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Toll-like receptor signalling

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Toll-like receptors (TLRs) recognize microbial products during infection and initiate signalling pathways that culminate in the increased expression of immune and inflammatory genes. TLRs that recognize nucleic acids signal from endosomes, whereas cell-surface TLRs sense lipids and proteins. Two major signalling pathways have been detailed. The core pathway activated by most TLRs leads to activation of the transcription factor nuclear factor-κB (NF-κB) and the mitogen-activated protein (MAP) kinases p38 and JNK. These signalling cascades increase the expression of many pro-inflammatory genes. The second pathway is activated by TLR3 and TLR4 and leads to activation of both NF-κB and another transcription factor interferon regulatory factor 3 (IRF3), allowing for an additional set of genes to be induced, including antiviral genes such as interferon-β (*IFN-β*). In this way, TLRs can tailor the innate response to pathogens.

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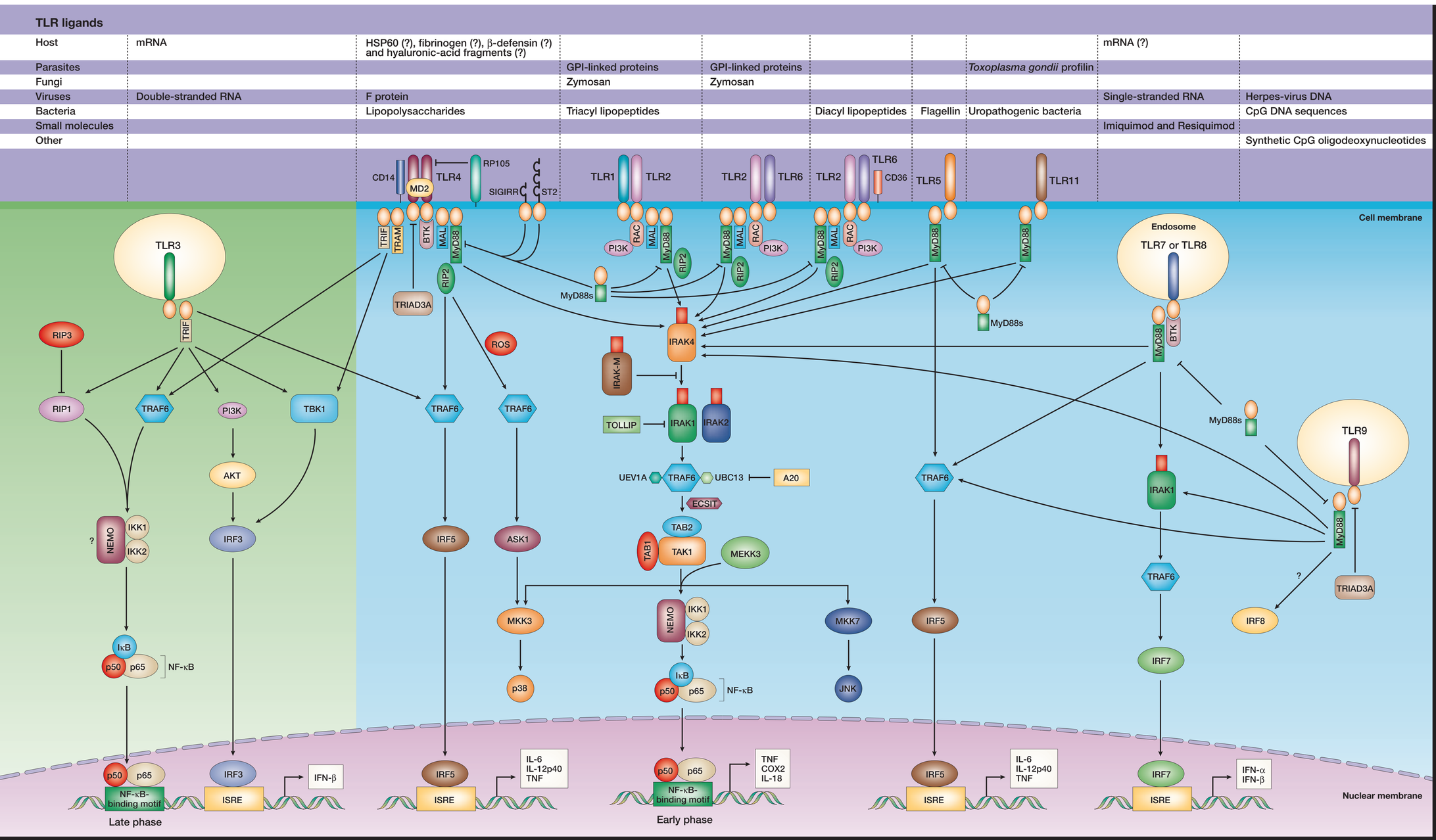
TLR ligands									
Host	mRNA	HSP60 (?), fibrinogen (?), β-defensin (?) and hyaluronic-acid fragments (?)						mRNA (?)	
Parasites			GPI-linked proteins	GPI-linked proteins			*Toxoplasma gondii* profilin		
Fungi			Zymosan	Zymosan					
Viruses	Double-stranded RNA	F protein						Single-stranded RNA	Herpes-virus DNA
Bacteria		Lipopolysaccharides	Triacyl lipopeptides		Diacyl lipopeptides	Flagellin	Uropathogenic bacteria		CpG DNA sequences
Small molecules								Imiquimod and Resiquimod	
Other									Synthetic CpG oligodeoxynucleotides



Adaptor molecules specify TLR-signalling effects

Central to TLR signalling are the receptor-proximal adaptors, MyD88, MAL (also known as TIRAP), TRIF (also known as TICAM1) and TRAM (also known as TICAM2 or TIRP). A fifth adaptor, SARM, has been described, but at least in the case of nematodes, it does not seem to be recruited by TLRs. MyD88 is widely used by TLRs, although MyD88 signalling initiated by TLR2 and TLR4, but not other TLRs, also involves the adaptor MAL. MyD88 recruits IRAKs, ultimately leading to the activation of MAP3 kinases, two of which have been identified, MEKK3 and TAK1, which activate NF-κB and the MAP kinases p38 and JNK. Activation of TAK1 by IRAKs requires TRAF6, as well as the ubiquitylation of both TRAF6 and TAK1. BTK and PI3K also participate in TLR signalling, although their precise role has yet to be defined. The kinase RIP2 has been shown to be essential for signalling by certain TLRs, in particular TLR2 and TLR4. By contrast, RIP1 is involved only in TLR3 signalling. The adaptor molecule TRIF engages the protein kinase TBK1, leading to IRF3 activation downstream of TLR3 and TLR4 signalling, and can also interact directly with TRAF6. Interestingly, TRIF-mediated signalling downstream of TLR4 also requires the adaptor TRAM, whereas TLR3 signalling through TRIF does not. Another IRF, IRF8, has recently been shown to be activated by TLR9 through MyD88. The process of NF-κB activation downstream of TLR4 ligation has added complexity, with the early response involving MyD88 and MAL, and the later response involving TRAM and TRIF. Although much has been learnt about the importance of adaptors in defining unique innate immune responses, the full consequences of specific adaptor usage by TLRs have yet to be resolved.

Negative regulation of TLR signalling

TLR signalling is negatively regulated by various proteins. The cell-surface receptors ST2 (also known as T1) and SIGIRR function as inhibitory receptors, sequestering proteins from signalling complexes and preventing TLR2, TLR4 and TLR9 signalling. IRAK-M, TOLLIP and a splice variant of MyD88, known as MyD88s, probably interfere with the recruitment and activation of IRAK4 and IRAK1. Recently, TRIAD3A, a RING-finger E3 ligase, has been shown to promote ubiquitylation of TLR4 and TLR9, targeting these TLRs for degradation and thereby negatively regulating the intensity and duration of TLR signalling. The balance between activation and inhibition is likely to be the key determinant of signal strength.

For the purpose of clarity, the pathways depicted here are limited to those that are well understood and known to have an important role in TLR signalling. For a more comprehensive overview of the TLR-signalling pathways, please see the review article by Shizuo Akira and Kiyoshi Takeda in the July issue of *Nature Reviews Immunology*. This article, as well as the poster, is freely available online for 3 months as part of a focus on TLR signalling: www.nature.com/nri/focus.tlr. In addition, the online version of the poster will be updated every 3 months to include new data that become available.

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ASK1, apoptosis signal-regulating kinase 1; BTK, Bruton's tyrosine kinase; COX2, cyclo-oxygenase 2; ECSIT, evolutionarily conserved signalling intermediate in Toll pathways; GPI, glycosylphosphatidylinositol; HSP60, heat-shock protein 60; IFN, interferon; IκB, inhibitor of NF-κB; IKK, inhibitor of NF-κB kinase; IRAK, IL-1-receptor-associated kinase; IL, interleukin; IRF, IFN regulatory factor; JNK, JUN N-terminal kinase; MAL, MyD88 adaptor-like protein; MAP, mitogen-activated protein; MEKK3, MAPK/ERKK kinase 3; MKK, MAP kinase kinase; MyD88, myeloid differentiation primary-response gene 88; NEMO, NF-κB essential modulator; NF-κB, nuclear factor-κB; PI3K, phosphatidylinositol 3-kinase; RIP, receptor-interacting protein; ROS, reactive oxygen species; SARM, sterile α and armadillo motifs; SIGIRR, single immunoglobulin IL-1-receptor-related molecule; TAB, TAK1-binding protein; TAK1, TGF-β-activated protein kinase 1; TANK, TRAF-family-member-associated NF-κB activator; TBK1, TANK-binding kinase 1; TGF-β, transforming growth factor-β; TICAM, TIR-domain-containing adaptor molecule; TIR, Toll/IL-1 receptor; TIRAP, TIR-domain-containing adaptor protein; TLR, Toll-like receptor; TNF, tumour-necrosis factor; TOLLIP, Toll-interacting protein; TRAF, TNF-receptor-associated factor; TRAM, TRIF-related adaptor molecule; TRIF, TIR-domain-containing adaptor protein inducing IFN-β; UBC13, ubiquitin-conjugating enzyme 13; UEV1A, ubiquitin-conjugating enzyme E2 variant 1.