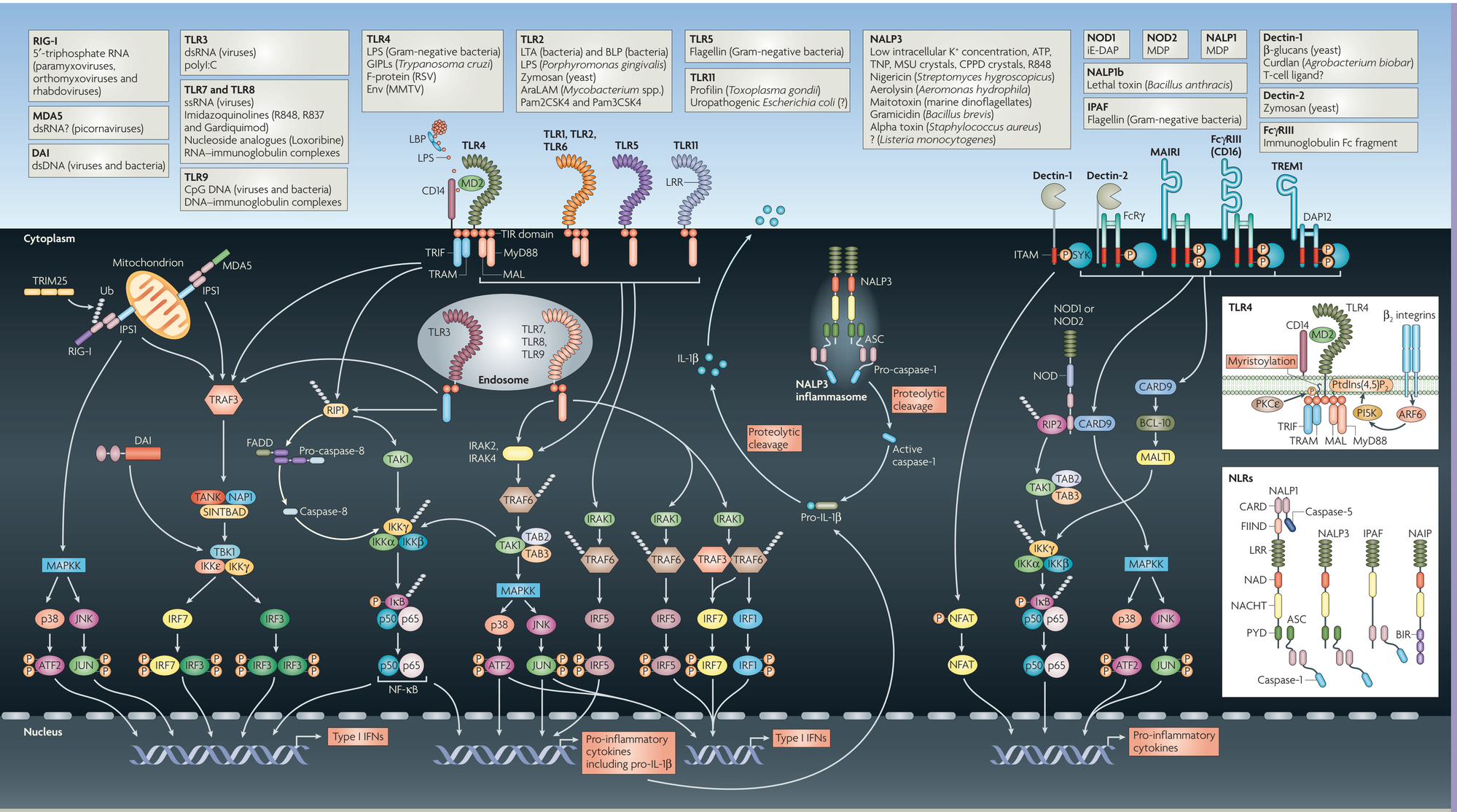
nature REVIEWS
IMMUNOLOGY

Innate immunity: sensing and signalling

Eicke Latz and Katherine A. Fitzgerald

In response to microbial products, distinct families of pattern-recognition receptors initiate intracellular signalling events that lead to complex immune responses designed to eliminate invading pathogens. These include receptors that recognize conserved molecular patterns derived from bacteria, viruses, protozoa and fungi (the TLRs), receptors that sense fungi (the CLRs), and receptors in the cytosol that sense viral nucleic acids (the RLRs and DAI) or bacterial products (the NLRs). The NLRs also sense endogenous products released by dying cells. These receptors, with the exception of the NALP proteins of the NLR family, recruit adaptor molecules, which in turn create multi-protein platforms to which additional kinases, transcription factors and possibly other molecules are recruited. These events ultimately lead to the expression of genes that encode key factors that regulate the immune response. Some of these factors require additional processing, which is carried out by members of the NLR family. Given the rapidity at which such interactions have been described, here, we attempt to summarize our current understanding of these events in an effort to provide a framework for future studies.



Innate immune receptors

RLRs and DAI. The cytoplasm contains proteins that sense DNA or RNA derived from invading viruses. RNA is recognized by the RLR family of proteins, which consists of at least two members, RIG-I and MDA5. LGP2, a related family member (not depicted), may act as a negative regulator of these receptors by sequestering RNA. RIG-I recognizes 5′-triphosphate RNAs, whereas MDA5 is thought to sense dsRNA. The E3-ubiquitin ligase TRIM25 induces ubiquitylation of RIG-I, which is essential for RIG-I function.

The RLRs contain CARD domains that recruit IPS1 (also known as CARDIF, MAVS or VISA), which is an adaptor molecule that is tethered to the mitochondria. IPS1 associates with the E3-ubiquitin ligase TRAF3 and activates the IKK-related kinases TBK1 and IKKε, which phosphorylate and activate IRF3 and IRF7, the key regulators of type I IFN gene transcription in most cell types. IKKγ, TANK, NAP1 and SINTBAD form a complex with these kinases. IPS1 also induces NF-κB activation through FADD and caspase-8 and/or caspase-10, and activates the MAPKs p38 and JNK. Cells also contain DNA sensors in the cytoplasm. One such protein DAI (also known as ZBP1) binds dsDNA and activates IRF3 through TBK1.

TLRs. The TLRs are type I transmembrane receptors found on the plasma membrane or in endosomal compartments. Upon ligand binding, they recruit adaptor molecules through TIR–TIR interactions. Signalling by TLR5, TLR7, TLR8, TLR9 and TLR11 relies solely on MyD88, whereas TLR1, TLR2 and TLR6 also recruit MAL (also known as TIRAP). TLR3 signals independently of MyD88 and MAL through TRIF (also known as TICAM1). TLR4 uses MAL and TRAM to recruit MyD88 and TRIF. MAL is targeted to the plasma membrane through a PtdIns(4,5)P_2-binding domain, whereas TRAM is anchored though myristoylation at its N-terminus. PKCε regulates TRAM function (see TLR4 inset). Signalling through these adaptors leads to either NF-κB or IRF3 activation.

IRAK2 and IRAK4, activated by MyD88, are crucial for NF-κB activation. They enable the recruitment and activation of TRAF6, which activates TAK1 through K63-linked polyubiquitylation. TAK1 in turn activates the IKK complex, which phosphorylates IκB and targets it for ubiquitylation and subsequent degradation by the proteasome. NF-κB is then released, translocates to the nucleus and regulates the expression of its target genes, which include pro-inflammatory cytokines. TAK1 also controls activation of the MAPK pathway. TRIF activates NF-κB through RIP1, and activates IRF3 through TRAF3, which associates with TBK1 and IKKε leading to type I IFN gene transcription.

TLR7, TLR8 and TLR9 activate NF-κB as well as IRF1, IRF5 and IRF7 through MyD88. In plasmacytoid DCs IRF7 is a crucial factor for IFN production, whereas IRF1 and IRF5 control the IFN response in conventional DCs. IKKα is thought to have a role in IRF7 activation in plasmacytoid DCs. IRF5 is activated downstream of most, if not all, the TLRs through MyD88 and IRAK1 and in this case regulates pro-inflammatory cytokine production.

NLRs. This large receptor family of more than 20 proteins in humans contains NOD1, NOD2, NALPs, IPAF and NAIP. The NOD proteins recognize different moieties of bacterial PGN and activate NF-κB through RIP2 (also known as RICK) and MAPK through CARD9. NALPs and IPAF form multimolecular complexes termed 'inflammasomes' following their activation. NALP3 recruits the adaptor molecule ASC that in turn recruits pro-caspase-1, which is activated by autocatalytic cleavage. Cleaved caspase-1 catalyses proteolytic processing of pro-IL-1β (and pro-IL-18, not shown) into the active cytokines that are then released.

CLRs. Activation of members of the CLR protein family can induce the production of pro-inflammatory cytokines, promote phagocytosis and elicit a respiratory burst. SYK interacts with phosphotyrosines within ITAMs in dectin-1 or in associated signalling chains to initiate a CARD9-dependent activation of the BCL-10–MALT1 complex. This complex can subsequently initiate NF-κB signalling through the activation of the IKK complex. TREM proteins also associate with adaptor proteins that contain ITAMs to initiate CARD9 signalling. The CLRs trigger MAPK activation and in the case of dectin-1 activate NFAT in myeloid cells to regulate pro-inflammatory cytokine production.

Abbreviations
AraLAM, non-mannose-capped lipoarrabinomannan; ASC, apoptosis-associated speck-like protein containing a CARD; ATF2, activating transcription factor 2; BCL-10, B-cell lymphoma 10; BIR, baculoviral IAP repeat; CARD, caspase-recruitment domain; CLR, C-type lectin receptor; CPPD, calcium pyrophosphate dihydrate; DAI, DNA-dependent activator of IRFs; DC, dendritic cell; dsDNA, double-stranded DNA; FADD, FAS-associated via death domain; FcγR, Fc receptor for IgG; FcR, Fc receptor; FIIND, function-to-find domain; GIPL, glycoinositolphospholipid; IκB, inhibitor of NF-κB; iE-DAP, γ-D-glutamyl-*meso*-diaminopimelic acid; IFN, interferon; IKK, IκB kinase; IL, interleukin; IPAF, ICE-protease activating factor; IPS1, *IFNB*-promoter stimulator 1; IRAK, IL-1 receptor-associated kinase; IRF, IFN-regulatory factor; ITAM, immunoreceptor tyrosine-based activation motif; JNK, JUN N-terminal kinase; LBP, LPS-binding protein; LPS, lipopolysaccharide; LRR, leucine-rich repeat; LTA, lipoteichoic acid; MAL, MyD88-adaptor-like protein; MALT1, mucosa-associated-lymphoid-tissue lymphoma-translocation gene 1; MAPK, mitogen-activated protein kinase; MAPKK, MAPK kinase; MDA5, melanoma differentiation-associated gene 5; MDP, muramyl dipeptide; MMTV, mouse mammary tumour virus; MSU, monosodium urate; MyD88, myeloid differentiation primary-response gene 88; NACHT, domain present in NAIP, CIITA, HET-E and TP1; NAIP, neuronal apoptosis inhibitory protein; NALP, NACHT-, LRR- and PYD-domain-containing protein; NAP1; NAK-associated protein 1; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor-κB; NLR, nucleotide-binding domain LRR-containing family; NOD, nucleotide-binding oligomerization domain; Pam2CSK4, Pam2Cys-Ser-Lys-Lys-Lys-Lys; PGN, peptidoglycan; PI5K, phosphoinositide 5-kinase; PKC, protein kinase C; polyI:C, polyinosinic–polycytidylic acid; PtdIns(4,5)P_2, phosphatidylinositol-4,5-bisphosphate; PYD, pyrin domain; RIG-I, retinoic-acid-inducible gene I; RIP, receptor-interacting protein; RLH, RIG-I-like RNA helicases; RLR, RIG-I-like receptor; RSV, respiratory syncytial virus; SINTBAD, similar to NAP1 TBK1 adaptor; ssRNA, single-stranded RNA; SYK, spleen tyrosine kinase; TAB, TAK1-binding protein 1; TAK, TGFβ-activated kinase; TANK, TRAF-family-member-associated NF-κB activator; TBK, TANK-binding kinase; TIR, Toll/IL-1 receptor; TLR, Toll-like receptor; TNP, trinitrophenyl; TRAF, TNF-receptor-associated factor; TRAM, TRIF-related adaptor molecule; TREM, triggering receptor expressed on myeloid cells; TRIF, TIR-domain-containing adaptor protein inducing IFNβ; TRIM25, tripartite-motif-containing 25; Ub, ubiquitin.

Affiliations
Eicke Latz and Katherine Fitzgerald are at the Division of Infectious Diseases & Immunology, University of Massachusetts Medical School, 364 Plantation Street, Worcester, Massachusetts 01605, USA.
e-mails: eicke.latz@umassmed.edu; kate.fitzgerald@umassmed.edu

Edited by Olive Leavy; copy edited by Marta Tufet;
designed by Simon Bradbrook.

http://www.nature.com/nri/poster/innate