Review
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Innate Immunity

The innate immune system is an evolutionarily conserved system acting as a first-line of defense against exogenous and endogenous threats to the host, such as pathogenic infection, tissue damage or cancer. It includes diverse cells such as macrophages, dendritic cells (DCs), neutrophils, natural killer (NK) cells and innate lymphoid cells (ILCs). The destruction and clearance of invading pathogens, and the resolution of other threats to the host, requires complex coordination of multiple innate immune pathways.

Importantly, the innate immune system not only precedes the highly specialized adaptive immune system chronologically, but also enables the long-lasting immunological memory characteristic of adaptive immunity. This is done partly through the work of innate antigen-presenting cells (APCs), which interact with adaptive immune components such as B cells and T cells.

In order to detect and gauge threats, innate immunity employs an arsenal of specialized receptors. Chief among these are the numerous pattern-recognition receptors (PRRs), which are found at varying levels in immune and non-immune cells alike. The cognate ligands of PRRs comprise pathogen-associated molecular patterns (PAMPs), which are found exclusively on or in viruses, bacteria, fungi and other microbes, and danger-associated molecular patterns (DAMPs), which are released by damaged or dying host cells.

The recognition of PAMPs and DAMPs by PRRs generates an acute inflammatory response. This involves secretion of cytokines and chemokines, production of antimicrobial peptides, triggering of apoptotic or pyroptotic cell death, induction of autophagyand recruitment of phagocytic cells.

The main PRR families are the Toll-Like receptors (TLRs), the NOD-Like receptors (NLRs), the RIG-I-Like receptors (RLRs), cytosolic DNA sensors (CDSs), the C-type lectin receptors (CLRs) and inflammasomes. Many of these processes induce, or are regulated by, autophagy.

TOLL-LIKE RECEPTORS (TLRS)

TLRs were the first PRRs to be identified and remain the best characterized. Signaling by TLRs initiates key inflammatory responses and also shapes adaptive immunity.

All TLRs (10 in humans and 12 in mice) are type I transmembrane proteins characterized by an extracellular leucine-rich domain and a cytoplasmic tail that contains a conserved Toll/IL-1 receptor (TIR) domain. TLRs recognize various PAMPs, including lipid-based bacterial cell wall components such as lipopolysaccharide (LPS) and lipopeptides; microbial protein components such as flagellin; and viral or microbial nucleic acids such as single-stranded or double-stranded RNA, and CpG DNA. TLR ligands also include DAMPs liberated from damaged or dying host cells, including nucleic acids and proteins.

TLRs initiate shared and distinct signaling pathways by recruiting different combinations of four TIR-domain-containing adaptor molecules: MyD88, TIRAP (Mal), TRIF and/or TRAM. These signaling pathways activate the transcription factors NF-kB and AP-1, leading to production of inflammatory cytokines and chemokines. They also activate interferon regulatory factors (IRFs) such as IRF3 and IRF7, which lead to production of type I interferons (IFNs) and upregulation of interferon-stimulated genes (ISGs).

TLRs can be organized by cellular localization: TLRs 1, 2, 4, 5 and 6 are cell-surface receptors, whereas TLRs 3, 7, 8, 9 and 13 are endosomal receptors. This localization mirrors the chronology of PAMP contact with host cells: the surface TLRs detect surface components from incoming microbes, whereas the endosomal TLRs detect nucleic acids released by pathogens into the host cell cytoplasm. Intriguingly, upon activation, TLR2 and TLR4 move from the surface into endosomes.

An exceptional case among TLRs is TLR10, a surface TLR that provides anti-inflammatory, rather than pro-inflammatory, responses. It does this by negatively regulating other TLR pathways.

TLR	PRINCIPAL LOCALIZATION	ADAPTOR PROTEIN	PRINCIPAL LIGANDS
TLR1/TLR2 (dimer)	Surface	MyD88,TIRAP and TRAM	Bacterial cell-wall components
TLR1/TLR6 (dimer)			
TLR4			LPS
TLR5		MyD88	Flagellin
TRL10			Unknow
TLR3	Endosome	TRIF	dsRNA
TLR7			ssRNA
TLR8			
TLR9			CpG DNA
TLR13			23S rRNA

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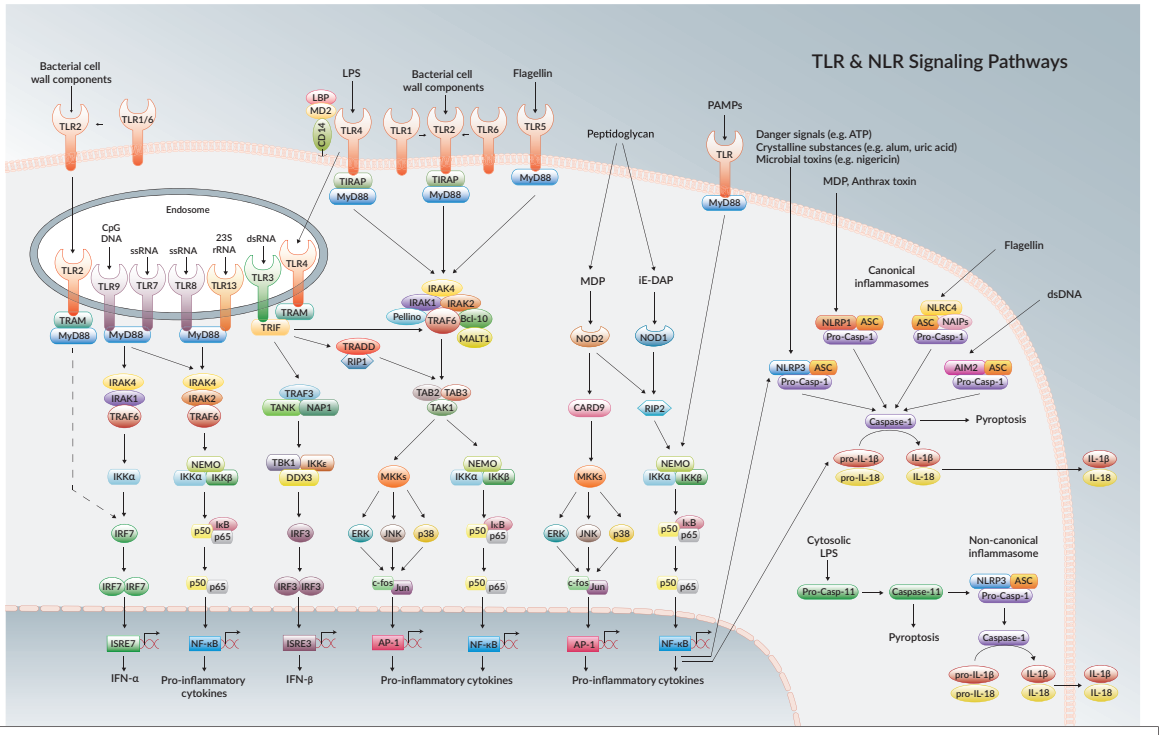
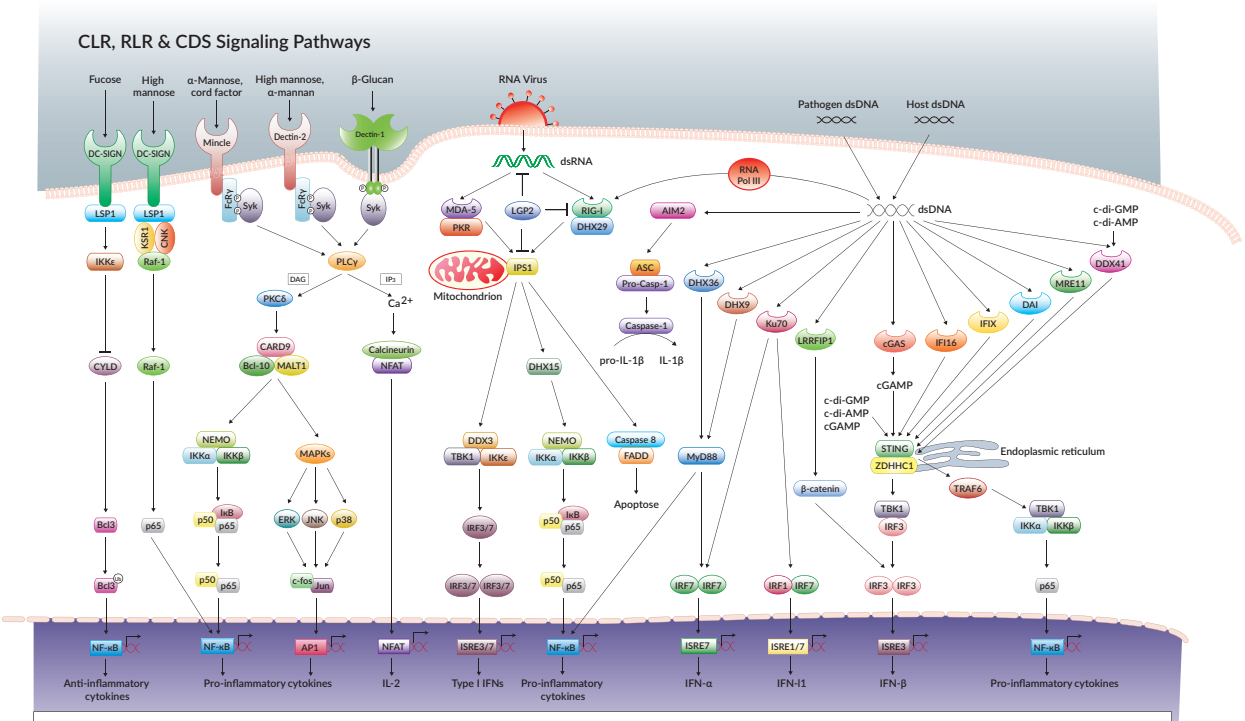
TLR-NLR PATHWAYS



CLR-RLR-CDS PATHWAYS



NOD-LIKE RECEPTORS (NLRS)

NLRs constitute a family of intracellular pattern recognition receptors (PRRs) that contains more than 20 members in mammals. Although the ligands and functions of many of these receptors are not known, their primary role is to recognize cytoplasmic pathogen-associated molecular patterns (PAMPs) and/or DAMPs, inducing immune responses.

NLRs are characterized by a tripartite-domain organization with a conserved nucleotide binding oligomerization domain (NACHT/NOD), leucine-rich repeats (LRRs) involved in microbial sensing and one of four N-terminal effector domains.

NLRs are classified in to four sub-families, which are named according to the N-terminal effector domain: NLRA (Acidic transactivation domain), NLRB (Baculovirus inhibitor repeat domain), NLRC (Caspase recruitment domain) and NLRP (Pyrin domain). There is also a sub-family known as NLRX, whose members do not contain an effector domain analogous to those mentioned above.

PRODUCT	DESCRIPTION	UNIT SIZE
NLRA	Acidic transactivation (A)	CIITA
NLRB	Baculovirus inhibitor repeat (BIR)	NAIP
NLRC	CARD (Caspase recruitment domain)	NOD1/2, NLRC 3/4
NLRP	Pyrin	NLRP1, NLRP3

RIG-I-LIKE RECEPTORS (RLRS) AND CYTOSOLIC DNA SENSORS (CDS)

RLRs are a family of cytoplasmic RNA helicases that are critical for host anti-viral responses. The RLRs include the RNA sensors RIG-I and MDA-5, which, upon activation, drive transcription factors that control the transcription of genes encoding interferons and other cytokines.

RIG-I and MDA-5 sense double-stranded RNA, a replication intermediate for RNA viruses. Upon binding of specific types of dsRNA, each of these sensors activates the mitochondrial-bound adaptor protein MAVS, which leads to production of type I interferons. The cytosolic protein LGP2, which contains a RNA-binding domain, acts as a negative feedback regulator of both RIG-I and MDA-5.

Recent advances in the recognition of nucleic acids have identified several CDSs, which detect double-stranded DNA (dsDNA) of pathogen, self or tumor origin, leading to the induction of interferons and/or the processing of pro-inflammatory cytokines. The best-known CDSs are cGAS, AIM2 and IFI16.

Upon detection of dsDNA and DNA/RNA hybrids, cGAS produces the cyclic dinucleotide 2'3'-cGAMP, which is the endogenous ligand of the adaptor protein STING. Once activated, STING induces type I IFNs and pro-inflammatory cytokines through the IRF3 and NF-kB pathways, respectively.

AIM2 is unique among CDSs in that it forms an inflammasome (see "Inflammasomes" section, below), which, like other inflammasomes, contains the accessory proteins ASC and Pro-Casp-1.

Unlike other CDSs, IFI16 shuttles between the cytoplasm and the nucleus.

Other noteworthy CDSs include DAI, DDX41, IFIX and LRRFIP1.

C-TYPE LECTIN RECEPTORS (CLRS)

CLRs, also called the C-type lectin receptors encompass a large family of phagocytic receptor proteins that bind to carbohydrate moieties of various pathogens. The importance of CLRs in shaping the adaptive immune response is becoming increasingly apparent.

The lectin activity of CLRs is mediated by conserved carbohydrate-recognition domains (CRDs). These receptors are involved in fungal recognition and in modulation of innate immune mechanisms for pathogen clearance or for antigen presentation to T lymphocytes.

The principal human CLRs are the surface receptors DC-SIGN, Dectin-1, Dectin-2 and Mincle, and the soluble receptor mannose-binding lectin (MBL).

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INFLAMMASOMES

Inflammasomes are caspase-1-activating protein complexes assembled by certain NLRs. Caspase-1 is activated by inflammasomes through autoproteolytic maturation, leading to processing and secretion of the pro-inflammatory cytokines IL-1b and IL-18.

Four inflammasomes have been identified to date. These include three inflammasomes defined by their constituent NLR protein: the NLRP1 (or NALP1b) inflammasome, the NLRC4 (or IPAF) inflammasome and the NLRP3 (or NALP3) inflammasome. There is also an inflammasome built around the DNA sensor AIM2, a member of the IFI16 family.

Inflammasomes fulfill a central role in innate immunity by detecting and responding to specific DAMPS and PAMPS, see table.

PRODUCT	DESCRIPTION
AIM2	dsDNA
NLRC4	Flagellin
NLRP1	MPD, anthrax, toxin
NLRP3	ATP, uric, acid, alum, nigericin, oxidized mtDNA, bacterial RNA

AUTOPHAGY AND INNATE IMMUNITY

Autophagy is a mechanism that cells use to sequester, remove and recycle waste. In autophagy, macromolecules in the cytosol are engulfed in a newly formed phagocytic body and subsequently digested in a lysosome that releases the resultant metabolites back into the cytosol.

Autophagy, often referred to as macroautophagy, serves to recycle large chunks of cytoplasm as a source of nutrients, which enables cells to maintain macromolecular synthesis and energy homeostasis during starvation and other stressful conditions.

Moreover, cells use autophagy to regulate the activity of specific signaling proteins, to prevent accumulation of damaged organelles or long-lived, aggregate-prone proteins, and to remove incoming threats such as intracellular pathogens. Thus, autophagy has emerged as a critical component of innate immunity.

The interplay between autophagy, PRRs and inflammation is highly complex and encompasses several regulatory mechanisms that ensure balanced innate immune responses.

PRR & INNATE IMMUNITY - INVIVOGEN.COM

PRRS FAMILIES	
Toll-Like Receptors - TLRs	Best characterized receptors involved in early innate immune response to invading pathogens
NOD-Like Receptors - NLRs	Intracellular pattern recognition receptors that recognize cytoplasmic pathogen-associated molecular patterns
RIG-I-Like Receptors - RLRs	Cytoplasmic RNA helicases that are critical for host antiviral responses
C-type Lectin Receptors - CLRs	Receptors involved in fungal recognition and modulation of the innate immune response
Cytosolic DNA Sensors & STING	Receptors to diverse molecules of microbial origin (PAMPs), or released from damaged or dying cells (DAMPs)
Inflammasome	Large intracellular multiprotein complexes that play a central role in innate immunity

TOOLS FOR PRRS STUDY	
PRR & PAMP Detection	Rapid, convenient and reliable detection of pattern recognition receptors and pathogen-associated molecular patterns

For more information, please visit : www.invivogen.com

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