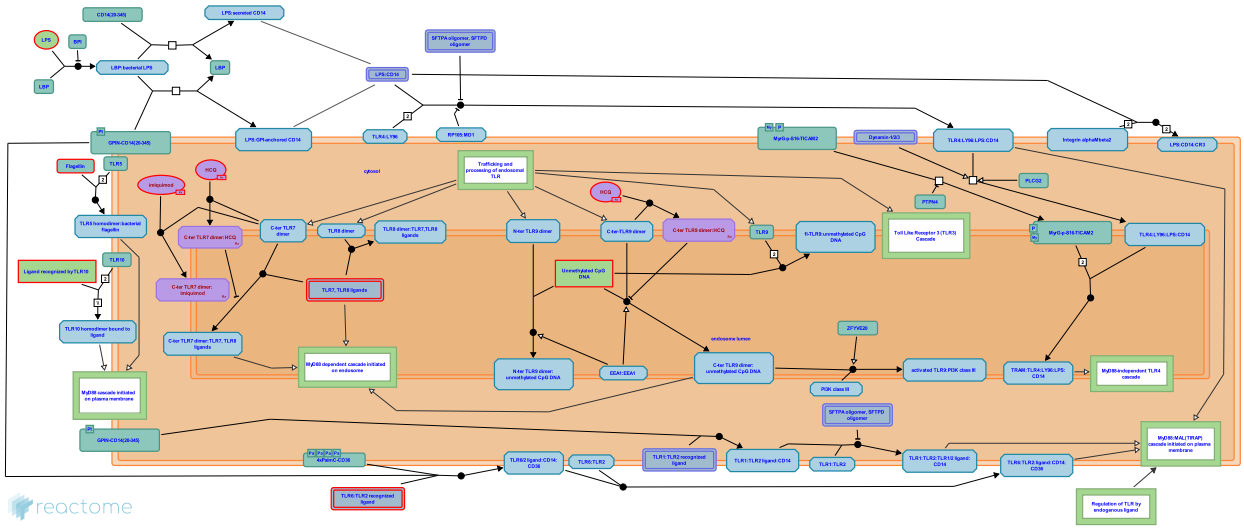
Toll-like Receptor Cascades



D'Eustachio, P., Gale M, Jr., Gay, NJ., Gillespie, ME., Granucci, F., Leifer, CA., Luo, F., Rose II, WA., Shamovsky, V., Zanoni, I., Zwaginga, JJ., de Bono, B.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

28/04/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

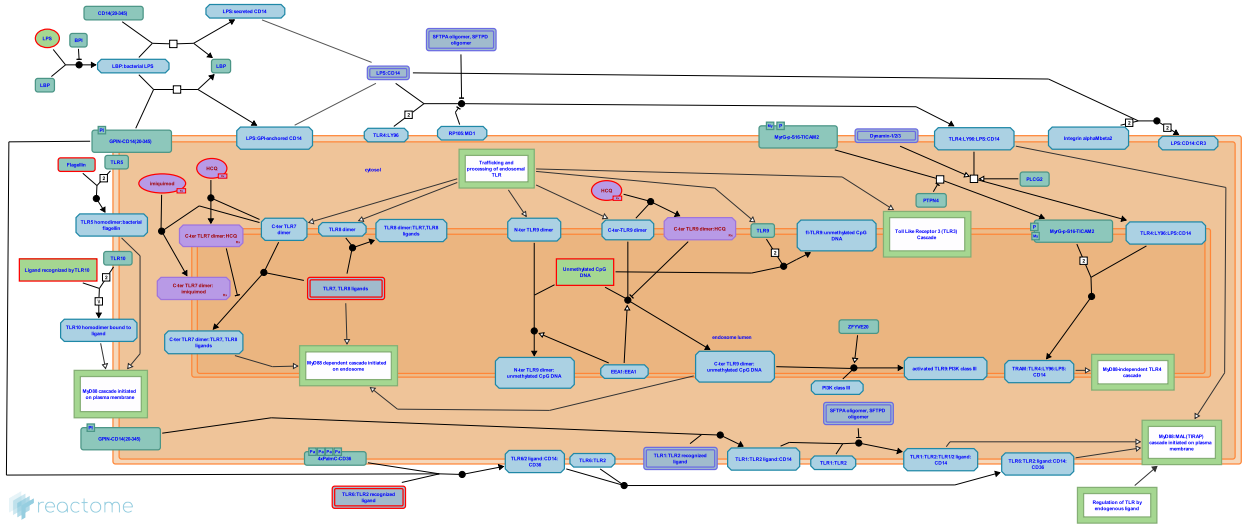
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 10 pathways (see Table of Contents)

Toll-like Receptor Cascades ↗

Stable identifier: R-HSA-168898



In human, ten members of the Toll-like receptor (TLR) family (TLR1-TLR10) have been identified (TLR11 has been found in mouse, but not in human). All TLRs have a similar Toll/IL-1 receptor (TIR) domain in their cytoplasmic region and an Ig-like domain in the extracellular region, where each is enriched with a varying number of leucine-rich repeats (LRRs). Each TLR can recognize specific microbial pathogen components. The binding pathogenic component to TLR initializes signaling pathways that lead to induction of Interferon alpha/beta and inflammatory cytokines. There are two main signaling pathways. The first is a MyD88-dependent pathway that is common to all TLRs, except TLR3; the second is a TRIF(TICAM1)-dependent pathway that is peculiar to TLR3 and TLR4. TLR4-mediated signaling pathway via TRIF requires adapter molecule TRAM (TRIF-related adapter molecule or TICAM2). TRAM is thought to bridge between the activated TLR4 complex and TRIF.(Takeda & Akira 2004; Akira 2003; Takeda & Akira 2005; Kawai 2005; Heine & Ulmer 2005). This pathway is organized as trafficking and processing of TLR, various TLR cascades (TLR10,TLR3,TLR5,TLR7/8,TLR9,TLR4,TLR2) and their regulation.

Literature references

Takeda, K., Akira, S. (2004). TIR domains, which are conserved among all TLRs. Recent accumulating. *Semin Immunol, 16*, 3-9. ↗

Ulmer, AJ., Heine, H. (2005). Recognition of bacterial products by toll-like receptors. *Chem Immunol Allergy, 86*, 99-119. ↗

Takeda, K., Akira, S. (2005). TIRAP/Mal, TRIF and TRAM. Differential utilization of these TIR. *Int Immunol, 17*, 1-14. ↗

Kawai, T. (2005). Pathogen recognition with Toll-like receptors. *Curr Opin Immunol, 17*, 338-44. ↗

Akira, S. (2003). Toll-like receptor signaling. *J Biol Chem, 278*, 38105-8. ↗

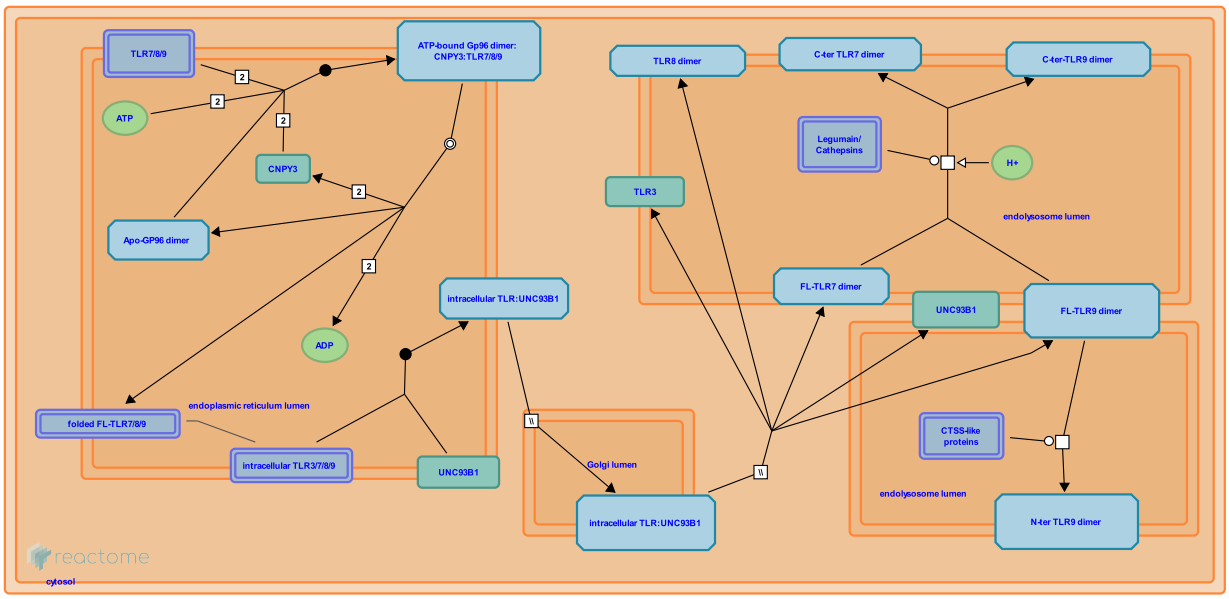
Editions

2006-10-31	Reviewed	D'Eustachio, P., Gay, NJ., Gale M, Jr.
2024-03-06	Authored	Gillespie, ME., de Bono, B., Gay, NJ., Luo, F.

Trafficking and processing of endosomal TLR ↗

Location: Toll-like Receptor Cascades

Stable identifier: R-HSA-1679131



Mammalian TLR3, TLR7, TLR8, TLR9 are endosomal receptors that sense nucleic acids that have been released from endocytosed/phagocytosed bacteria, viruses or parasites. These TLRs have a ligand-recognition domain that faces the lumen of the endosome (which is topologically equivalent to the outside of the cell), a transmembrane domain, and a signaling domain that faces the cytosol.

Under normal conditions, self nucleic acids are not recognized by TLRs due to multiple levels of regulation including receptor compartmentalization, trafficking and proteolytic processing (Barton GM et al 2006, Ewald SE et al 2008). At steady state TLR3, TLR7, TLR8, TLR9 reside primarily in the endoplasmic reticulum (ER), however, their activation by specific ligands only occurs within acidified endolysosomal compartments (Hacker H et al 1998, Funami K et al 2004, Gibbard RJ et al 2006). Several chaperon proteins associate with TLRs in the ER to provide efficient translocation to endolysosome. Upon reaching endolysosomal compartments the ectodomains of TLR7 and TLR9 are proteolytically cleaved by cysteine endoproteases. Both full-length and cleaved C-terminus of TLR9 bind CpG-oligodeoxynucleotides, however it has been proposed that only the processed receptor is functional.

Although similar cleavage of TLR3 has been reported by Ewald et al 2011, other studies demonstrated that the N-terminal region of TLR3 ectodomain was implicated in ligand binding, thus TLR3 may function as a full-length receptor (Liu L et al 2008, Tokisue T et al 2008).

There are no data on TLR8 processing, although the cell biology of TLR8 is probably similar to TLR9 and TLR7 (Gibbard RJ et al 2006, Wei T et al 2009).

Literature references

Barton, GM., Kagan, JC., Medzhitov, R. (2006). Intracellular localization of Toll-like receptor 9 prevents recognition of self DNA but facilitates access to viral DNA. *Nat Immunol, 7*, 49-56. ↗

Morley, PJ., Gibbard, RJ., Gay, NJ. (2006). Conserved features in the extracellular domain of human toll-like receptor 8 are essential for pH-dependent signaling. *J Biol Chem, 281*, 27503-11. ↗

Stark, RW., Jamitzky, F., Gong, J., Heckl, WM., Rössle, SC., Wei, T. (2009). Homology modeling of human Toll-like receptors TLR7, 8, and 9 ligand-binding domains. *Protein Sci, 18*, 1684-91. ↗

Miethke, T., Sparwasser, T., Hacker, H., Heeg, K., Schmid, R., Lipford, GB. et al. (1998). CpG-DNA-specific activation of antigen-presenting cells requires stress kinase activity and is preceded by non-specific endocytosis and endosomal maturation. *EMBO J, 17*, 6230-40. ↗

de Bouteiller, O., Caux, C., Hubac, S., Merck, E., Trinchieri, G., Benguigui, B. et al. (2005). Recognition of double-stranded RNA by human toll-like receptor 3 and downstream receptor signaling requires multimerization and an acidic pH. *J Biol Chem, 280*, 38133-45. ↗

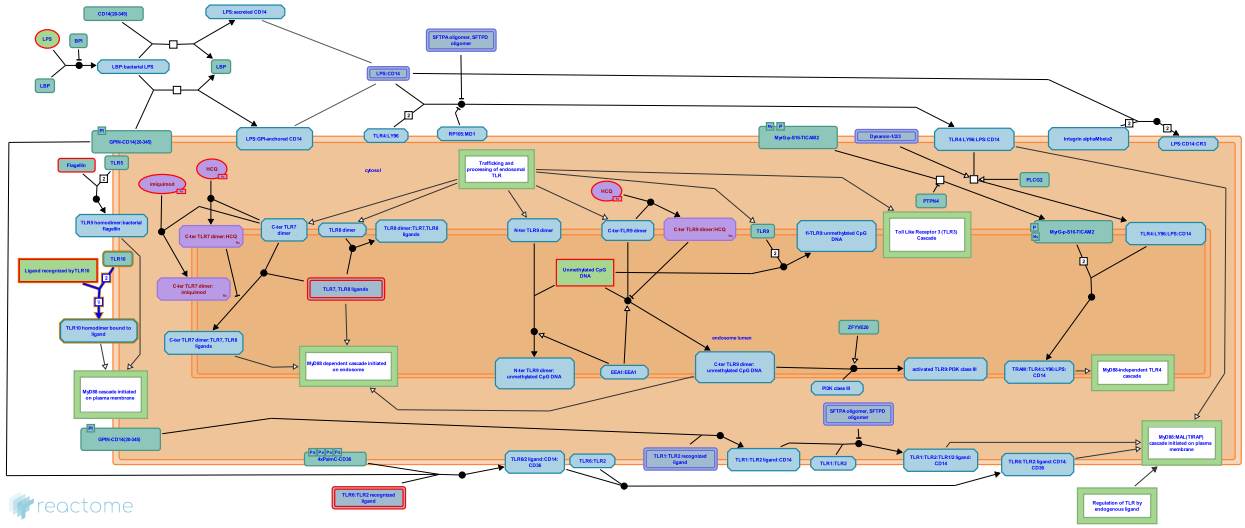
Editions

2011-10-19	Authored	Shamovsky, V.
2012-02-09	Reviewed	Gillespie, ME.
2012-02-19	Edited	Shamovsky, V.
2012-02-28	Reviewed	Leifer, CA., Rose II, WA.

Toll Like Receptor 10 (TLR10) Cascade ↗

Location: Toll-like Receptor Cascades

Stable identifier: R-HSA-168142



Little is known about TLR10 ligands. It has been established that the receptor homodimerizes upon binding and signals in an MyD88-dependent manner (Hasan U et al 2005; Nyman T et al 2008). It may also heterodimerize with TLRs 1 and 2. It is expressed in a restricted fashion as a highly N-glycosylated protein detectable in B cells and dendritic cells.

Literature references

Merck, E., Chaffois, C., Trinchieri, G., Vlach, J., Saulnier, V., Hasan, U. et al. (2005). Human TLR10 is a functional receptor, expressed by B cells and plasmacytoid dendritic cells, which activates gene transcription through MyD88. *J Immunol, 174*, 2942-50. ↗

Hammarström, M., Johansson, I., Nordlund, P., Stenmark, P., Flodin, S., Nyman, T. (2008). The crystal structure of the human toll-like receptor 10 cytoplasmic domain reveals a putative signaling dimer. *J Biol Chem, 283*, 11861-5. ↗

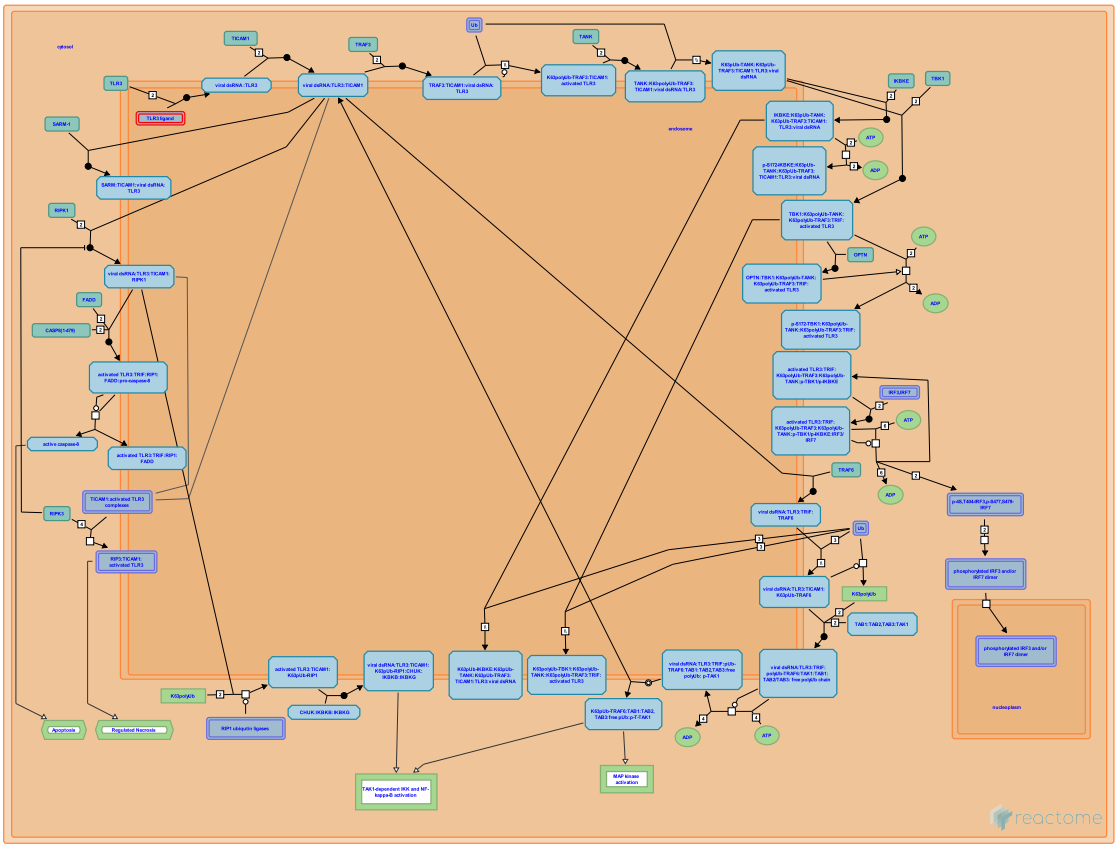
Editions

2005-11-10	Authored	Luo, F.
2006-10-31	Reviewed	Gale M, Jr.
2011-02-10	Reviewed	Gillespie, ME.
2011-08-12	Edited	Shamovsky, V.

Toll Like Receptor 3 (TLR3) Cascade ↗

Location: Toll-like Receptor Cascades

Stable identifier: R-HSA-168164



Toll-like receptor 3 (TLR3) as was shown for mammals is expressed in various tissues and cells, including myeloid dendritic cells, macrophages, respiratory and intestinal epithelium, neurons and microglial cells to induce antiviral and inflammatory responses of the innate immunity in combating viral infections.

TLR3 recognizes dsRNA in the endosome and that triggers the receptor dimerization. TLR3 recruits the adaptor TRIF (TICAM1), leading to the activation of NF-kappa-B and the production of type I interferons (IFNs). dsRNA-stimulated phosphorylation of two specific TLR3 tyrosine residues (Tyr759 and Tyr858) is essential for initiating TLR3 signaling pathways.

Literature references

O'Neill, LA., Carpenter, S. (2009). Recent insights into the structure of Toll-like receptors and post-translational modifications of their associated signalling proteins. *Biochem J, 422*, 1-10. ↗

Beyaert, R., Staal, J., Vercammen, E. (2008). Sensing of viral infection and activation of innate immunity by toll-like receptor 3. *Clin Microbiol Rev, 21*, 13-25. ↗

Sarkar, SN., Sen, GC. (2005). Transcriptional signaling by double-stranded RNA: role of TLR3. *Cytokine Growth Factor Rev, 16*, 1-14. ↗

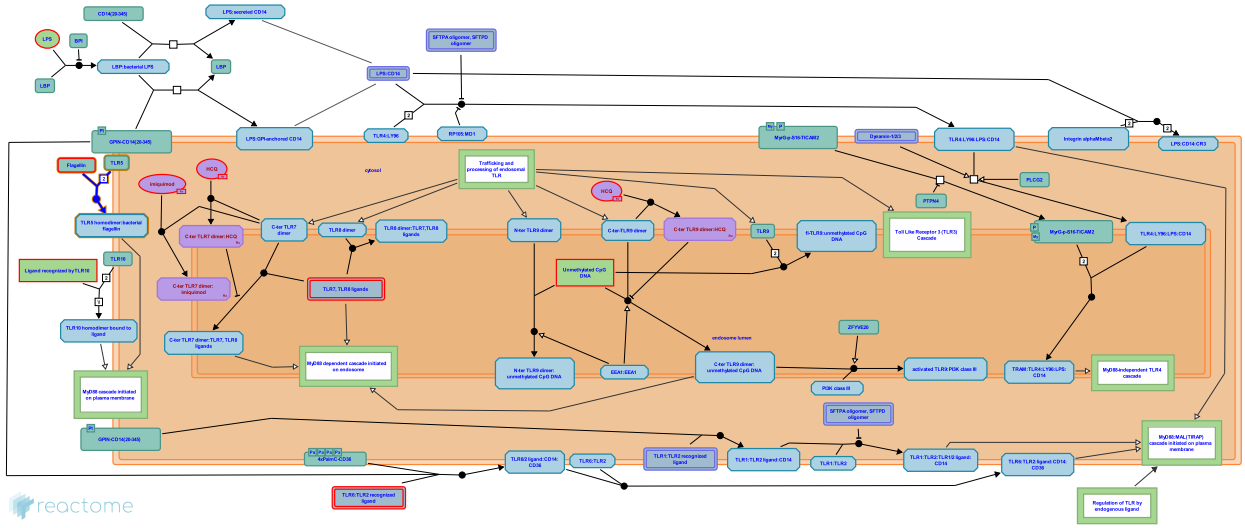
Editions

2005-11-10	Authored	Luo, F.
2006-04-24	Reviewed	Gay, NJ.
2009-09-29	Revised	Shamovsky, V.
2011-08-12	Edited	Shamovsky, V.

Toll Like Receptor 5 (TLR5) Cascade ↗

Location: Toll-like Receptor Cascades

Stable identifier: R-HSA-168176



TLR5 is the receptor for flagellin, the protein that forms bacterial flagella. Unlike most other Pathogen-Associated Molecular Patterns (PAMPs), flagellin does not undergo any posttranslational modifications that would distinguish it from cellular proteins. However, flagellin is extremely conserved at its amino- and carboxyl-termini, which presumably explains why it was selected as a ligand for innate immune recognition. TLR5 is expressed on epithelial cells as well as on macrophages and dendritic cells. Expression of TLR5 on intestinal epithelium is polarized such that TLR5 is expressed only on the basolateral side of the cell, as pathogenic but not commensal microbes cross the epithelial barrier. This ensures that innate immune responses are confined to pathogenic but not commensal microbes (Paul 2004; Hayashi et al. 2001; Gewirtz et al. 2001).

Literature references

Paul, W. (2003). Innate Immune System, Fundamental Immunology. *Lippincott Williams & Wilkins*, 497-518.

Smith, KD., Underhill, DM., Hawn, TR., Goodlett, DR., Ozinsky, A., Aderem, A. et al. (2001). The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5. *Nature, 410*, 1099-103. ↗

Lyons, S., Madara, JL., Gewirtz, AT., Godowski, PJ., Navas, TA. (2001). Cutting edge: bacterial flagellin activates basolaterally expressed TLR5 to induce epithelial proinflammatory gene expression. *J Immunol, 167*, 1882-5. ↗

Editions

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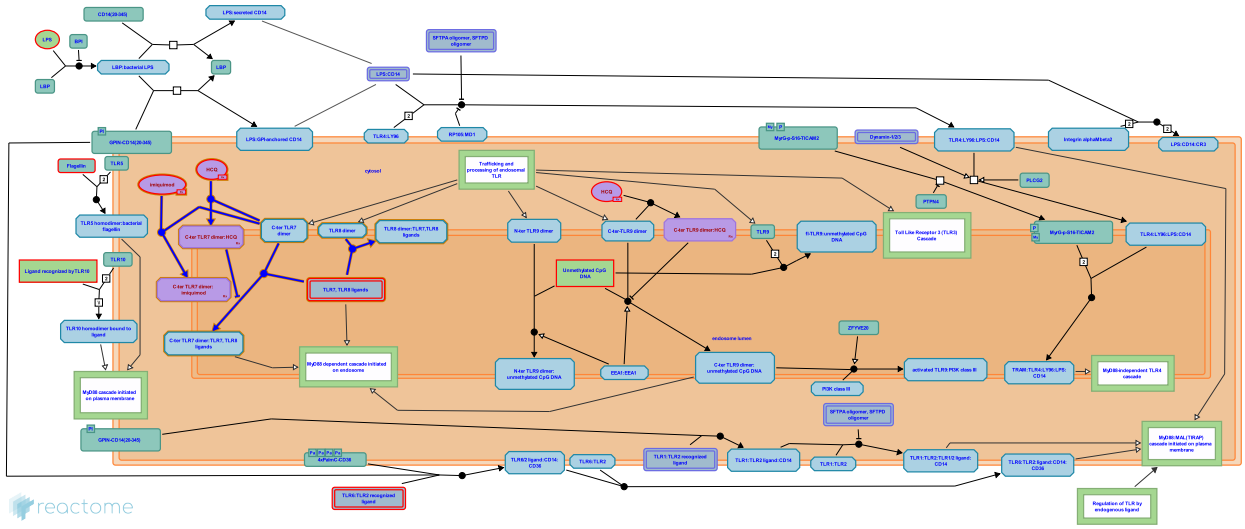
2011-08-12	Edited	Shamovsky, V.

Toll Like Receptor 7/8 (TLR7/8) Cascade ↗

Location: Toll-like Receptor Cascades

Stable identifier: R-HSA-168181

Compartments: endosome membrane, nucleoplasm, cytosol



RNA can serve as a danger signal, both in its double-stranded form as well as single-stranded RNA (ssRNA). Toll like receptor 7 (TLR7) and TLR8 are endosomal receptors that sense ssRNA oligonucleotides containing guanosine (G)- and uridine (U)-rich sequences from RNA viruses (Jurk M et al. 2002; Heil F et al. 2004; Diebold SS et al. 2004; Li Y et al. 2013; reviewed in Lester SN & Li K 2014). TLR7 is primarily expressed in plasmacytoid dendritic cells (pDCs) and, to some extent, in B cells, monocytes and macrophages, whereas TLR8 is mostly expressed in monocytes, macrophages and myeloid DCs. Upon engagement of ssRNAs in endosomes, TLR7/8 initiate the myeloid differentiation factor 88 (MyD88)-dependent pathway, culminating in synthesis of type I and type III IFNs and proinflammatory mediators via activation of IFN regulatory factor 7 (IRF7) and NF-κB, respectively, depending on the cell type (reviewed in Lester SN & Li K 2014). TLR7 and TLR8 are able to detect GU-rich ssRNA sequences from the viral genomes of influenza, human immunodeficiency virus-1 (HIV-1), vesicular stomatitis virus (VSV), coxsackie B virus, coronavirus and flaviviruses (hepatitis C virus, HCV and West Nile virus, WNV; reviewed in Lester SN & Li K 2014). Specifically, GU-rich ssRNA oligonucleotides derived from HIV-1, for example, stimulate dendritic cells (DC) and macrophages to secrete interferon-alpha and proinflammatory, as well as regulatory, cytokines (Heil F et al. 2004). This has been found to be mediated by TLR7, as well as TLR8. Similarly, severe acute respiratory syndrome-associated coronavirus type 1 (SARS-CoV-1) GU-rich ssRNAs had powerful immunostimulatory activities in mononuclear phagocytes to induce considerable level of pro-inflammatory cytokine TNF-a, IL-6 and IL-12 release via the TLR7 and TLR8 (Li Y et al. 2013). Further, mice deficient in either Tlr7 or the TLR adaptor protein Myd88 demonstrated reduced responses to in vivo infection with VSV (Lund JM et al. 2004), mouse-adapted SARS-CoV-1 (Sheahan et al. 2008; Totura et al., 2015). Upon Middle East respiratory syndrome-related coronavirus (MERS-CoV) infection, lack of MyD88 signaling resulted in delayed viral clearance and increased lung pathology in mice (Zhao et al. 2014). Consistently, another study showed that Tlr7-/- mice have reduced IFN expression compared with wild-type mice (Channappanavar et al. 2019). In addition, loss of function TLR7 variants identified in the patients with SARS-CoV-2 (COVID-19) resulted in defective upregulation of type I IFN–related genes in the TLR7 pathway (Figure 3) in response to the TLR7 agonist imiquimod as compared with controls (Van der Made CI et al. 2020). Separate studies showed that synthetic imidazoquinoline compounds (e.g. imiquimod and R-848, low-molecular-weight immune response modifiers that can induce the synthesis of interferon-alpha) also exert their effects in a MyD88-dependent fashion through TLR7 or TLR8 (Hemmi H et al. 2002; Jurk M et al. 2002; Diebold SS et al. 2004). Some viruses utilize multiple strategies to evade antiviral innate immune signaling, as is seen with influenza or SARS coronaviruses. TLR7-mediated innate immunity, for example, was associated with the negative regulation through removing Lys63-linked polyubiquitin chains of TRAF3/TRAF6 by papin-like protease (PLpro) catalytic domain of nsp3 from SARS-CoV-1 (Li SW et al. 2016). Thus, TLR7 and TLR8 play a critical role in sensing of viral ssRNA in the endosome.

Literature references

Kirschning, C., Bauer, S., Lipford, G., Hochrein, H., Akira, S., Wagner, H. et al. (2004). Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. *Science, 303*, 1526-9. ↗

Editions

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2010-10-29	Reviewed	Gillespie, ME.
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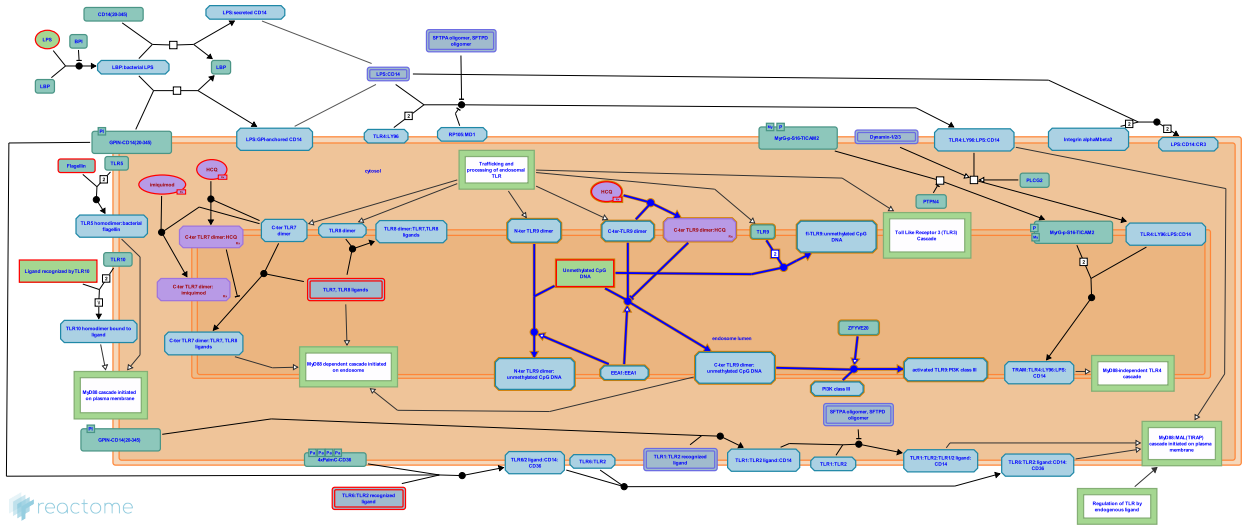
Toll Like Receptor 9 (TLR9) Cascade ↗

Location: Toll-like Receptor Cascades

Stable identifier: R-HSA-168138

Compartments: endosome membrane, nucleoplasm, cytosol



CpG DNA is an unusual Pathogen-Associated Molecular Pattern (PAMP). Cytosine methylation exists in mammalian but not bacterial cells, and most (but not all) CpG in the mammalian genome is methylated. Therefore, unmethylated CpG DNA may signal the presence of microbial infection. Evidence of CpG recognition by TLR9 was demonstrated both in human and mouse, and this type of signaling requires its internalization into late endosomal/lysosomal compartments. TLR9 has been reported to be able to discern different types of CpG motifs, and therefore that it presumably recognizes CpG DNA directly. It appears that over evolutionary periods, TLR9 molecules expressed by different species have diverged. This has led to differences in the precise sequence motif (CpG dinucleotide plus flanking regions) that optimally stimulate the innate immune system of different animals.

Literature references

Klinman, DM., Gursel, M., Ishii, KJ., Suzuki, K., Gursel, I., Takeshita, F. (2004). Signal transduction pathways mediated by the interaction of CpG DNA with Toll-like receptor 9. *Semin Immunol, 16*, 17-22. ↗

Editions

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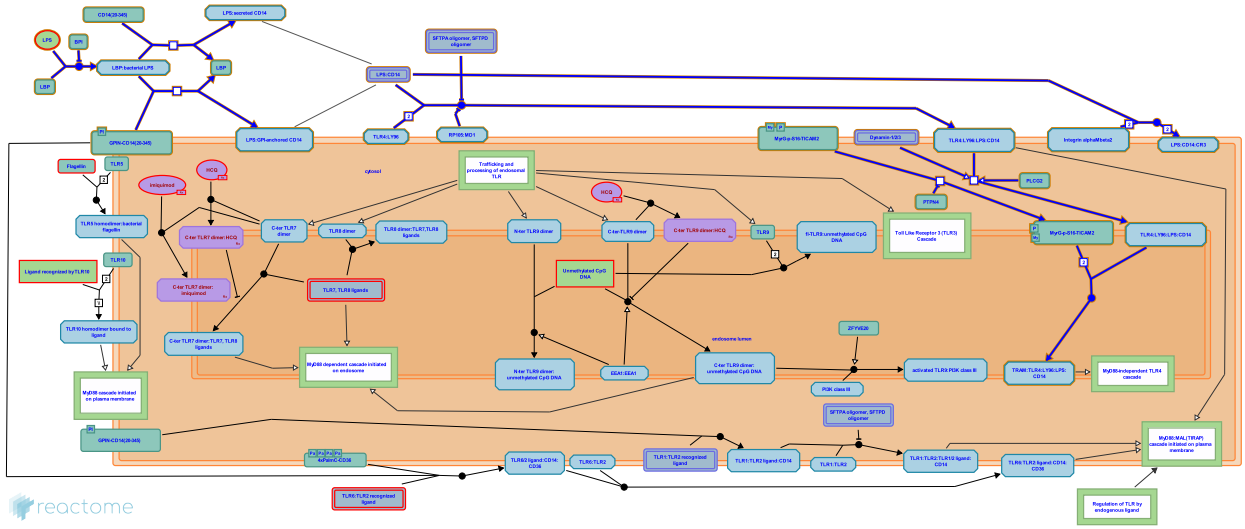
Toll Like Receptor 4 (TLR4) Cascade ↗

Location: Toll-like Receptor Cascades

Stable identifier: R-HSA-166016



Toll-like Receptor 4 is a microbe associated molecular pattern receptor well known for it's sensitivity to bacterial lipopolysaccharides (LPS). LPS is assembled within diverse Gram-negative bacteria, many of which are human or plant pathogens. It is a component of the outer membrane of Gram-negative bacteria and consists of lipid A, a core polysaccharide and an O-polysaccharide of variable length (often more than 50 monosaccharide units). LPS is a potent activator of the innate immune response in humans, causing reactions including fever, headache, nausea, diarrhoea, changes in leukocyte and platelet counts, disseminated intravascular coagulation, multiorgan failure, shock and death. All these reactions are induced by cytokines and other endogenous mediators which are produced after interaction of LPS with the humoral and cellular targets of the host. In macrophages and dendritic cells, LPS-mediated activation of TLR4 triggers the biosynthesis of diverse mediators of inflammation, such as TNF-alpha and IL6, and activates the production of co-stimulatory molecules required for the adaptive immune response. In mononuclear and endothelial cells, LPS also stimulates tissue factor production. These events are desirable for clearing local infections, but when these various mediators and clotting factors are overproduced, they can damage small blood vessels and precipitate shock accompanied by disseminated intravascular coagulation and multiple organ failure.
TLR4 is unique among the TLR family in its ability to recruit four adapters to activate two distinct signaling pathways. One pathway is activated by the pair of the adapters Mal or TIRAP (Toll/interleukin-1-receptor (TIR)-domain-containing adapter protein) and MyD88, which leads to the NFkB activation and the induction of pro-inflammatory cytokines. The second pathway is activated by the adapters TRIF (TIR-domain-containing adapter protein inducing interferon-beta) and TRAM (TRIF-related adapter molecule). The combined use of TRIF and TRAM adapters is specific for TLR4 signaling pathway and leads to the induction of type I interferons and delayed activation of NFkB.

The previous model of TLR4 signaling pathway described the simultaneous activation of these two signaling pathways at the plasma membrane, however the later studies suggested that upon activation TLR4 first induces TIRAP-MyD88 signaling at the plasma membrane and is then endocytosed and activates TRAM-TRIF signaling from the early endosome [Kagan JC et al 2008; Tanimura N et al 2008; Zanoni I et al 2011].

Literature references

Andreakos, E., Feldmann, M., Foxwell, BM., Sacre, SM. (2004). Endotoxin signaling in human macrophages: signaling via an alternate mechanism. *J Endotoxin Res, 10,* 445-52. ↗

Fitzgerald, KA., Rowe, DC., Golenbock, DT. (2004). Endotoxin recognition and signal transduction by the TLR4/MD2-complex. *Microbes Infect, 6,* 1361-7. ↗

Zimmer, SM., Datta, A., Zughaier, SM., Stephens, DS., Carlson, RW. (2005). Differential induction of the toll-like receptor 4-MyD88-dependent and -independent signaling pathways by endotoxins. *Infect. Immun., 73,* 2940-50. ↗

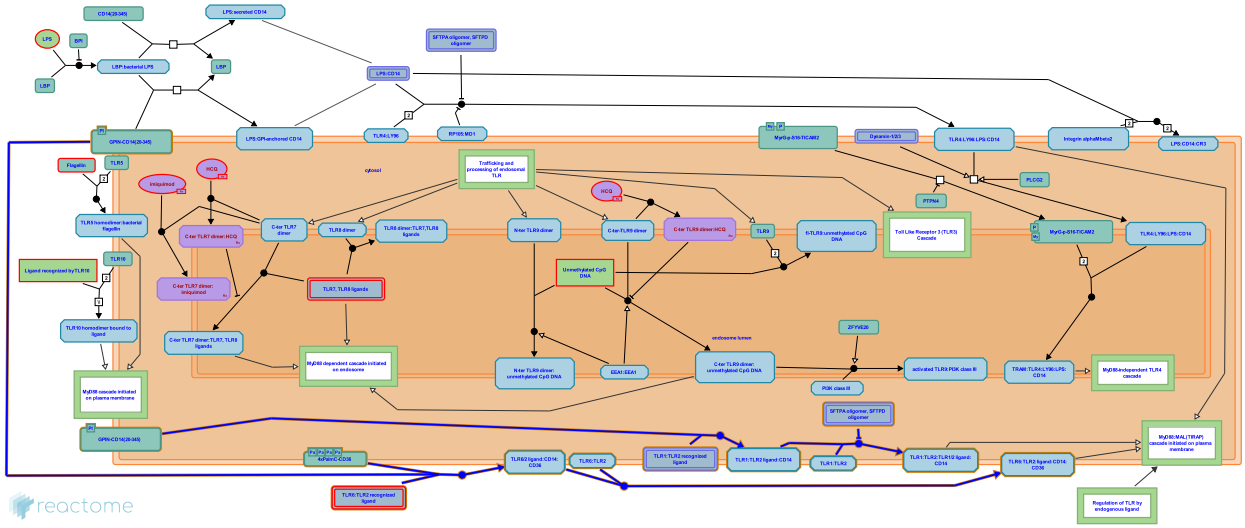
Editions

2005-08-16	Authored	de Bono, B.
2006-04-24	Reviewed	Gay, NJ.
2010-11-15	Edited	Shamovsky, V.
2010-11-30	Reviewed	Gillespie, ME.
2012-11-02	Revised	Shamovsky, V.

Toll Like Receptor 2 (TLR2) Cascade ↗

Location: Toll-like Receptor Cascades

Stable identifier: R-HSA-181438



TLR2 is involved in recognition of peptidoglycan from gram-positive bacteria, bacterial lipoproteins, mycoplasma lipoprotein and mycobacterial products. It is quite possible that recognition of at least some other TLR2 ligands may be assisted by additional accessory proteins, particularly in association with TLR1 or TLR6. TLR2 is expressed constitutively on macrophages, dendritic cells, and B cells, and can be induced in some other cell types, including epithelial cells. TLR1 and TLR6, on the other hand, are expressed almost ubiquitously (Muzio et al. 2000). TLR2 may be a sensor and inductor of specific defense processes, including oxidative stress and cellular necrosis initially spurred by microbial compounds.

Literature references

Mantovani, A., van't Veer, C., Bosisio, D., Penton-Rol, G., Polentarutti, N., Allavena, P. et al. (2000). Differential expression and regulation of toll-like receptors (TLR) in human leukocytes: selective expression of TLR3 in dendritic cells. *J Immunol, 164*, 5998-6004. ↗

Editions

2006-04-19	Authored	D'Eustachio, P., Gay, NJ., Gale M, Jr., Zwaginga, JJ.
2006-07-04	Reviewed	D'Eustachio, P.
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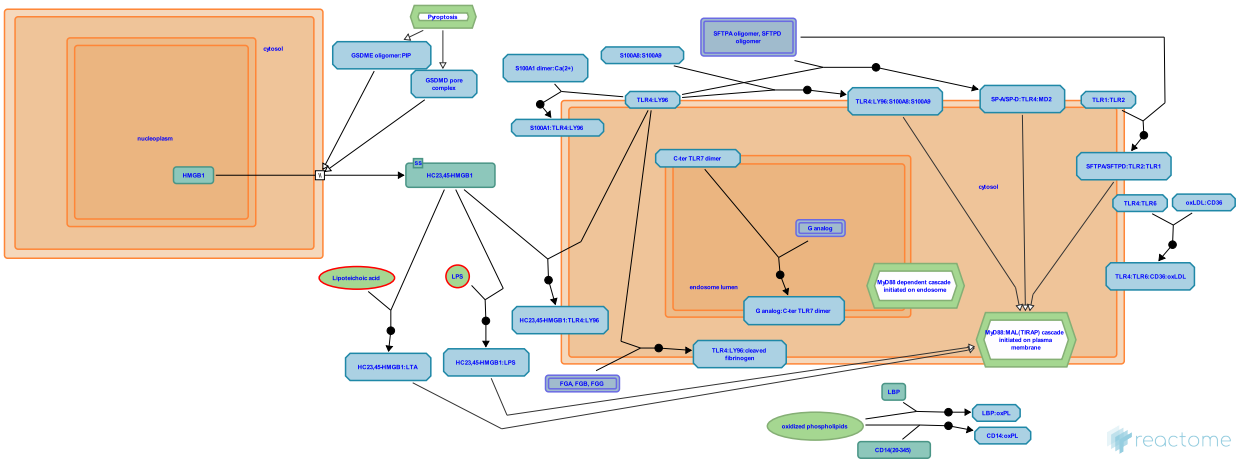
Regulation of TLR by endogenous ligand ↗

Location: Toll-like Receptor Cascades

Stable identifier: R-HSA-5686938



Diverse molecules of host-cell origin may serve as endogenous ligands of Toll-like receptors (TLRs) (Erridge C 2010; Piccinini AM & Midwood KS 2010). These molecules are known as damage-associated molecular patterns (DAMPs). DAMPs are immunologically silent in healthy tissues but become active upon tissue damage during both infectious and sterile insult. DAMPs are released from necrotic cells or secreted from activated cells in response to tissue damage to mediate tissue repair by promoting inflammatory responses. However, DAMPs have also been implicated in the pathogenesis of many inflammatory and autoimmune diseases, including rheumatoid arthritis (RA), cancer, and atherosclerosis. The mechanism underlying the switch from DAMPs that initiate controlled tissue repair, to those that mediate chronic, uncontrolled inflammation is still unclear. Recent evidence suggests that an abnormal increase in protein citrullination is involved in disease pathophysiology (Anzilotti C et al. 2010; Sanchez-Pernaute O et al. 2013; Sokolove J et al. 2011; Sharma P et al. 2012). Citrullination is a post-translational modification event mediated by peptidyl-arginine deaminase enzymes which catalyze the deimination of proteins by converting arginine residues into citrullines in the presence of calcium ions.

Literature references

Erridge, C. (2010). Endogenous ligands of TLR2 and TLR4: agonists or assistants?. *J. Leukoc. Biol., 87*, 989-99. ↗

Schaefer, L. (2014). Complexity of danger: the diverse nature of damage-associated molecular patterns. *J. Biol. Chem. , 289*, 35237-45. ↗

Yu, L., Wang, L., Chen, S. (2010). Endogenous toll-like receptor ligands and their biological significance. *J. Cell. Mol. Med., 14*, 2592-603. ↗

Piccinini, AM., Midwood, KS. (2010). DAMPening inflammation by modulating TLR signalling. *Mediators Inflamm., 2010*. ↗

Editions

2015-09-12	Reviewed	D'Eustachio, P.
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2016-05-10	Edited	Shamovsky, V.
2016-05-12	Reviewed	Zanoni, I., Granucci, F.

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