-1, a cardinal receptor in antifungal immunity, can autonomously signal through its intrinsic ITAM domain to initiate an immune response. However, it can also engage with various receptors, encompassing TLR2, TLR4, NOD2 and MINCLE, to modulate reactions to fungal pathogens. At the same time, TLR2 and NOD2 also work synergistically to both strengthen and dampen pro-inflammatory reactions. In the case of a fungal infection, the pathogens would first encounter and activate TLR2 on the plasma membrane of a cell and thus stimulate the Myd88-dependant NFKB pathway, resulting in the production of pro-inflammatory cytokines, while NOD2, due to its intracellular location, senses fungal ligands after the proteins are taken up by the cell. TLR2 signalling increases NOD2 expression and the two receptors synergistically enhance the cells' inflammatory response. During an infection with *A. fumigatus*, this is precisely what happens [27]. However, it may also be harmful to the infected patient as this fungus infects the eye. To preserve vision, inflammatory responses and immune reactions inside the eye are limited, an effect known as ocular immune privileged [50]. The phenomenon of bacteria-sensing NLRs enhancing pro-inflammatory effects of fungal recognizing PRRs has also been demonstrated between the transmembrane CLRs Dectin-1, and to a lesser extent Mincle, and NOD1/-2, illustrating how modular immune reactions are. Most fungi, however, are non-pathogenic and even a beneficial component of the human biome. We separate the two branches of immunity in inborn innate signalling and trained adaptive immunity, but studies have shown that fungal species, such as *S. cerevisiae*, can induce so-called trained immunity in innate immune cells strengthening defences against later infections. Such a process requires crosstalk between Dectin-1 or DC-SIGN and TLR4. Previous engagement of the CLR by chitin, a cell-wall component of *S. cerevisiae*, leads to enhanced production of pro-inflammatory cytokines after subsequent TLR engagement, resulting in a better defence against various infectious pathogens. Furthermore, stronger cytokine production modulation was observed in chitin-rich strains, enriched in clinical isolates of patients suffering from Crohn's disease [36]. This may be due to a stronger response to the non-self-polysaccharide, and further research on this topic is needed elucidate the exact underlying mechanism.

Parasites are a form of pathogens that require the host to survive for prolonged periods of time and therefore need to mask themselves from immunological recognition from the immune system. Most parasites have both intracellular and extracellular states, requiring different responses. Crosstalk between DC-SIGN and TLRs could be important here as it allows for modulation of the immune response to suit both states. The parasite *S. mansoni*, a trematode able to cause deadly schistosomiasis in humans, exploits this during its multiple life stages. After infecting their mammalian host, adult worms exist in either the large or small intestine before laying eggs which are then released through faeces or urine and, after hatching in fresh water, infect their other host, snails [51]. Before egg-laying, *S. mansoni* induces a TH1 skewed inflammatory phenotype induced via DC-SIGN-mediated TLR4 activation, which

quickly changes towards an immunosuppressive TH2 environment after egg-laying. This transition is likely due to fucosylated glycans present on the soluble antigens produced by the helminths eggs, which results in the upregulation of IL-10 and inhibition of pro-inflammatory IL-6 and IL-12 [39]. As there is no detailed structural data available for the glycan composition of adult worms, we can only hypothesize about the origin of the initial TH1 response. They may contain high-mannose carbohydrates, therefore inducing the previously mentioned Raf-1-mediated acetylation and enhancement of TLR4-induced NFKB signalling. Or it could be attributed to the fact that infecting human hosts requires the passage of the skin barrier and the hereby inflicted damage results in an early inflammatory response mounted by present immune cells.

According to a study by the Global Research on Antimicrobial Resistance (GRAM) Project, bacterial infections represented the second leading cause of death in 2019, and were at the time linked to one in eight deaths worldwide [52]. During the course of evolution, the human immune system has developed various host defence mechanisms to control bacterial growth and fight infections, including the innate Toll-like receptors and NOD-like receptors. Both families are crucial in detecting early microbial infections and mounting a rapid pro-inflammatory immune response. Recently, studies investigating the crosstalk between PRRs have shown that TLRs and NLRs synergistically enhance their pro-inflammatory cytokine production, characterized by an enhanced NFKB response [23, 26, 53]. The main Toll-like receptors involved are TLR2 and TLR4, both present on the plasma membrane of cells and therefore able to recognize intracellular as well as extracellular bacteria. NOD-like receptors, on the other hand, are located within the cytosol and either signal through the induction of the inflammasome or, in the case of NOD1 or NOD2, via the NFKB pathway. Crosstalk between them also leads to an enhanced B cell response, crucial in mounting longer lasting effective immune responses against evading bacteria [31]. Active B cells are involved directly in the clearance of infections via the production of specific pathogen-binding opsonizing antibodies, and they can also differentiate into long-lived memory cells, thereby protecting against subsequent infections [54]. Crosstalk between NOD2 and TLR2, however is not as straightforward as it seems. As mentioned previously, early engagement of TLR2, for example by fungal or bacterial ligands, results in the upregulation of NOD2 and synergistic enhancement of the pro-inflammatory NFKB pathway. Initial intracellular NOD2 activation on the other hand, negatively affects TLR2-mediated responses while upregulating the expression of TH2 inducing IL-10 [28, 29]. The resulting effect could be either used by intracellular bacteria to circumvent host defences or it could also be a way of limiting excess inflammation. TLR-NLR crosstalk is not the only receptor interaction during bacterial infections. DC-SIGNs ability to modulate and thereby shape immune pathways through TLRs has been demonstrated in the context of bacterial infections. Mannose-high bacteria, such as the mycobacterium *M. tuberculosis*, induce a pro-inflammatory environment via DC-SIGN-dependent modulation of TLR signalling and enhanced NFKB -mediated transcription [38]. The respiratory pathogen is the causative agent of tuberculosis, attributed to have caused more human deaths over the course of history than any other infectious disease. Infection, and subsequent recognition by innate PRRs, leads to the production of pro-inflammatory cytokines and shifts the immune system towards a type 1 response. Although usually associated with pathogen clearance and infection control, *M. tuberculosis* uses excess inflammation to promote pathogenesis [55]. As mentioned previously, DC-SIGNs' immunomodulatory effects depend on the carbohydrate moiety of its ligands. *Heliobacter pylori*, a gram-negative bacterium able to colonize the human stomach, can cause prolonged infections and circumvents immune responses for years without resulting in acute disease [56]. Its long-time persistence might be achieved by exploiting DC-SIGN's ability to shape downstream signalling. The CLR recognizes the fucosylated carbohydrates on *H. pylori,* resulting in the induction of an immunosuppressive environment. Another example of a bacterium using DC-SIGN's ability to mediate an anti-inflammatory environment is the opportunistic

pathogen *P. gingivalis*. Usually cleared via TLR2-mediated autophagy, the invasive bacterium escapes autophagic destruction by targeting DC-SIGN, thereby achieving survival through PRR crosstalk exploitation [41].

Viruses are unlike any other microorganisms covered in the scope of this review. As obligate intracellular pathogens, they rely on their host for replication and dissemination. This introduces a complex game of cat and mouse between the virus and the human immune system, constantly outmanoeuvring and rapidly evolving to escape the other. In response, the host has evolved an array of defence mechanisms targeted at recognizing and eradicating the invading pathogen. Front of the line are the transmembrane toll-like receptors TLR3, TLR7, TLR8 and TLR9 as well as the cytosolic RLRs Rig-I and MDA5. Equipped to recognize viral nucleic acids, they induce robust anti-viral immune responses via the pro-inflammatory NFKB pathway and type I IFNs, which induce an anti-viral state in both infected as well as surrounding cells. Toll-like receptor and RIG-I like receptor crosstalk resulting in an enhanced antiviral immune response is of particular interest in the context of HIV-1 infections. Although the disease is, as of today, still uncurable, antiretroviral therapy (ART) has been shown to significantly improve the survival chances of people living with HIV. Successful ART regimes are associated with heightened IFN activity, as well as CD8+ T cell activation and IL-12p70 production [57]. As mentioned earlier, the dual stimulation of dendritic cells with TLR8 and RLR agonists leads to an enhanced production of both these immune responses compared to only TLR stimulation. Additionally, it also lead to the enhanced protein secretion of the ISG IL-27 as well as IFN-ß [20]. The cytokine IL-27 has been implicated to induce potent antiviral innate and adaptive immune responses against numerous viruses, including HIV-1. IL-27 has also been shown to hinder viral infections through the inhibition of replication in CD4+ T cells as well as the induction of further ISGs such as *MX1* or *OAS2*, both prolific in further restricting viral replication [58, 59]. HIV-1 signals both TLRs and also engages CLRs. DC-SIGN recognizes the viral envelope glycoprotein gp120, thereby inducing the formation of the previously mentioned Raf-1 signalosome and subsequent acetylation and phosphorylation of the NFKB subunit p65 [38]. It has been previously shown that full length HIV-1 transcript production, and therefore productive DC infection requires pTEF-b-mediated phosphorylation of the RNA Polymerase II at Ser2. This transcription and elongation factor is recruited to the viral genome by phosphorylated p65. Thus, HIV-1 uses the receptor crosstalk between DC-SIGN and TLR8 to enable replication and transmission in DCs [38, 60]. Measle virus (MV) also has developed mechanisms to subvert anti-viral immune responses by hijacking DC-SIGN crosstalk. The virus-activated CLR recruits Raf-1, but contrasting with its enhancement of anti-bacterial signalling via the NFKB pathway, in this instance it is rather detrimental to the human host. Here, the kinase induces complex formation of PP1, the phosphatase required to activate RIG-I signalling, and its inhibitor I-1. Therefore, MV uses the hosts' own immune signalling pathways to impede RLR activation, and consequently downstream type I IFN signalling, by purposefully activating DC-SIGN [47]. MV is not the only high mannose expressing virus. HIV-1 also engages DC-SIGN in a mannose-dependant manner and thereby results in the recruitment and activation of Raf-1. This inhibitory crosstalk mechanism might not be specific to MV, but rather utilized by a plethora of viral pathogens. However, as this is only speculation, further research is needed to make more substantial statements. Interestingly, dengue virus (DENV) also engages DC-SIGN via its high-mannosylated E-glycan but does not inhibit RLR activation. Contrasting to MV, which immediately engages DC-SIGN upon infection, DENV is sensed 18 hours later [13, 61]. These timing differences might be the reason for such contrasting signalling outcomes. Although pro-inflammatory immune responses aid in the destruction and clearance of viral infections, more does not always equal better. Too much of a good thing can also be detrimental to human health, as shown by the deadly effect the so-called "cytokine storms" can have. Previously referred to as influenza-like syndrome, it describes an excess production of cytokines that likely exaggerated the lethality of

the 1919 influenza pandemic [62]. Most of the PRR crosstalk mentioned in this segment has been focused on either enhanced inflammatory signalling or virus-induced augmentation of pro-inflammatory processes to subvert the immune system and persistently infect their host. Concurrent activation of the viral RNA sensing receptors TLR7 and TLR8 results in the downregulation of pro-inflammatory cytokines [45]. With TLR7 mainly expressed on pDCs and TLR8 more widely expressed on myeloid cells, this might be a way of limiting an over-active immune response during a viral infection, thereby preventing a potential cytokine storm. Inhibitory effects have also been shown for the co-stimulation of TLR7 and TLR9. As mentioned previously, viral-TLR activation on pDCs enhances RLR expression, likely resulting in a more robust anti-viral immune response. However, triggering of TLR7 and TLR9 simultaneously lead to a lower expression of RIG-I than by either toll-like receptor on its own [21].

Conclusion

The intricate and dynamic interplay between pattern recognition receptors within the human immune system unveils a fascinating realm of immunological responses. These receptors are the first line of defense, deciphering the molecular signatures of invading pathogens through the recognition of distinct, evolutionary conserved PAMPs. The diversity of existing PRR families, including TLRs, CLRs, NLRs, RLRs and ALRs, highlights the immune systems' sophistication in tailoring responses to different infectious agents, a prowess heightened through various forms of interplay.

By delving into the realms of crosstalk, we have illuminated a new dimension of immune regulation. Crosstalk between PRR families not only underscores the complexity of immune signaling but also offers a mechanism through which the immune system fine-tunes its reactions to diverse threats. In the vast arena of infectious diseases, the interplay between pathogens and the human immune system unravels as a mesmerizing world of adaptation, response, and survival. The intricacies we have explored across viruses, bacteria, parasites, and fungi underscore the complexity of these interactions, highlighting the strategies that both sides employ to secure their existence. The orchestrated cooperation and communication among PRRs results in pathogen-specific responses that are finely tuned to address the unique challenges posed by various pathogens. From viruses that manipulate receptor families via the tolerogenic nature of DC-SIGN immunomodulation, to bacteria that orchestrate crosstalk to balance inflammation and defense, the dance of immune recognition and response is a dynamic spectacle. Parasites, adept at exploiting dual immune responses to ensure survival at various life stages, and fungi, with their multifaceted immune interactions, reveal the multitude of strategies within the pathogen world.

As our understanding of these immunological interaction's advances, new avenues for therapeutic interventions and vaccine development may arise. Targeting specific points of crosstalk or enhancing synergistic pathways could potentially lead to innovative strategies to bolster immune responses against infectious agents or even dysregulated immune conditions. From understanding the mechanisms underlying immune evasion to designing targeted interventions that exploit receptor crosstalk, the field holds promise for revolutionizing our approach to infectious diseases, ultimately leading to improved treatments, better disease management, and a deeper appreciation of the intricate symphony that safeguards our health.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts to declare.

REFERENCES

1. Li, D. and Wu, M. 2021, Signal Transduction and Targeted Therapy, 6, 291.
2. Annunziato, F., Romagnani, C., Romagnani, S. 2015, Journal of Allergy and Clinical Immunology, 135(3), 626-635.
3. Takeuchi, O. and Akira, S. 2010, Cell, 140(6), 805-820.
4. Fernandes-Alnemri, T., Yu, J.-W., Datta, P., Wu, J. and Alnemri, E. S. 2009, Nature, 458(7237), 509-513.
5. Bermejo-Jambrina, M., Eder, J., Helgers, L. C., Hertoghs, N., Nijmeijer, B. M., Stunnenberg, M. and Geijtenbeek, T. B. H. 2018, Frontiers in Immunology, 9, 590.

6. Brown, G. D., Willment, J. A. and Whitehead, L. 2018, Nature Reviews Immunology, 18(6), 374-389.
7. Kramer, M., Schulte, B. M., Eleveld-Trancikova, D., van Hout-Kuijer, M., Toonen, L. W. J., Tel, J., de Vries, I. J. M., van Kuppeveld, F. J. M., Jansen, B. J. H. and Adema, G. J. 2010, J. Innate Immun., 2(4), 360-370.
8. Lukhele, S., Boukhaled, G. M. and Brooks, D. G. 2019, Semin. Immunol., 43, 101277.
9. Powell, M. D., Read, K. A., Sreekumar, B. K., Jones, D. M. and Oestreich, K. J. 2019, Scientific Reports, 9(1), 13991.
10. Panzer, M., Sitte, S., Wirth, S., Drexler, I., Sparwasser, T. and Voehringer D. 2012, J. Immunol., 188(2), 615-623.
11. Geijtenbeek, T. B. and Gringhuis, S. I., 2016, Nat. Rev. Immunol., 16(7), 433-448.
12. Takeda, K. and Akira, S. 2015, Curr. Protoc. Immunol., 109, 14.2.1-.2.0.
13. Sprokholt, J. K., Kaptein, T. M., Van Hamme, J. L., Overmars, R. J., Gringhuis, S. I. and Geijtenbeek, T. B. H. 2017, PLoS Pathogens, 13(11), e1006738.
14. Crotty, S. 2011, Annual Review of Immunology, 29(1), 621-663.
15. Kortekaas Krohn, I., Aerts, J. L., Breckpot, K., Goyvaerts, C., Knol, E., Van Wijk, F. and Gutermuth, J. 2022, Allergy, 77(3), 827-842.
16. Wagener, M., Hoving, J. C., Ndlovu, H. and Marakalala, M. J. 2018, Front. Immunol., 9, 225.
17. Saijo, S. and Iwakura Y. 2011, Int. Immunol., 23(8), 467-472.
18. Sameer, A. S. and Nissar, S. 2021, Biomed. Res. Int., 2021, 1157023.
19. Liu, T., Zhang, L., Joo, D. and Sun, S.-C. 2017, Signal Transduction and Targeted Therapy, 2(1), 1-9.
20. Vlaming, K. E., van Wijnbergen, K., Kaptein, T. M., Nijhuis, M., Kootstra, N. J., de Bree, G. J. and Geijtenbeek, T. B. 2023, Front. Med. (Lausanne), 10, 1146457.
21. Szabo, A., Magyarics, Z., Pazmandi, K., Gopcsa, L., Rajnavolgyi, E. and Bacsi, A. 2014, Immunology & Cell Biology, 92(8), 671-678.
22. Kadowaki, N., Ho, S., Antonenko, S., de Waal Malefyt, R., Kastelein, R. A., Bazan, F. and Liu, Y.-J. 2001, The Journal of Experimental Medicine, 194(6), 863-870.
23. Vierbuchen, T., Bang, C., Rosigkeit, H., Schmitz, R. A. and Heine, H. 2017, Frontiers in Immunology, 8, 1535.
24. Trinchieri, G. 2003, Nature Reviews Immunology, 3(2), 133-146.
25. Kany, S., Vollrath, J. T. and Relja, B. 2019, International Journal of Molecular Sciences, 20(23), 6008.
26. Budikhina, A. S., Murugina, N. E., Maximchik, P. V., Dagil, Y. A., Nikolaeva, A. M., Balyasova, L. S., Murugin, V. V., Selezneva, E. M., Pashchenkova, Y. G., Chkadua, G. Z., Pinegin, B. V. and Pashenkov, M. V. 2021, Journal of Immunology (Baltimore, Md: 1950), 206(9), 2206-2220.
27. Wu, J., Zhang, Y., Xin, Z. and Wu, X. 2015, Molecular Immunology, 64(2), 235-243.
28. Watanabe, T., Kitani, A., Murray, P. J. and Strober, W. 2004, Nature Immunology, 5(8), 800-808.
29. Netea, M. G., Kullberg, B. J., de Jong, D. J., Franke, B., Sprong, T., Naber, T. H. J., Drenth, J. P. H. and van der Meer, J. W. M. 2004, Eur. J. Immunol., 34, 2052-2059.
30. Watanabe, T., Asano, N., Murray, P. J., Ozato, K., Tailor, P., Fuss, I. J., Kitani, A. and Strober, W. 2008, The Journal of Clinical Investigation, 118(2), 545-559.
31. Petterson, T., Jendholm, J., Månsson, A., Bjartell, A., Riesbeck, K. and Cardell, L.-O. 2011, Journal of Leukocyte Biology, 89(2), 177-187.
32. Geijtenbeek, T. B. and Gringhuis, S. I. 2009, Nat. Rev. Immunol., 9(7), 465-479.
33. Gringhuis, S. I., den Dunnen, J., Litjens, M., van der Vlist, M., Wevers, B., Bruijns, S. C. M. and Geijtenbeek, T. B. H. 2009, Nature Immunology, 10(2), 203-213.
34. Wittmann, A., Lamprinaki, D., Bowles, K. M., Katzenellenbogen, E., Knirel, Y. A., Whitfield, C., Nishimura, T., Matsumoto, N., Yamamoto, K., Iwakura, Y., Saijo, S. and Kawasaki, N. 2016, J. Biol. Chem., 291(34), 17629-17638.

35. Gringhuis, S. I., den Dunnen, J., Litjens, M., van der Vlist, M., Wevers, B., Bruijns, S. C. and Geijtenbeek, T. B. 2009, Nat. Immunol., 10(2), 203-213.
36. Rizzetto, L., Ifrim, D. C., Moretti, S., Tocci, N., Cheng, S.-C., Quintin, J., Renga, G., Oikonomou, V., De Filippo, C., Weil, T., Blok, B. A., Lenucci, M. S., Santos, M. A. S., Romani, L., Netea, M. G. and Cavalieri, D. 2016, The Journal of Biological Chemistry, 291(15), 7961-7972.
37. Goyal, S., Castrillón-Betancur, J. C., Klaile, E. and Slevogt, H. 2018, Frontiers in Immunology, 9, 1261.
38. Gringhuis, S. I., den Dunnen, J., Litjens, M., van der Vlist, M. and Geijtenbeek, T. B. 2009, Nat. Immunol.,10(10), 1081-1088.
39. van Stijn, C. M. W., Meyer, S., van den Broek, M., Bruijns, S. C. M., van Kooyk, Y., Geyer, R., van Die, I., 2010, Molecular Immunology, 47(7-8), 1544-1552.
40. Cvetkovic, J., Ilic, N., Gruden-Movsesijan, A., Tomic, S., Mitic, N., Pinelli, E., Sofronic-Milosavljevic, L., 2020, Scientific Reports, 10(1), 20283.
41. El-Awady, A. R., Miles, B., Scisci, E., Kurago, Z. B., Palani, C. D., Arce, R. M., Waller, J. L., Genco, C. A., Slocum, C., Manning, M., Schoenlein, P. V. and Cutler, C. W. 2015, PLoS Pathogens, 10(2), e1004647.
42. Meyer-Wentrup, F., Cambi, A., Joosten, B., Looman, M. W., de Vries, I. J. M., Figdor, C. G. and Adema, G. J. 2009, Journal of Leukocyte Biology, 85(3), 518-525.
43. Merlo, A., Calcaterra, C., Mènard, S. and Balsari, A. 2007, Journal of Leukocyte Biology, 82(3), 509-518.
44. Sabbatucci, M., Purificato, C., Fantuzzi, L. and Gessani, S. 2011, Immunobiology, 216(10), 1135-1142.
45. Odoardi, N., Kourko, O., Petes, C., Basta, S. and Gee, K. 2021, J. Innate Immun., 13(6), 345-358.
46. Palomino, D. C. T. and Marti, L. C. 2015, Einstein (Sao Paulo), 13(3), 469-473.
47. Mesman, A. W., Zijlstra-Willems, E. M., Kaptein, T. M., de Swart, R. L., Davis, M. E., Ludlow, M., Duprex, W. P., Gack, M. U., Gringhuis, S. I. and Geijtenbeek, T. B. H. 2014, Cell Host Microbe, 16(1), 31-42.
48. Tukhvatulin, A. I., Dzharullaeva, A. S., Erokhova, A. S., Scheblyakov, D. V., Naroditsky, B. S., Gintsburg, A. L. and Logunov, D. Y. 2020, J. Inflamm. Res., 13, 357-368.
49. Bongomin, F., Gago, S., Oladele, R. O. and Denning, D. W. 2017, Journal of Fungi, 3(4), 57.
50. Zhou, R. and Caspi, R. R. 2010, F1000 Biol. Rep., 2, 3.
51. Nelwan, M. L. 2019, Curr. Ther. Res. Clin. Exp., 91, 5-9.
52. Murray, C. J. L., Ikuta, K. S., Sharara, F., Swetschinski, L., Aguilar, G. R., Gray, A., Han, C., Bisignano, C., Rao, P., Wool, E., Johnson, S. C., Browne, A. J., Chipeta, M. G., Fell, F., Hackett, S., Haines-Woodhouse, G., Hamadani, B. H. K., Kumaran, E. A. P., McManigal, B., Achalapong, S., Agarwal, R., Akech, S., Albertson, S., Amuasi, J., Andrews, J., Aravkin, A., Ashley, E., Babin, F.-X., Bailey, F., Baker, S., Basnyat, B., Bekker, A., Bender, R., Berkley, J. A., Bethou, A., Bielicki, J., Boonkasidecha, S., Bukosia, J., Carvalheiro, C., Castañeda-Orjuela, C., Chansamouth, V., Chaurasia, S., Chiurchiù, S., Chowdhury, F., Donatien, R. C., Cook, A. J., Cooper, B., Cressey, T. R., Criollo-Mora, E., Cunningham, M., Darboe, S., Day, N. P. J., Luca, M. D., Dokova, K., Dramowski, A., Dunachie, S. J., Bich, T. D., Eckmanns, T., Eibach, D., Emami, A., Feasey, N., Fisher-Pearson, N., Forrest, K., Garcia, C., Garrett, D., Gastmeier, P., Giref, A. Z., Greer, R. C., Gupta, V., Haller, S., Haselbeck, A., Hay, S. I., Holm, M., Hopkins, S., Hsia, Y., Iregbu, K. C., Jacobs, J., Jarovsky, D., Javanmardi, F., Jenney, A. W. J., Khorana, M., Khusuwan, S., Kissoon, N., Kobeissi, E., Kostyanev, T., Krapp, F., Krumkamp, R., Kumar, A., Kyu, H. H., Lim, C., Lim, K., Limmathurotsakul, D., Loftus, M. J., Lunn, M., Ma, J., Manoharan, A., Marks, F., May, J., Mayxay, M., Mturi, N., Munera-Huertas, T., Musicha, P., Musila, L. A., Mussi-Pinhata, M. M., Naidu, R. N., Nakamura, T., Nanavati, R., Nangia, S., Newton, P., Ngoun, C., Novotney, A., Nwakanma, D., Obiero, C. W., Ochoa, T. J., Olivas-Martinez, A., Olliaro, P., Ooko, E.,

Ortiz-Brizuela, E., Ounchanum, P., Pak, G. D., Paredes, J. L., Peleg, A. Y., Perrone, C., Phe, T., Phommasone, K., Plakkal, N., Ponce-de-Leon, A., Raad, M., Ramdin, T., Rattanavong, S., Riddell, A., Roberts, T., Robotham, J. V., Roca, A., Rosenthal, V. D., Rudd, K. E., Russell, N., Sader, H. S., Saengchan, W., Schnall, J., Scott, J. A. G., Seekaew, S., Sharland, M., Shivamallappa, M., Sifuentes-Osornio, J., Simpson, A. J., Steenkeste, N., Stewardson, A. J., Stoeva, T., Tasak, N., Thaiprakong, A., Thwaites, G., Tigoi, C., Turner, C., Turner, P., Doorn, H. R. V., Velaphi, S., Vongpradith, A., Vongsouvath, M., Vu, H., Walsh, T., Walson, J. L., Waner, S., Wangrangsimakul, T., Wannapinij, P., Wozniak, T., Sharma, T. E. M. W. Y., Yu, K. C., Zheng, P., Sartorius, B., Lopez, A. D., Stergachis, A., Moore, C., Dolecek, C. and Naghavi, M. 2022, The Lancet, 399(10325), 629-655.

53. Triantafilou, K., Ward, C. J. K., Czubala, M., Ferris, R. G., Koppe, E., Haffner, C., Piguet, V., Patel, V. K., Amrine-Madsen, H., Modis, L. K., Masters, S. L. and Triantafilou, M. 2021, PLoS Pathogens, 17(4), e1009417.
54. Nothelfer, K., Sansonetti, P. J. and Phalipon, A. 2015, Nature Reviews Microbiology, 13(3), 173-184.
55. Ravesloot-Chávez, M. M., van Dis, E. and Stanley, S. A. 2021, Annual Review of Immunology, 39(1), 611-637.
56. Robinson, E. K., Jagannatha, P., Covarrubias, S., Cattle, M., Smaliy, V., Safavi, R., Shapleigh, B., Abu-Shumays, R., Jain, M., Cloonan, S. M., Akeson, M., Brooks, A. N. and Carpenter, S. 2021, eLife, 10, e69431.
57. Byrnes, A. A., Harris, D. M., Atabani, S. F., Sabundayo, B. P., Langan, S. J., Margolick, J. B. and Karp, C. L. 2008, Journal of Leukocyte Biology, 84(6), 1447-1453.
58. Chen, Q., Swaminathan, S., Yang, D., Dai, L., Sui, H., Yang, J., Hornung, R. L., Wang, Y., Huang, D. W., Hu, X., Lempicki, R. A. and Imamichi, T. 2013, PLoS One, 8(3), e59194.
59. Amsden, H., Kourko, O., Roth, M. and Gee, K. 2022, Frontiers in Immunology, 13, 902853.
60. Gringhuis, S. I., van der Vlist, M., van den Berg, L. M., den Dunnen, J., Litjens, M. and Geijtenbeek, T. B. 2010, Nat. Immunol., 11(5), 419-426.
61. Pokidysheva, E., Zhang, Y., Battisti, A. J., Bator-Kelly, C. M., Chipman, P. R., Xiao, C., Gregorio, G. G., Hendrickson, W. A., Kuhn, R. J. and Rossmann, M. G. 2006, Cell, 124(3), 485-493.
62. Fajgenbaum, D. C. and June, C. H. 2020, N. Engl. J. Med., 383(23), 2255-2273.