



# Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 75 on 22/03/2021. The web link to these results is:

<https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMTAzMjIwMjAxMDhfNTcwODA%3D>

Please keep in mind that analysis results are temporarily stored on our server. The storage period depends on usage of the service but is at least 7 days. As a result, please note that this URL is only valid for a limited time period and it might have expired.

# **Table of Contents**

1. Introduction
2. Properties
3. Genome-wide overview
4. Most significant pathways
5. Pathways details
6. Identifiers found
7. Identifiers not found

# 1. Introduction

Reactome is a curated database of pathways and reactions in human biology. Reactions can be considered as pathway 'steps'. Reactome defines a 'reaction' as any event in biology that changes the state of a biological molecule. Binding, activation, translocation, degradation and classical biochemical events involving a catalyst are all reactions. Information in the database is authored by expert biologists, entered and maintained by Reactome's team of curators and editorial staff. Reactome content frequently cross-references other resources e.g. NCBI, Ensembl, UniProt, KEGG (Gene and Compound), ChEBI, PubMed and GO. Orthologous reactions inferred from annotation for *Homo sapiens* are available for 17 non-human species including mouse, rat, chicken, puffer fish, worm, fly, yeast, rice, and *Arabidopsis*. Pathways are represented by simple diagrams following an SBGN-like format.

Reactome's annotated data describe reactions possible if all annotated proteins and small molecules were present and active simultaneously in a cell. By overlaying an experimental dataset on these annotations, a user can perform a pathway over-representation analysis. By overlaying quantitative expression data or time series, a user can visualize the extent of change in affected pathways and its progression. A binomial test is used to calculate the probability shown for each result, and the p-values are corrected for the multiple testing (Benjamini–Hochberg procedure) that arises from evaluating the submitted list of identifiers against every pathway.

To learn more about our Pathway Analysis, please have a look at our relevant publications:

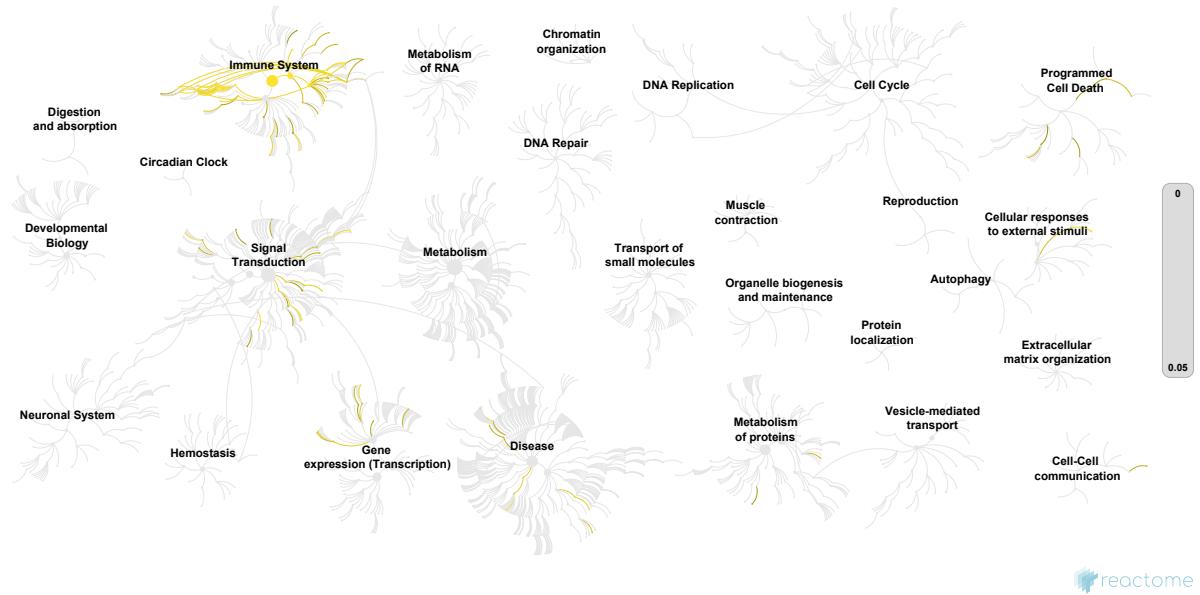
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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

## 2. Properties

- This is an **overrepresentation** analysis: A statistical (hypergeometric distribution) test that determines whether certain Reactome pathways are over-represented (enriched) in the submitted data. It answers the question 'Does my list contain more proteins for pathway X than would be expected by chance?' This test produces a probability score, which is corrected for false discovery rate using the Benjamani-Hochberg method. ↗
- 232 out of 466 identifiers in the sample were found in Reactome, where 860 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent. ↗
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAyMTAzMjIwMjAxMDhfNTcwODA%3D. This ID is valid for at least 7 days in Reactome's server. Use it to access Reactome services with your data.

### 3. Genome-wide overview



This figure shows a genome-wide overview of the results of your pathway analysis. Reactome pathways are arranged in a hierarchy. The center of each of the circular "bursts" is the root of one top-level pathway, for example "DNA Repair". Each step away from the center represents the next level lower in the pathway hierarchy. The color code denotes over-representation of that pathway in your input dataset. Light grey signifies pathways which are not significantly over-represented.

## 4. Most significant pathways

The following table shows the 25 most relevant pathways sorted by p-value.

Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Interleukin-10 signaling	36 / 86	0.006	1.11e-16	3.56e-14	13 / 15	0.001
Cytokine Signaling in Immune system	104 / 1,108	0.075	1.11e-16	3.56e-14	324 / 687	0.052
Signaling by Interleukins	78 / 647	0.044	1.11e-16	3.56e-14	229 / 493	0.037
Interleukin-4 and Interleukin-13 signaling	37 / 216	0.015	3.84e-14	9.26e-12	10 / 47	0.004
Chemokine receptors bind chemokines	12 / 57	0.004	2.20e-06	4.25e-04	8 / 19	0.001
Toll Like Receptor 3 (TLR3) Cascade	14 / 102	0.007	3.90e-05	0.005	38 / 61	0.005
Toll Like Receptor 4 (TLR4) Cascade	17 / 144	0.01	3.95e-05	0.005	62 / 95	0.007
Immune System	138 / 2,713	0.184	4.50e-05	0.005	556 / 1,593	0.12
MyD88-independent TLR4 cascade	14 / 107	0.007	6.45e-05	0.006	38 / 60	0.005
TRIF(TICAM1)-mediated TLR4 signaling	14 / 107	0.007	6.45e-05	0.006	36 / 58	0.004
Interleukin-1 processing	4 / 8	5.43e-04	2.53e-04	0.021	2 / 5	3.78e-04
MyD88:MAL(TIRAP) cascade initiated on plasma membrane	13 / 111	0.008	3.35e-04	0.021	41 / 64	0.005
Toll Like Receptor TLR6:TLR2 Cascade	13 / 111	0.008	3.35e-04	0.021	42 / 66	0.005
Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways	10 / 70	0.005	3.55e-04	0.021	19 / 46	0.003
Toll Like Receptor TLR1:TLR2 Cascade	13 / 114	0.008	4.29e-04	0.023	42 / 66	0.005
Toll Like Receptor 2 (TLR2) Cascade	13 / 114	0.008	4.29e-04	0.023	43 / 68	0.005
TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation	12 / 101	0.007	4.94e-04	0.023	26 / 48	0.004
MyD88 dependent cascade initiated on endosome	12 / 102	0.007	5.38e-04	0.023	29 / 63	0.005
Toll Like Receptor 7/8 (TLR7/8) Cascade	12 / 104	0.007	6.36e-04	0.026	29 / 66	0.005
Toll-like Receptor Cascades	17 / 185	0.013	7.07e-04	0.027	101 / 185	0.014
RAF-independent MAPK1/3 activation	6 / 28	0.002	7.08e-04	0.027	4 / 12	9.07e-04
TNF signaling	8 / 51	0.003	7.49e-04	0.028	25 / 32	0.002
Toll Like Receptor 9 (TLR9) Cascade	12 / 107	0.007	8.11e-04	0.028	29 / 68	0.005

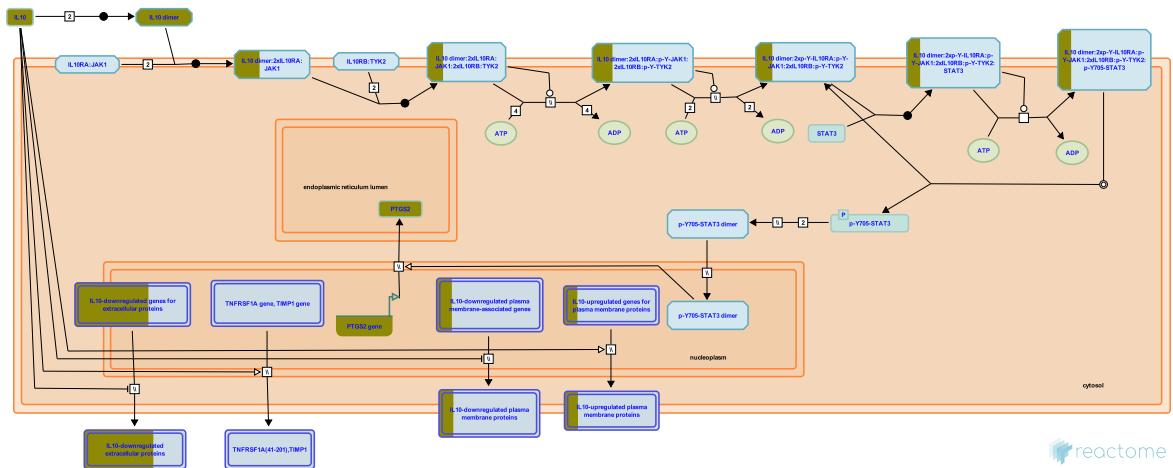
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
MyD88 cascade initiated on plasma membrane	11 / 94	0.006	9.43e-04	0.029	29 / 58	0.004
Toll Like Receptor 5 (TLR5) Cascade	11 / 94	0.006	9.43e-04	0.029	29 / 59	0.004

\* False Discovery Rate

## 5. Pathways details

For every pathway of the most significant pathways, we present its diagram, as well as a short summary, its bibliography and the list of inputs found in it.

### 1. Interleukin-10 signaling (R-HSA-6783783)



Interleukin-10 (IL10) was originally described as a factor named cytokine synthesis inhibitory factor that inhibited T-helper (Th) 1 activation and Th1 cytokine production (Fiorentino et al. 1989). It was found to be expressed by a variety of cell types including macrophages, dendritic cell subsets, B cells, several T-cell subpopulations including Th2 and T-regulatory cells (Tregs) and Natural Killer (NK) cells (Moore et al. 2001). It is now recognized that the biological effects of IL10 are directed at antigen-presenting cells (APCs) such as macrophages and dendritic cells (DCs), its effects on T-cell development and differentiation are largely indirect via inhibition of macrophage/dendritic cell activation and maturation (Pestka et al. 2004, Mocellin et al. 2004). T cells are thought to be the main source of IL10 (Hedrich & Bream 2010). IL10 inhibits a broad spectrum of activated macrophage/monocyte functions including monokine synthesis, NO production, and expression of class II MHC and costimulatory molecules such as IL12 and CD80/CD86 (de Waal Malefyt et al. 1991, Gazzinelli et al. 1992). Studies with recombinant cytokine and neutralizing antibodies revealed pleiotropic activities of IL10 on B, T, and mast cells (de Waal Malefyt et al. 1993, Rousset et al. 1992, Thompson-Snipes et al. 1991) and provided evidence for the in vivo significance of IL10 activities (Ishida et al. 1992, 1993). IL10 antagonizes the expression of MHC class II and the co-stimulatory molecules CD80/CD86 as well as the pro-inflammatory cytokines IL1Beta, IL6, IL8, TNFalpha and especially IL12 (Fiorentino et al. 1991, D'Andrea et al. 1993). The biological role of IL10 is not limited to inactivation of APCs, it also enhances B cell, granulocyte, mast cell, and keratinocyte growth/differentiation, as well as NK-cell and CD8+ cytotoxic T-cell activation (Moore et al. 2001, Hedrich & Bream 2010). IL10 also enhances NK-cell proliferation and/or production of IFN-gamma (Cai et al. 1999).

IL10-deficient mice exhibited inflammatory bowel disease (IBD) and other exaggerated inflammatory responses (Kuhn et al. 1993, Berg et al. 1995) indicating a critical role for IL10 in limiting inflammatory responses. Dysregulation of IL10 is linked with susceptibility to numerous infectious and autoimmune diseases in humans and mouse models (Hedrich & Bream 2010).

IL10 signaling is initiated by binding of homodimeric IL10 to the extracellular domains of two adjoining IL10RA molecules. This tetramer then binds two IL10RB chains. IL10RB cannot bind to IL10 unless bound to IL10RA (Ding et al. 2001, Yoon et al. 2006); binding of IL10 to IL10RA without the co-presence of IL10RB fails to initiate signal transduction (Kotenko et al. 1997).

IL10 binding activates the receptor-associated Janus tyrosine kinases, JAK1 and TYK2, which are constitutively bound to IL10R1 and IL10R2 respectively. In the classic model of receptor activation assembly of the receptor complex is believed to enable JAK1/TYK2 to phosphorylate and activate each other. Alternatively the binding of IL10 may cause conformational changes that allow the pseudokinase inhibitory domain of one JAK kinase to move away from the kinase domain of the other JAK within the receptor dimer-JAK complex, allowing the two kinase domains to interact and trans-activate (Waters & Brooks 2015).

The activated JAK kinases phosphorylate the intracellular domains of the IL10R1 chains on specific tyrosine residues. These phosphorylated tyrosine residues and their flanking peptide sequences serve as temporary docking sites for the latent, cytosolic, transcription factor, STAT3. STAT3 transiently docks on the IL10R1 chain via its SH2 domain, and is in turn tyrosine phosphorylated by the receptor-associated JAKs. Once activated, it dissociates from the receptor, dimerizes with other STAT3 molecules, and translocates to the nucleus where it binds with high affinity to STAT-binding elements (SBEs) in the promoters of IL-10-inducible genes (Donnelly et al. 1999).

## References

Moore KW, de Waal Malefyt R, Coffman RL & O'Garra A (2001). Interleukin-10 and the interleukin-10 receptor. *Annu. Rev. Immunol.*, 19, 683-765. [🔗](#)

## Edit history

Date	Action	Author
2015-06-17	Authored	Jupe S
2015-06-17	Created	Jupe S
2016-09-05	Reviewed	Meldal BH
2016-11-14	Edited	Jupe S
2020-11-24	Modified	Shorser S

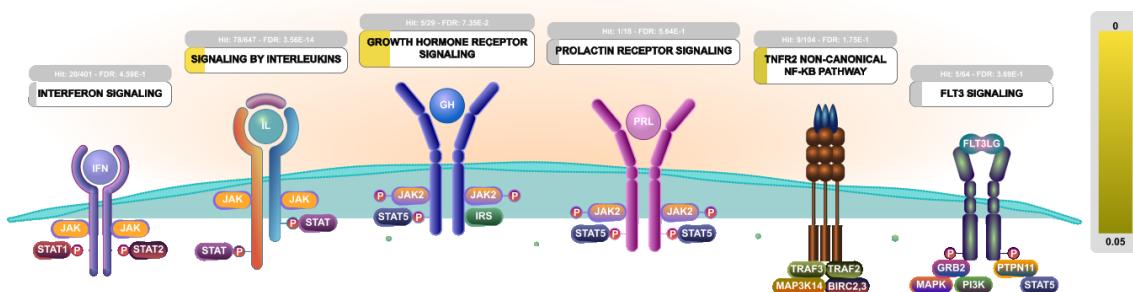
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ENSG00000275302	ENSG00000275302	ENSG00000277632	ENSG00000277632		

## 2. Cytokine Signaling in Immune system (R-HSA-1280215)



Cytokines are small proteins that regulate and mediate immunity, inflammation, and hematopoiesis. They are secreted in response to immune stimuli, and usually act briefly, locally, at very low concentrations. Cytokines bind to specific membrane receptors, which then signal the cell via second messengers, to regulate cellular activity.

### References

Oppenheim J & Feldmann M (2002). *Cytokines and the immune system*, *Cytokine Reference*.

IMMPORT: Bioinformatics for the future of immunology. Retrieved from <https://www.immport.org/immportWeb/queryref/geneListSummary.do>

COPE. Retrieved from <http://www.copewithcytokines.org/cope.cgi>

Santamaria P (2003). Cytokines and chemokines in autoimmune disease: an overview. *Adv Exp Med Biol*, 520, 1-7. [\[CrossRef\]](#)

### Edit history

Date	Action	Author
2011-05-12	Created	Garapati P V
2011-05-22	Edited	Ray KP, Jupe S, Garapati P V
2011-05-22	Authored	Ray KP, Jupe S, Garapati P V
2011-05-29	Reviewed	Abdul-Sater AA, Schindler C, Pinteaux E
2020-11-20	Modified	Shorser S

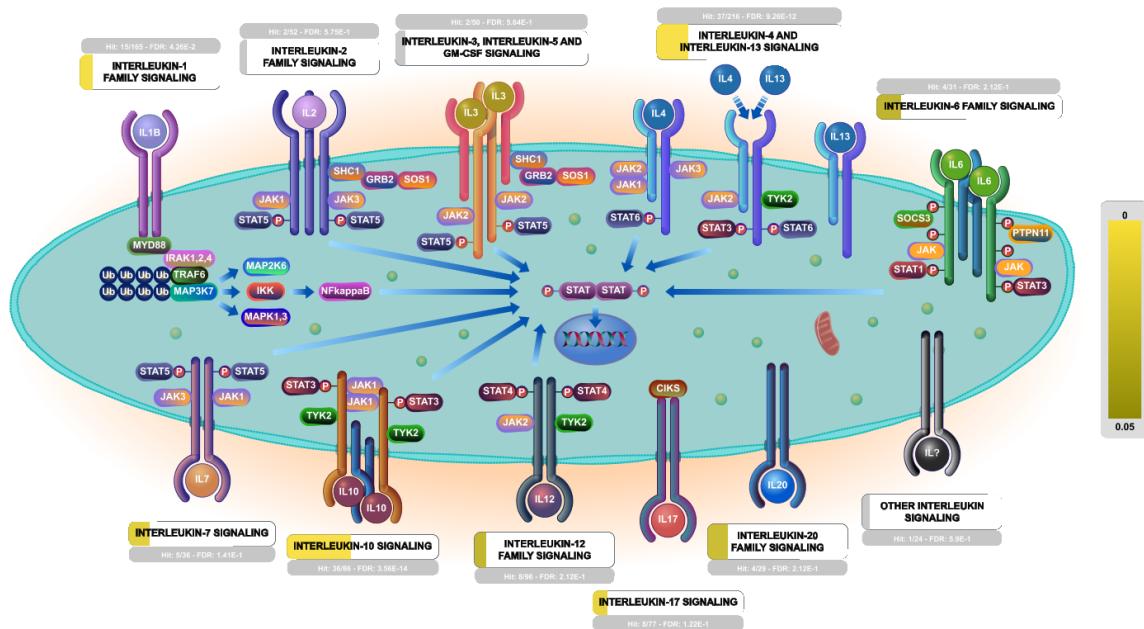
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ENSG0000275302	ENSG0000275302	ENSG0000277632	ENSG0000277632		

### 3. Signaling by Interleukins (R-HSA-449147)



**Cellular compartments:** plasma membrane.

Interleukins are low molecular weight proteins that bind to cell surface receptors and act in an autocrine and/or paracrine fashion. They were first identified as factors produced by leukocytes but are now known to be produced by many other cells throughout the body. They have pleiotropic effects on cells which bind them, impacting processes such as tissue growth and repair, hematopoietic homeostasis, and multiple levels of the host defense against pathogens where they are an essential part of the immune system.

## References

- Vosshenrich CA & Di Santo JP (2002). Interleukin signaling. *Curr Biol*, 12, R760-3. [🔗](#)
- Dinarello CA (2009). Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol*, 27, 519-50. [🔗](#)
- Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Crameri R, ... Akdis CA (2016). Interleukins (from IL-1 to IL-38), interferons, transforming growth factor , and TNF-: Receptors, functions, and roles in diseases. *J. Allergy Clin. Immunol.*, 138, 984-1010. [🔗](#)

## Edit history

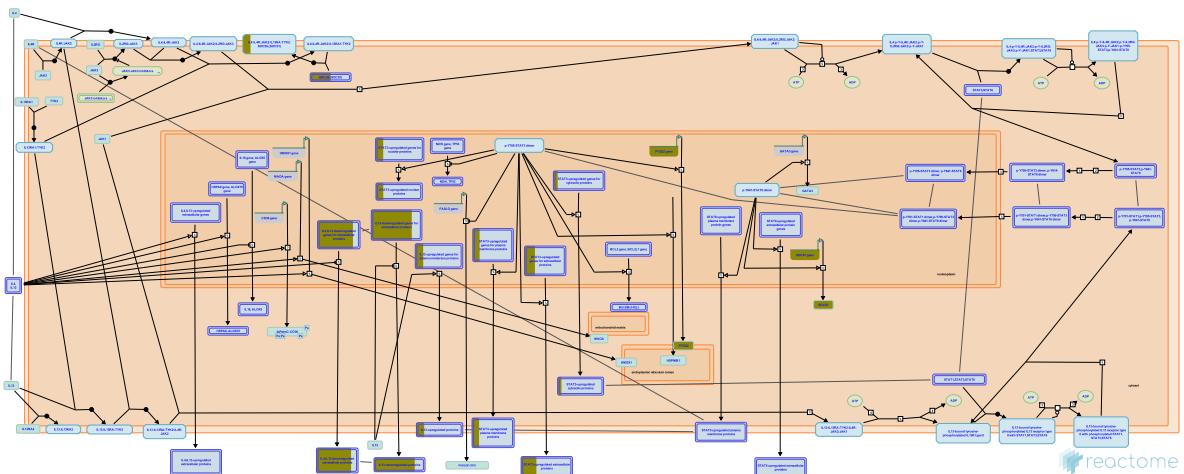
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2010-05-26	Edited	Jupe S
2020-11-20	Modified	Shorser S

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ENSG0000164400	ENSG0000164400	ENSG0000169429	ENSG0000169429	ENSG0000171223	ENSG0000171223
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ENSG0000232810	ENSG0000232810	ENSG0000271503	ENSG0000271503	ENSG0000275302	ENSG0000275302
ENSG0000277632	ENSG0000277632				

#### 4. Interleukin-4 and Interleukin-13 signaling (R-HSA-6785807)



Interleukin-4 (IL4) is a principal regulatory cytokine during the immune response, crucially important in allergy and asthma (Nelms et al. 1999). When resting T cells are antigen-activated and expand in response to Interleukin-2 (IL2), they can differentiate as Type 1 (Th1) or Type 2 (Th2) T helper cells. The outcome is influenced by IL4. Th2 cells secrete IL4, which both stimulates Th2 in an autocrine fashion and acts as a potent B cell growth factor to promote humoral immunity (Nelms et al. 1999).

Interleukin-13 (IL13) is an immunoregulatory cytokine secreted predominantly by activated Th2 cells. It is a key mediator in the pathogenesis of allergic inflammation. IL13 shares many functional properties with IL4, stemming from the fact that they share a common receptor subunit. IL13 receptors are expressed on human B cells, basophils, eosinophils, mast cells, endothelial cells, fibroblasts, monocytes, macrophages, respiratory epithelial cells, and smooth muscle cells, but unlike IL4, not T cells. Thus IL13 does not appear to be important in the initial differentiation of CD4 T cells into Th2 cells, rather it is important in the effector phase of allergic inflammation (Hershey et al. 2003).

IL4 and IL13 induce “alternative activation” of macrophages, inducing an anti-inflammatory phenotype by signaling through IL4R alpha in a STAT6 dependent manner. This signaling plays an important role in the Th2 response, mediating anti-parasitic effects and aiding wound healing (Gordon & Martinez 2010, Loke et al. 2002)

There are two types of IL4 receptor complex (Andrews et al. 2006). Type I IL4R (IL4R1) is predominantly expressed on the surface of hematopoietic cells and consists of IL4R and IL2RG, the common gamma chain. Type II IL4R (IL4R2) is predominantly expressed on the surface of nonhematopoietic cells, it consists of IL4R and IL13RA1 and is also the type II receptor for IL13. (Obiri et al. 1995, Aman et al. 1996, Hilton et al. 1996, Miloux et al. 1997, Zhang et al. 1997). The second receptor for IL13 consists of IL4R and Interleukin-13 receptor alpha 2 (IL13RA2), sometimes called Interleukin-13 binding protein (IL13BP). It has a high affinity receptor for IL13 ( $K_d = 250 \text{ pmol/L}$ ) but is not sufficient to render cells responsive to IL13, even in the presence of IL4R (Donaldson et al. 1998). It is reported to exist in soluble form (Zhang et al. 1997) and when overexpressed reduces JAK-STAT signaling (Kawakami et al. 2001). Its function may be to prevent IL13 signalling via the functional IL4R:IL13RA1 receptor. IL13RA2 is overexpressed and enhances cell invasion in some human cancers (Joshi & Puri 2012).

The first step in the formation of IL4R1 (IL4:IL4R:IL2RB) is the binding of IL4 with IL4R (Hoffman et al. 1995, Shen et al. 1996, Hage et al. 1999). This is also the first step in formation of IL4R2 (IL4:IL4R:IL13RA1). After the initial binding of IL4 and IL4R, IL2RB binds (LaPorte et al. 2008), to form IL4R1. Alternatively, IL13RA1 binds, forming IL4R2. In contrast, the type II IL13 complex (IL13R2) forms with IL13 first binding to IL13RA1 followed by recruitment of IL4R (Wang et al. 2009).

Crystal structures of the IL4:IL4R:IL2RG, IL4:IL4R:IL13RA1 and IL13:IL4R:IL13RA1 complexes have been determined (LaPorte et al. 2008). Consistent with these structures, in monocytes IL4R is tyrosine phosphorylated in response to both IL4 and IL13 (Roy et al. 2002, Gordon & Martinez 2010) while IL13RA1 phosphorylation is induced only by IL13 (Roy et al. 2002, LaPorte et al. 2008) and IL2RG phosphorylation is induced only by IL4 (Roy et al. 2002).

Both IL4 receptor complexes signal through Jak/STAT cascades. IL4R is constitutively-associated with JAK2 (Roy et al. 2002) and associates with JAK1 following binding of IL4 (Yin et al. 1994) or IL13 (Roy et al. 2002). IL2RG constitutively associates with JAK3 (Boussiotis et al. 1994, Russell et al. 1994). IL13RA1 constitutively associates with TYK2 (Umeshita-Suyama et al. 2000, Roy et al. 2002, LaPorte et al. 2008, Bhattacharjee et al. 2013).

IL4 binding to IL4R1 leads to phosphorylation of JAK1 (but not JAK2) and STAT6 activation (Takeda et al. 1994, Ratthe et al. 2007, Bhattacharjee et al. 2013).

IL13 binding increases activating tyrosine-99 phosphorylation of IL13RA1 but not that of IL2RG. IL4 binding to IL2RG leads to its tyrosine phosphorylation (Roy et al. 2002). IL13 binding to IL4R2 leads to TYK2 and JAK2 (but not JAK1) phosphorylation (Roy & Cathcart 1998, Roy et al. 2002).

Phosphorylated TYK2 binds and phosphorylates STAT6 and possibly STAT1 (Bhattacharjee et al. 2013).

A second mechanism of signal transduction activated by IL4 and IL13 leads to the insulin receptor substrate (IRS) family (Kelly-Welch et al. 2003). IL4R1 associates with insulin receptor substrate 2 and activates the PI3K/Akt and Ras/MEK/Erk pathways involved in cell proliferation, survival and translational control. IL4R2 does not associate with insulin receptor substrate 2 and consequently the PI3K/Akt and Ras/MEK/Erk pathways are not activated (Busch-Dienstfertig & González-Rodríguez 2013).

## References

- Nelms K, Keegan AD, Zamorano J, Ryan JJ & Paul WE (1999). The IL-4 receptor: signaling mechanisms and biologic functions. *Annu. Rev. Immunol.*, 17, 701-38. [🔗](#)
- Hershey GK (2003). IL-13 receptors and signaling pathways: an evolving web. *J. Allergy Clin. Immunol.*, 111, 677-90; quiz 691. [🔗](#)

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2016-09-02	Edited	Jupe S
2016-09-02	Reviewed	Leibovich SJ

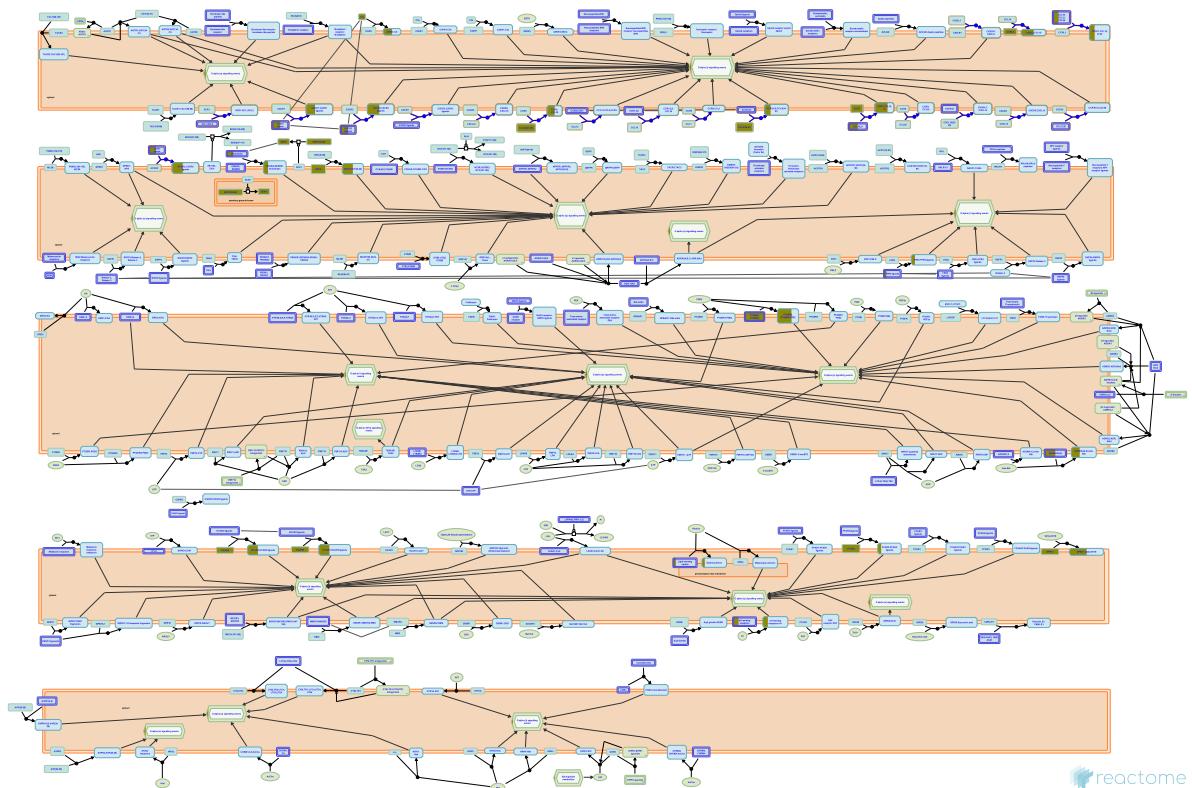
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## 5. Chemokine receptors bind chemokines (R-HSA-380108)



Chemokine receptors are cytokine receptors found on the surface of certain cells, which interact with a type of cytokine called a chemokine. Following interaction, these receptors trigger a flux of intracellular calcium which leads to chemotaxis. Chemokine receptors are divided into different families, CXC chemokine receptors, CC chemokine receptors, CX3C chemokine receptors and XC chemokine receptors that correspond to the 4 distinct subfamilies of chemokines they bind.

## References

- Murdoch C & Finn A (2000). Chemokine receptors and their role in inflammation and infectious diseases. *Blood*, 95, 3032-43. [🔗](#)
- Kim CH (2004). Chemokine-chemokine receptor network in immune cell trafficking. *Curr Drug Targets Immune Endocr Metabol Disord*, 4, 343-61. [🔗](#)
- Horuk R (2001). Chemokine receptors. *Cytokine Growth Factor Rev*, 12, 313-35. [🔗](#)

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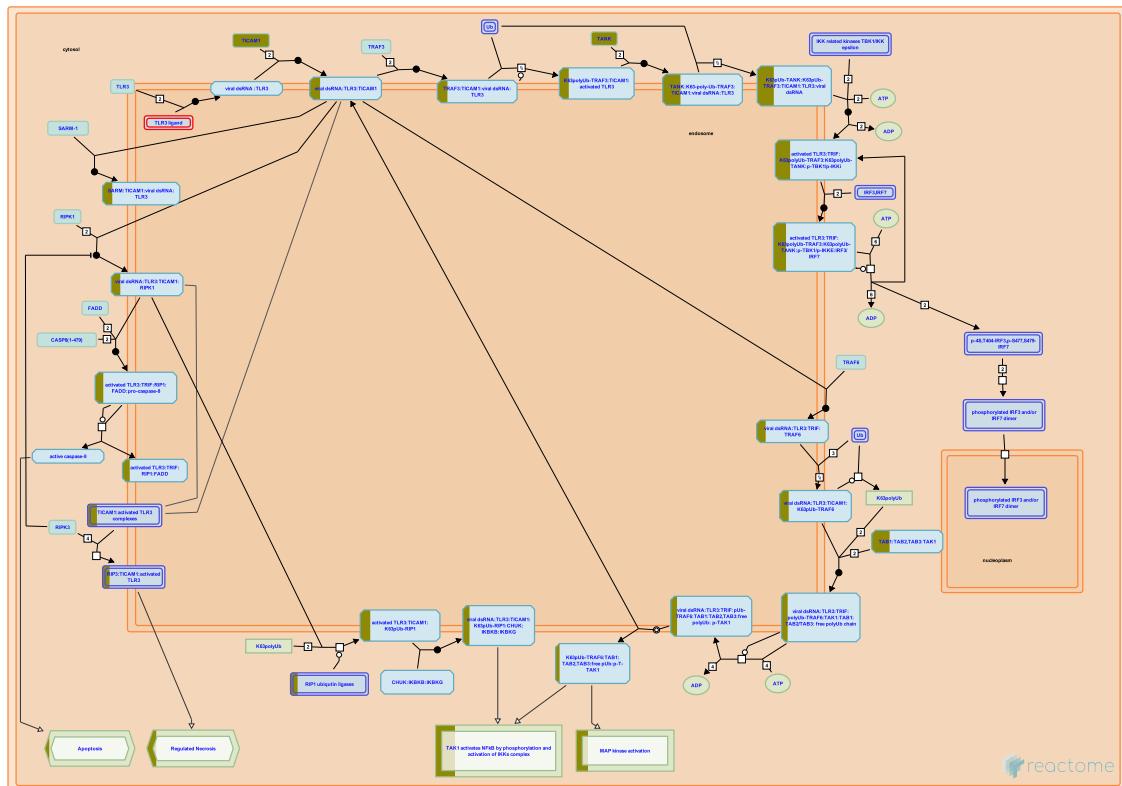
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## 6. Toll Like Receptor 3 (TLR3) Cascade (R-HSA-168164)



Toll-like receptor 3 (TLR3) as was shown for mammals is expressed on myeloid dendritic cells, respiratory epithelium, macrophages, and appears to play a central role in mediating the antiviral and inflammatory responses of the innate immunity in combating viral infections.

Mammalian TLR3 recognizes dsRNA, and that triggers the receptor to induce the activation of NF-κappaB 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.

## References

- Carpenter S & O'Neill LA (2009). Recent insights into the structure of Toll-like receptors and post-translational modifications of their associated signalling proteins. *Biochem J*, 422, 1-10. [View](#)
- Sen GC & Sarkar SN (2005). Transcriptional signaling by double-stranded RNA: role of TLR3. *Cytokine Growth Factor Rev*, 16, 1-14. [View](#)
- Vercammen E, Staal J & Beyaert R (2008). Sensing of viral infection and activation of innate immunity by toll-like receptor 3. *Clin Microbiol Rev*, 21, 13-25. [View](#)

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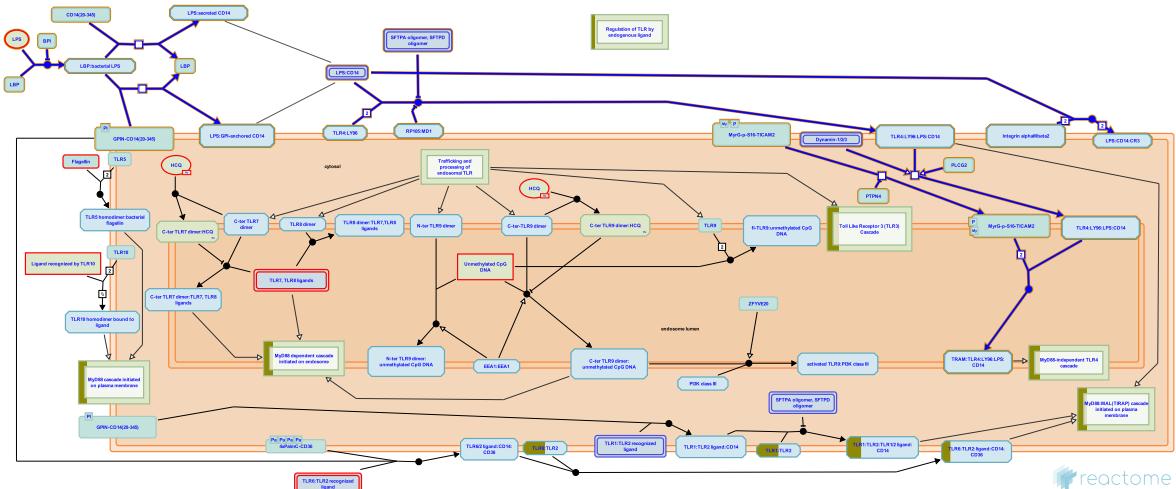
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2006-04-24	Reviewed	Gay NJ
2009-09-29	Revised	Shamovsky V

Date	Action	Author
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2020-11-24	Modified	Shorser S

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ENSG0000127666	Q8IUC6	ENSG0000134070	O43187	ENSG0000136560	Q92844
ENSG0000143479	P49137	ENSG0000168884	Q8NFZ5		

## 7. Toll Like Receptor 4 (TLR4) Cascade (R-HSA-166016)



Toll-like Receptor 4 is a microbe associated molecular pattern receptor well known for its 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].

## References

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

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

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

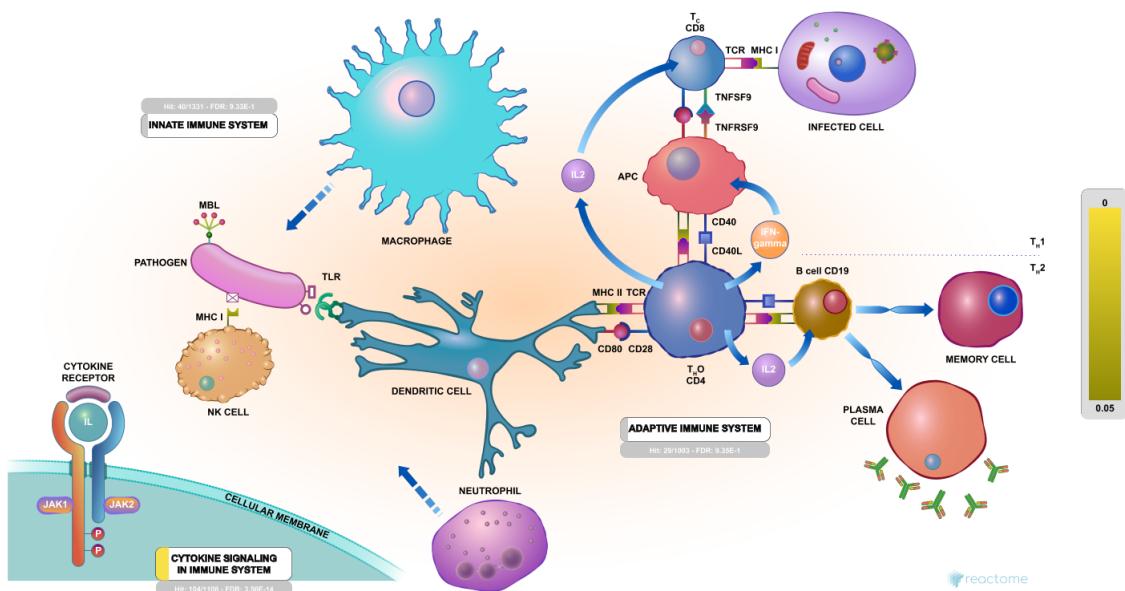
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2010-11-15	Edited	Shamovsky V
2010-11-30	Reviewed	Gillespie ME
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## 8. Immune System (R-HSA-168256)



Humans are exposed to millions of potential pathogens daily, through contact, ingestion, and inhalation. Our ability to avoid infection depends on the adaptive immune system and during the first critical hours and days of exposure to a new pathogen, our innate immune system.

## References

### Edit history

Date	Action	Author
2005-11-12	Created	Gillespie ME
2006-03-30	Authored	Luo F, Ouwehand WH, Gillespie ME, de Bono B
2006-04-19	Reviewed	Zwaginga JJ, D'Eustachio P, Gay NJ, Gale M Jr
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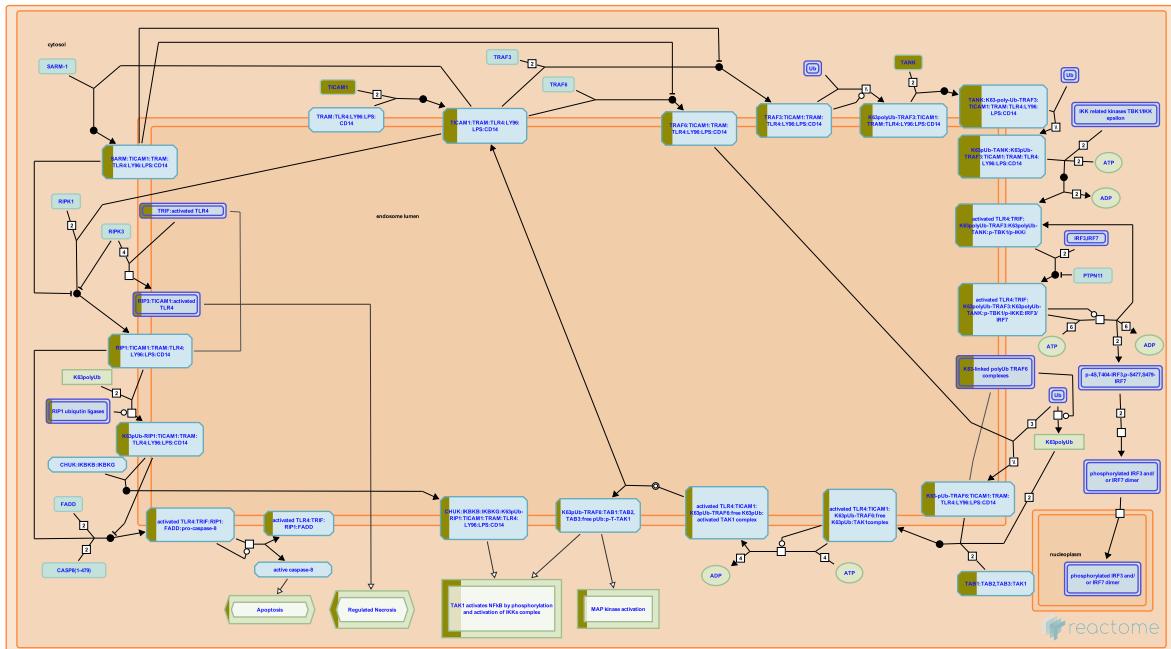
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## 9. MyD88-independent TLR4 cascade (R-HSA-166166)



**Cellular compartments:** cytosol.

MyD88-independent signaling pathway is shared by TLR3 and TLR4 cascades. TIR-domain-containing adapter-inducing interferon-beta (TRIF or TICAM1) is a key adapter molecule in transducing signals from TLR3 and TLR4 in a MyD88-independent manner (Yamamoto M et al. 2003a). TRIF is recruited to ligand-stimulated TLR3 or 4 complex via its TIR domain. TLR3 directly binds TRIF (Oshiumi H et al 2003). In contrast, TLR4-mediated signaling pathway requires two adapter molecules, TRAM (TRIF-related adapter molecule or TICAM2) and TRIF. TRAM(TICAM2) is thought to bridge between the activated TLR4 complex and TRIF (Yamamoto M et al. 2003b, Tanimura N et al. 2008, Kagan LC et al. 2008).

TRIF recruitment to TLR complex stimulates distinct pathways leading to production of type 1 interferons (IFNs), pro-inflammatory cytokines and induction of programmed cell death.

## References

Gangloff M & Gay NJ (2004). MD-2: the Toll 'gatekeeper' in endotoxin signalling. Trends Biochem Sci, 29, 294-300. [View](#)

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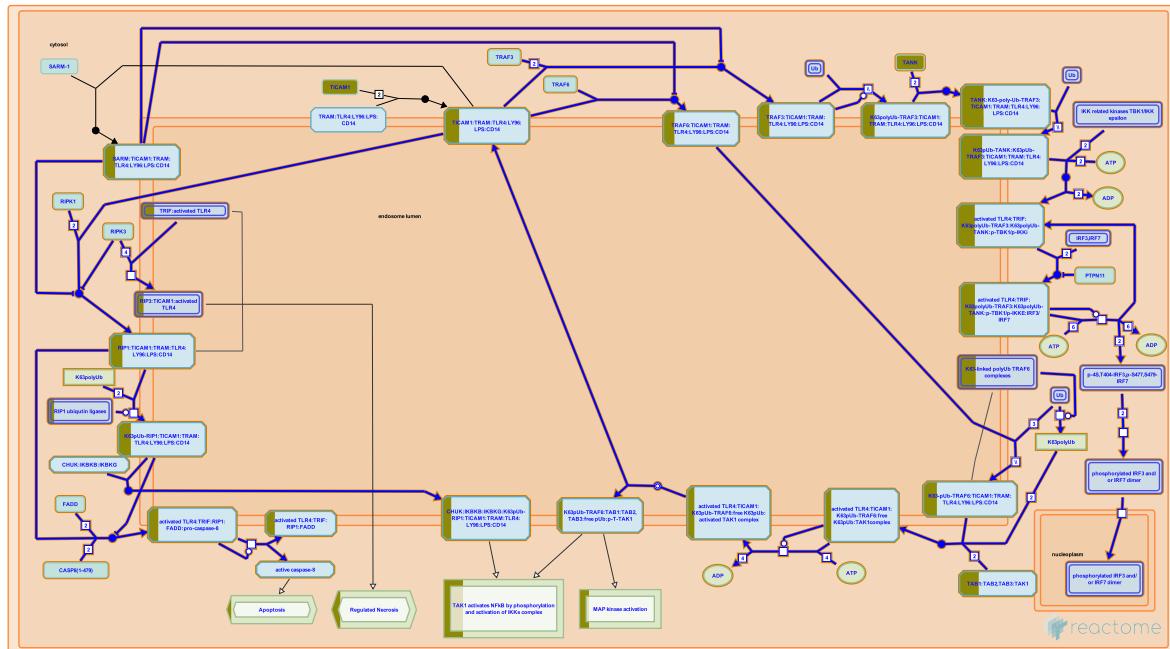
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2012-11-06	Edited	Shamovsky V
2012-11-13	Reviewed	Fitzgerald KA

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## 10. TRIF(TICAM1)-mediated TLR4 signaling (R-HSA-937061)



TRIF(TICAM1) was shown to induce IRF3/7 and NF $\kappa$ B activation and apoptosis through distinct intracellular signaling pathways [Han KJ et al 2004; Kaiser WJ and Offermann MK et al 2005]. TRIF consists of an N-terminal region (1-234), a TIR domain (235-500), and a C-terminal region (501-680).

The N-terminal region of TRIF harbors TRAF (TNF receptor associated factor) family proteins and forms complexes containing IRF-3 and/or NF $\kappa$ B -activating kinases. The C-terminal region of TRIF can recruit receptor-interacting protein-1 (RIP-1), and this event is followed by the activation of IKK complex.

## References

- Kaiser WJ & Offermann MK (2005). Apoptosis induced by the toll-like receptor adaptor TRIF is dependent on its receptor interacting protein homotypic interaction motif. *J Immunol*, 174, 4942-52. [\[PubMed\]](#)
- Han KJ, Su X, Xu LG, Bin LH, Zhang J & Shu HB (2004). Mechanisms of the TRIF-induced interferon-stimulated response element and NF- $\kappa$ B activation and apoptosis pathways. *J. Biol. Chem.*, 279, 15652-61. [\[PubMed\]](#)
- Yamamoto M, Sato S, Hemmi H, Hoshino K, Kaisho T, Sanjo H, ... Takeda K (2003). Role of adaptor TRIF in the MyD88-independent toll-like receptor signaling pathway. *Science*, 301, 640-3. [\[PubMed\]](#)

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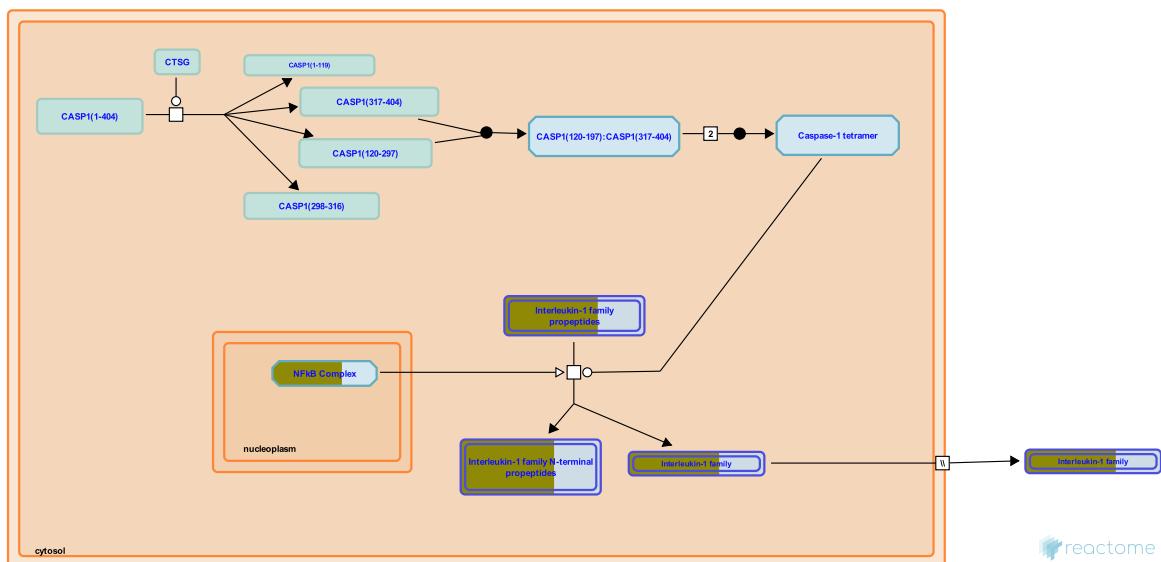
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## 11. Interleukin-1 processing (R-HSA-448706)



**Cellular compartments:** cytosol.

The IL-1 family of cytokines that interact with the Type 1 IL-1R include IL-1 (IL1A), IL-1 (IL1B) and the IL-1 receptor antagonist protein (IL1RAP). IL1RAP is synthesized with a signal peptide and secreted as a mature protein via the classical secretory pathway. IL1A and IL1B are synthesised as cytoplasmic precursors (pro-IL1A and pro-IL1B) in activated cells. They have no signal sequence, precluding secretion via the classical ER-Golgi route (Rubartelli et al. 1990). Processing of pro-IL1B to the active form requires caspase-1 (Thornberry et al. 1992), which is itself activated by a molecular scaffold termed the inflammasome (Martinon et al. 2002). Processing and release of IL1B are thought to be closely linked, because mature IL1B is only seen inside inflammatory cells just prior to release (Brough et al. 2003). It has been reported that in monocytes a fraction of cellular IL1B is released by the regulated secretion of late endosomes and early lysosomes, and that this may represent a cellular compartment where caspase-1 processing of pro-IL1B takes place (Andrei et al. 1999). Shedding of microvesicles from the plasma membrane has also been proposed as a mechanism of secretion (MacKenzie et al. 2001). These proposals supercede previous models in which non-specific release due to cell lysis and passage through a plasma membrane pore were considered. However, there is evidence in the literature that supports all of these mechanisms and there is still controversy over how IL1B exits from cells (Brough & Rothwell 2007). A calpain-like protease has been reported to be important for the processing of pro-IL1A, but much less is known about how IL1A is released from cells and what specific roles it plays in biology.

## References

Brough D & Rothwell NJ (2007). Caspase-1-dependent processing of pro-interleukin-1 $\beta$  is cytosolic and precedes cell death. *J Cell Sci*, 120, 772-81. [View](#)

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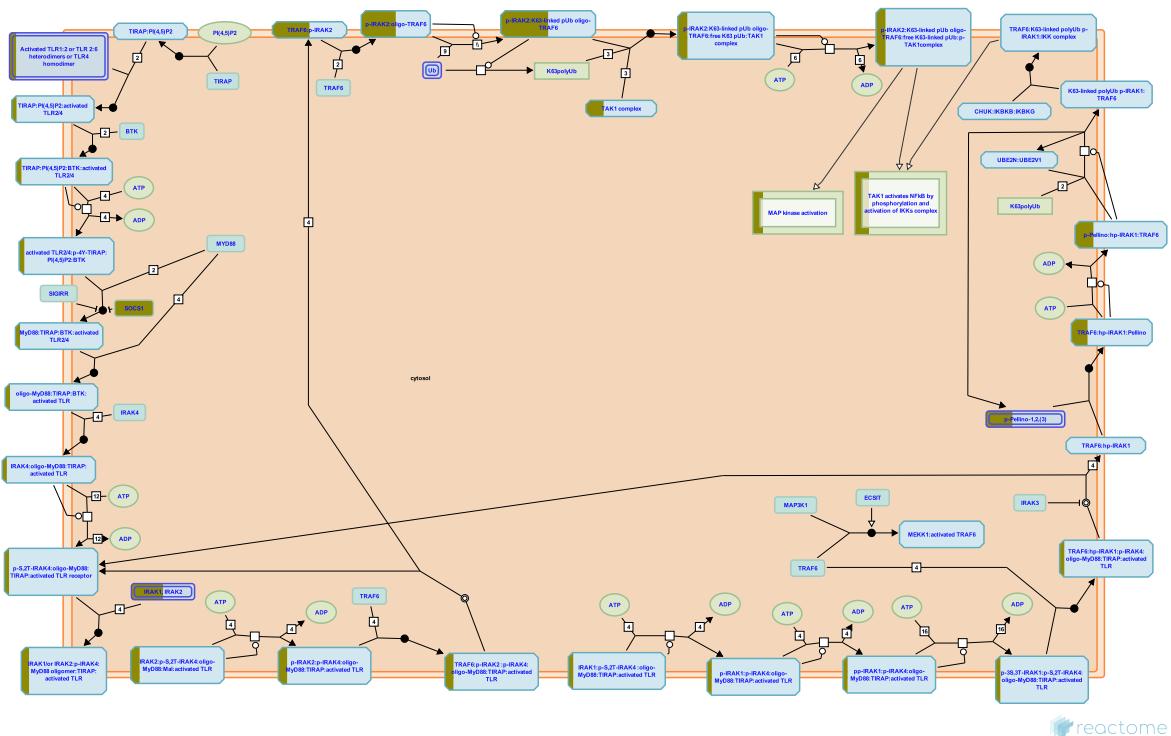
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2010-05-17	Authored	Ray KP
2010-08-06	Edited	Jupe S

Date	Action	Author
2010-09-06	Reviewed	Pinteaux E
2020-11-20	Modified	Shorser S

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## 12. MyD88:Mal(TIRAP) cascade initiated on plasma membrane (R-HSA-166058)



The first known downstream component of TLR4 and TLR2 signaling is the adaptor MyD88. Another adaptor MyD88-adaptor-like (Mal; also known as TIR-domain-containing adaptor protein or TIRAP) has also been described for TLR4 and TLR2 signaling. MyD88 comprises an N-terminal Death Domain (DD) and a C-terminal TIR, whereas Mal lacks the DD. The TIR homotypic interactions bring adapters into contact with the activated TLRs, whereas the DD modules recruit serine/threonine kinases such as interleukin-1-receptor-associated kinase (IRAK). Recruitment of these protein kinases is accompanied by phosphorylation, which in turn results in the interaction of IRAKs with TNF-receptor-associated factor 6 (TRAF6). The oligomerization of TRAF6 activates TAK1, a member of the MAP3-kinase family, and this leads to the activation of the I $\kappa$ B kinases. These kinases, in turn, phosphorylate I $\kappa$ B, leading to its proteolytic degradation and the translocation of NF- $\kappa$ B to the nucleus. Concomitantly, members of the activator protein-1 (AP-1) transcription factor family, Jun and Fos, are activated, and both AP-1 transcription factors and NF- $\kappa$ B are required for cytokine production, which in turn produces downstream inflammatory effects.

## References

Gangloff M & Gay NJ (2004). MD-2: the Toll 'gatekeeper' in endotoxin signalling. Trends Biochem Sci, 29, 294-300. [View](#)

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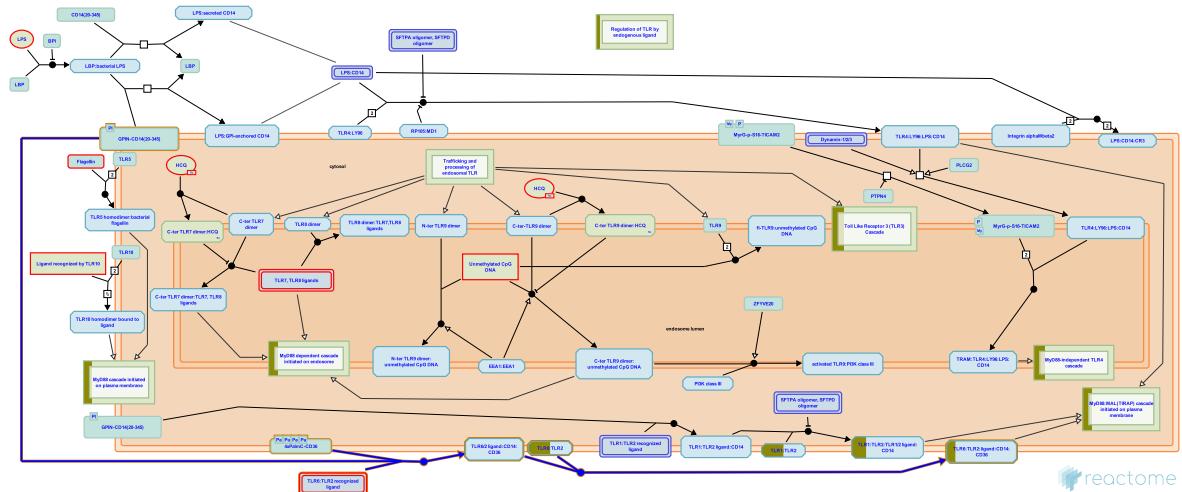
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2006-04-24	Reviewed	Gay NJ
2010-11-30	Reviewed	Gillespie ME
2012-11-02	Revised	Shamovsky V

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2012-11-16	Reviewed	Napetschnig J
2020-11-24	Modified	Shorser S

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ENSG00000143479	P49137	ENSG00000168884	Q8NFZ5	ENSG00000185338	O15524
ENSG00000197329	Q96FA3				

## 13. Toll Like Receptor TLR6:TLR2 Cascade (R-HSA-168188)



TLR2 and TLR4 recognize different bacterial cell wall components. While TLR4 is trained onto Gram-negative lipopolysaccharide components, TLR2 - in combination with TLR6 - plays a major role in recognizing peptidoglycan wall products from Gram-positive bacteria, as well as Mycobacterial diacylated lipopeptides. In particular, TLR6 appears to participate in discriminating the subtle differences between dipalmitoyl and tripalmitoyl cysteinyl residues (Okusawa et al. 2004).

## References

Okusawa T, Fujita M, Nakamura J, Into T, Yasuda M, Yoshimura A, ... Shibata K (2004). Relationship between structures and biological activities of mycoplasmal diacylated lipopeptides and their recognition by toll-like receptors 2 and 6. *Infect Immun*, 72, 1657-65. [View](#)

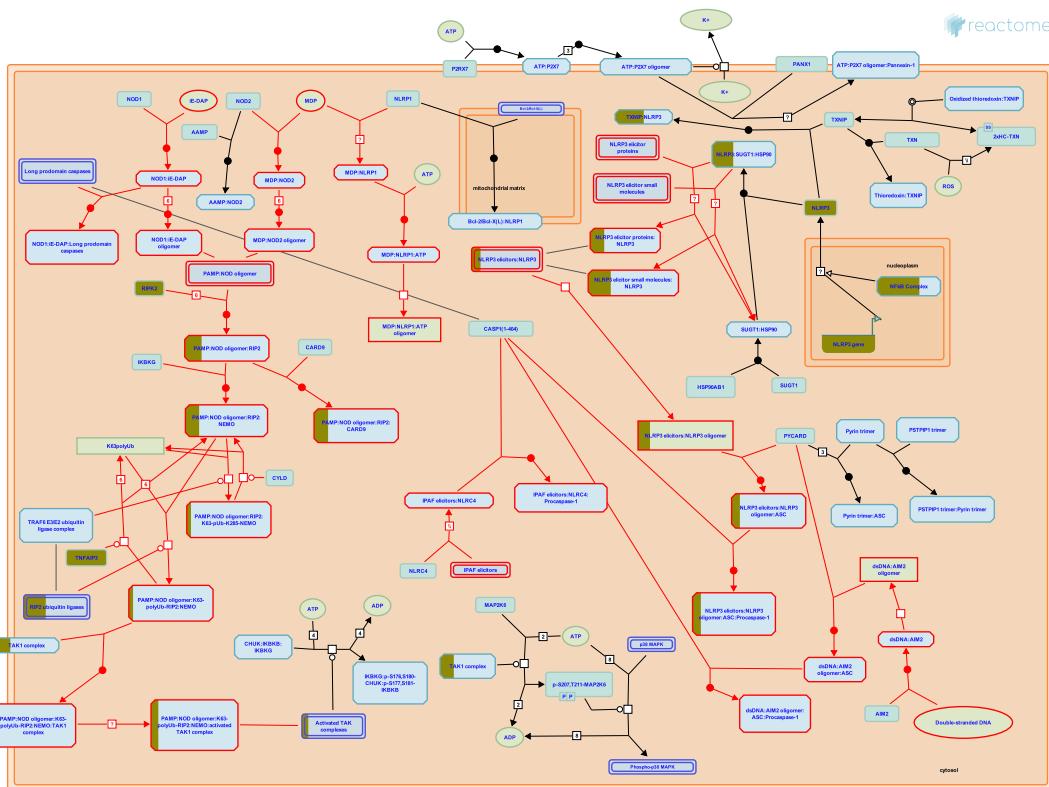
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2006-07-04	Reviewed	D'Eustachio P
2012-11-02	Revised	Shamovsky V
2012-11-20	Edited	Shamovsky V
2020-11-24	Modified	Shorser S

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ENSG00000197329	Q96FA3				

## 14. Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways (R-HSA-168643)



**Cellular compartments:** cytosol.

The innate immune system is the first line of defense against invading microorganisms, a broad specificity response characterized by the recruitment and activation of phagocytes and the release of anti-bacterial peptides. The receptors involved recognize conserved molecules present in microbes called pathogen-associated molecular patterns (PAMPs), and/or molecules that are produced as a result of tissue injury, the damage associated molecular pattern molecules (DAMPs). PAMPs are essential to the pathogen and therefore unlikely to vary. Examples are lipopolysaccharide (LPS), peptidoglycans (PGNs) and viral RNA. DAMPs include intracellular proteins, such as heat-shock proteins and extracellular matrix proteins released by tissue injury, such as hyaluronan fragments. Non-protein DAMPs include ATP, uric acid, heparin sulfate and dsDNA. The receptors for these factors are referred to collectively as pathogen- or pattern-recognition receptors (PRRs). The best studied of these are the membrane-associated Toll-like receptor family. Less well studied but more numerous are the intracellular nucleotide-binding domain, leucine rich repeat containing receptors (NLRs) also called nucleotide binding oligomerization domain (NOD)-like receptors, a family with over 20 members in humans and over 30 in mice. These recognise PAMPs/DAMPs from phagocytosed microorganisms or from intracellular infections (Kobayashi et al. 2003, Proell et al. 2008, Wilmanski et al. 2008). Some NLRs are involved in process unrelated to pathogen detection such as tissue homeostasis, apoptosis, graft-versus-host disease and early development (Kufer & Sansonetti 2011).

Structurally NLRs can be subdivided into the caspase-recruitment domain (CARD)-containing NLRCs (NODs) and the pyrin domain (PYD)-containing NLRPs (NALPs), plus outliers including ice protease (caspase-1) activating factor (IPAF) (Martinon & Tschoop, 2005). In practical terms, NLRs can be divided into the relatively well characterized NOD1/2 which signal via RIP2 primarily to NFκB, and the remainder, some of which participate in macromolecular structures called Inflammasomes that activate caspases. Mutations in several members of the NLR protein family have been linked to inflammatory diseases, suggesting these molecules play important roles in maintaining host-pathogen interactions and inflammatory responses.

Most NLRs have a tripartite structure consisting of a variable amino-terminal domain, a central nucleotide-binding oligomerization domain (NOD or NACHT) that is believed to mediate the formation of self oligomers, and a carboxy-terminal leucine-rich repeat (LRR) that detects PAMPs/DAMPs. In most cases the amino-terminal domain includes protein-interaction modules, such as CARD or PYD, some harbour baculovirus inhibitor repeat (BIR) or other domains. For most characterised NLRs these domains have been attributed to downstream signaling

Under resting conditions, NLRs are thought to be present in an autorepressed form, with the LRR folded back onto the NACHT domain preventing oligomerization. Accessory proteins may help maintain the inactive state. PAMP/DAMP exposure is thought to triggers conformational changes that expose the NACHT domain enabling oligomerization and recruitment of effectors, though it should be noted that due to the lack of availability of structural data, the mechanistic details of NLR activation remain largely elusive.

New terminology for NOD-like receptors was adopted by the Human Genome Organization (HUGO) in 2008 to standardize the nomenclature of NLRs. The acronym NLR, once standing for NOD-like receptor, now is an abbreviation of 'nucleotide-binding domain, leucine-rich repeat containing' protein. The term NOD-like receptor is officially outdated and replaced by NLRC where the C refers to the CARD domain. However the official gene symbols for NOD1 and NOD2 still contain NOD and this general term is still widely used.

## References

Chen G, Shaw MH, Kim YG & Nunez G (2009). NOD-like receptors: role in innate immunity and inflammatory disease. *Annu Rev Pathol*, 4, 365-98. [🔗](#)

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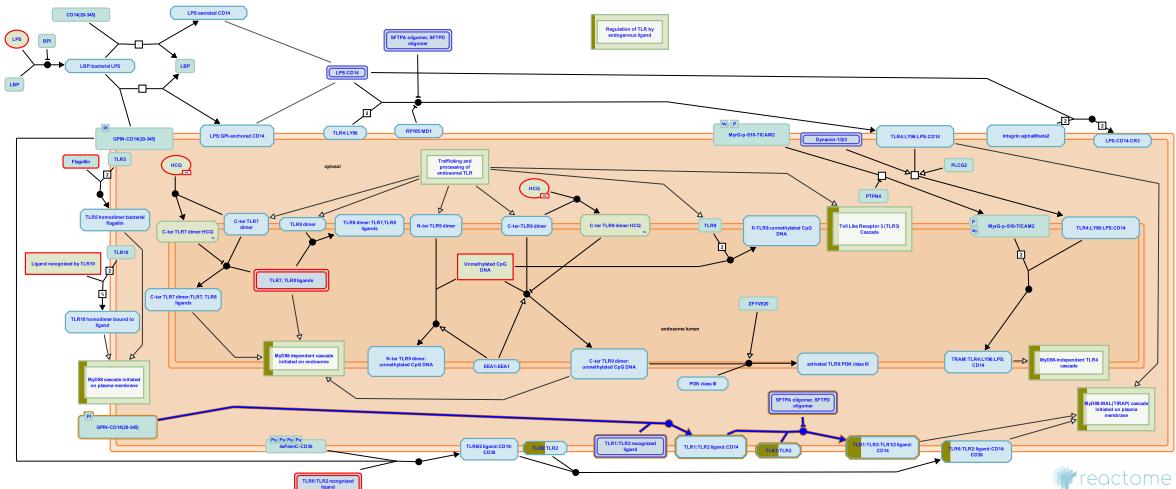
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2011-04-28	Edited	Jupe S
2011-04-28	Reviewed	Kufer TA
2011-06-06	Reviewed	Rittinger K, Wong E
2020-11-20	Modified	Shorser S

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## 15. Toll Like Receptor TLR1:TLR2 Cascade (R-HSA-168179)



TLR1 is expressed by monocytes. TLR1 and TLR2 cotranslationally form heterodimeric complexes on the cell surface and in the cytosol. The TLR2:TLR1 complex recognizes Neisserial PorB and Mycobacterial triacylated lipoproteins and peptides, amongst others, triggering up-regulation of nuclear factor- $\kappa$ B production and apoptotic cascades. Such cooperation between TLR1 and TLR2 on the cell surface of normal human peripheral blood mononuclear cells, for instance, leads to the activation of pro-inflammatory cytokine secretion (Sandor et al. 2003).

## References

Sandor F, Latz E, Re F, Mandell L, Repik G, Golenbock DT, ... Finberg RW (2003). Importance of extra- and intracellular domains of TLR1 and TLR2 in NF $\kappa$ B signaling. *J Cell Biol*, 162, 1099-110. [View](#)

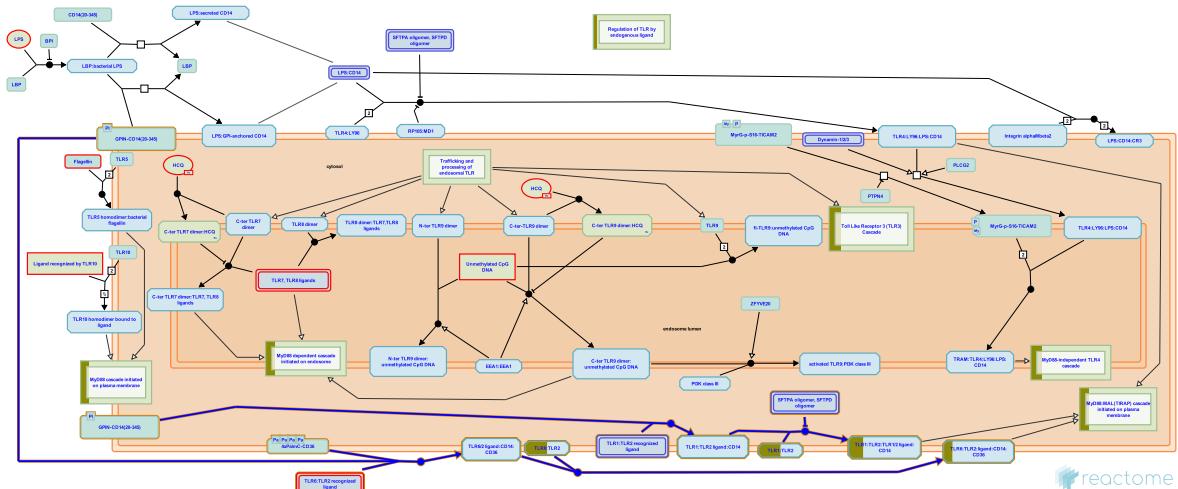
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2006-07-04	Reviewed	D'Eustachio P
2012-11-02	Revised	Shamovsky V
2012-11-06	Edited	Shamovsky V
2020-11-24	Modified	Shorser S

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ENSG0000143479	P49137	ENSG0000168884	Q8NFZ5	ENSG0000185338	O15524
ENSG0000197329	Q96FA3				

## 16. Toll Like Receptor 2 (TLR2) Cascade (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.

## References

Muzio M, Bosisio D, Polentarutti N, D'amico G, Stoppacciaro A, Mancinelli R, ... Mantovani A (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. [View](#)

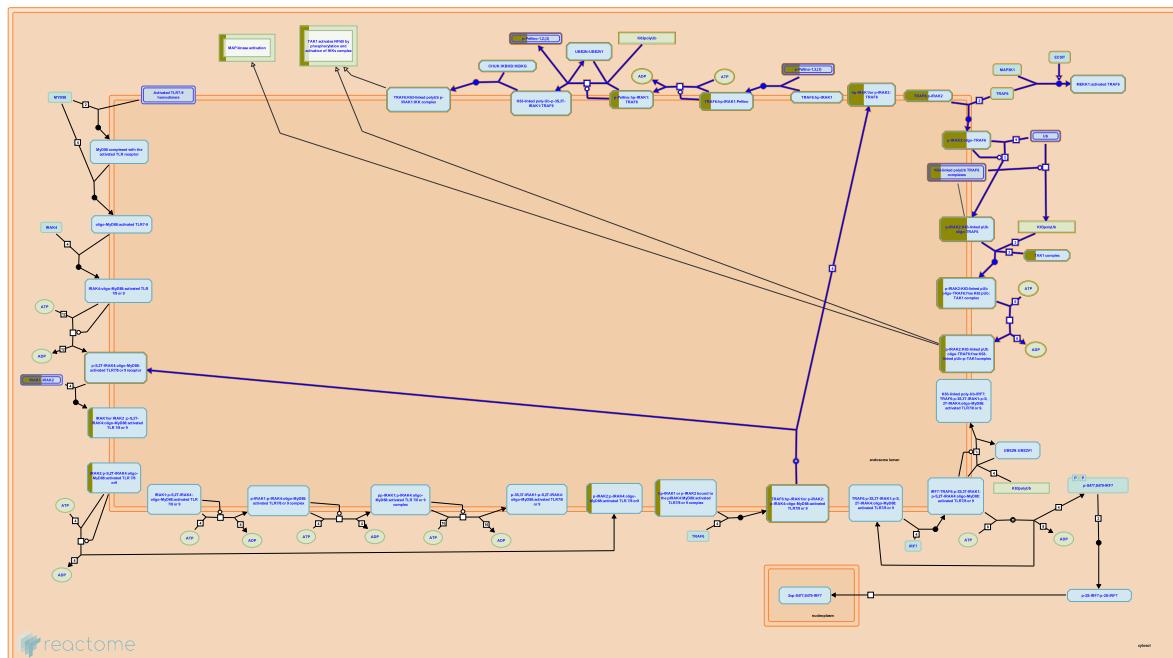
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2010-08-25	Revised	Shamovsky V
2010-11-17	Edited	Shamovsky V
2020-11-20	Modified	Shorser S

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ENSG00000197329	Q96FA3				

## 17. TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation (R-HSA-975138)



**Cellular compartments:** cytosol, endosome membrane, nucleoplasm.

TRAF6 mediates NFkB activation via canonical phosphorylation of IKK complex by TAK1. TRAF6 and TAK1 also regulate MAPK cascades leading to the activation of AP-1.

### References

Pauls E, Shapiro N, Peggie M, Young ER, Sorcek RJ, Tan L, ... Cohen P (2012). Essential role for IKK? in production of type 1 interferons by plasmacytoid dendritic cells. *J. Biol. Chem.*, 287, 19216-28. [\[CrossRef\]](#)

Fraczek J, Kim TW, Xiao H, Yao J, Wen Q, Li Y, ... Li X (2008). The kinase activity of IL-1 receptor-associated kinase 4 is required for interleukin-1 receptor/toll-like receptor-induced TAK1-dependent NFκB activation. *J. Biol. Chem.*, 283, 31697-705. [\[CrossRef\]](#)

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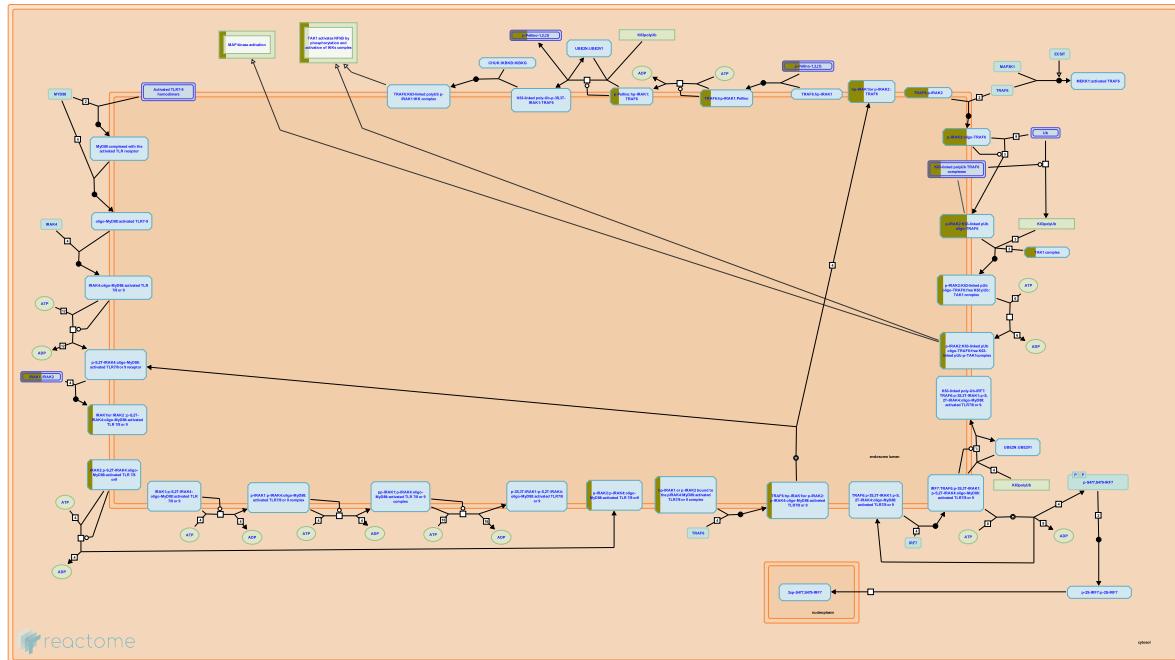
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2010-10-29	Reviewed	Gillespie ME
2010-11-15	Edited	Shamovsky V
2020-11-24	Modified	Shorser S

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## 18. MyD88 dependent cascade initiated on endosome (R-HSA-975155)



**Cellular compartments:** cytosol, endosome membrane, nucleoplasm.

Upon binding of their ligands, TLR7/8 and TLR9 recruit a cytoplasmic adaptor MyD88 and IRAKs, downstream of which the signaling pathways are divided to induce either inflammatory cytokines or type I IFNs.

### References

- Cherfils-Vicini J, Platonova S, Gillard M, Laurans L, Validire P, Caliandro R, ... Cremer I (2010). Triggering of TLR7 and TLR8 expressed by human lung cancer cells induces cell survival and chemoresistance. *J. Clin. Invest.*, 120, 1285-97. [🔗](#)
- Gangloff M & Gay NJ (2004). MD-2: the Toll 'gatekeeper' in endotoxin signalling. *Trends Biochem Sci*, 29, 294-300. [🔗](#)
- Hanten JA, Vasilakos JP, Riter CL, Neys L, Lipson KE, Alkan SS & Birmachu W (2008). Comparison of human B cell activation by TLR7 and TLR9 agonists. *BMC Immunol.*, 9, 39. [🔗](#)

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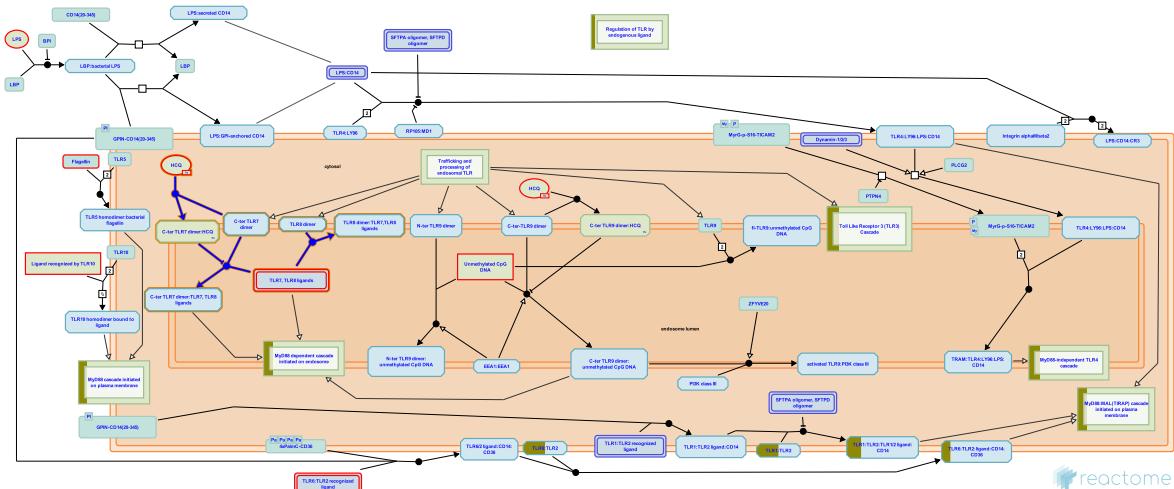
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2020-11-24	Modified	Shorser S

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## 19. Toll Like Receptor 7/8 (TLR7/8) Cascade (R-HSA-168181)



**Cellular compartments:** cytosol, endosome membrane, nucleoplasm.

RNA can serve as a danger signal, both in its double-stranded form (that is associated with viral infection), as well as single-stranded RNA (ssRNA). Specifically, guanosine (G)- and uridine (U)-rich ssRNA oligonucleotides derived from human immunodeficiency virus-1 (HIV-1), for example, stimulate dendritic cells (DC) and macrophages to secrete interferon-alpha and proinflammatory, as well as regulatory, cytokine (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 (SARS-CoV) ssRNAs had powerful immunostimulatory activities in mononuclear phagocytes to induce considerable level of pro-inflammatory cytokine TNF- $\alpha$ , IL-6 and IL-12 release via the TLR7 and TLR8 (Li Y et al. 2013). Moreover, SARS-CoV ssRNA was able to cause acute lung injury in mice with a high mortality rate in vivo experiment. It suggests that SARS-CoV specific GU-rich ssRNA plays a very important role in the cytokine storm associated with a dysregulation of the innate immunity (Li Y et al. 2013). Separate studies showed that 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 independently through TLR7 and 8 (Hemmi H et al. 2002; Jurk M et al. 2002; Diebold SS et al. 2004). TLR7 and TLR8 are endosomal receptors that sense viral ssRNA in the phagocytic lumen. Their activation leads to NF- $\kappa$ B-, AP1- and IFN regulatory factor (IRF)-mediated production of type I IFNs (IFN- $\beta$ ) and pro-inflammatory cytokines.

## References

Heil F, Hemmi H, Hochrein H, Ampenberger F, Kirschning C, Akira S, ... Bauer S (2004). Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. *Science*, 303, 1526-9. [\[CrossRef\]](#)

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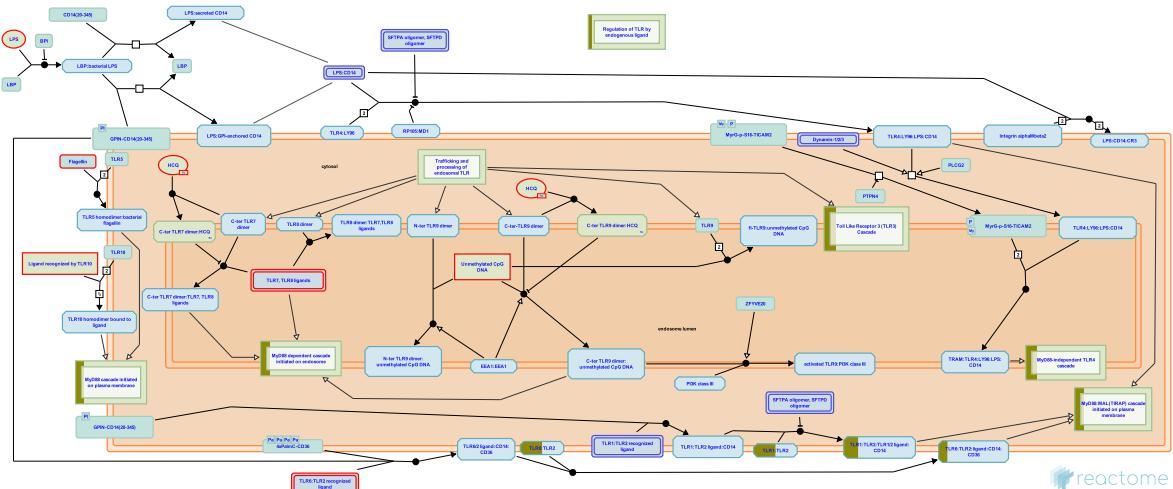
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2006-10-31	Reviewed	Gale M Jr
2010-02-22	Revised	Shamovsky V
2010-10-29	Reviewed	Gillespie ME

Date	Action	Author
2010-11-15	Edited	Shamovsky V
2020-11-24	Modified	Shorser S

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ENSG0000143479	P49137	ENSG0000168884	Q8NFZ5	ENSG0000197329	Q96FA3

## 20. Toll-like Receptor Cascades (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.

## References

- Takeda K & Akira S (2004). TIR domains, which are conserved among all TLRs. Recent accumulating. *Semin Immunol*, 16, 3-9. [🔗](#)
- Akira S (2003). Toll-like receptor signaling. *J Biol Chem*, 278, 38105-8. [🔗](#)
- 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. [🔗](#)
- Heine H & Ulmer AJ (2005). Recognition of bacterial products by toll-like receptors. *Chem Immunol Allergy*, 86, 99-119. [🔗](#)

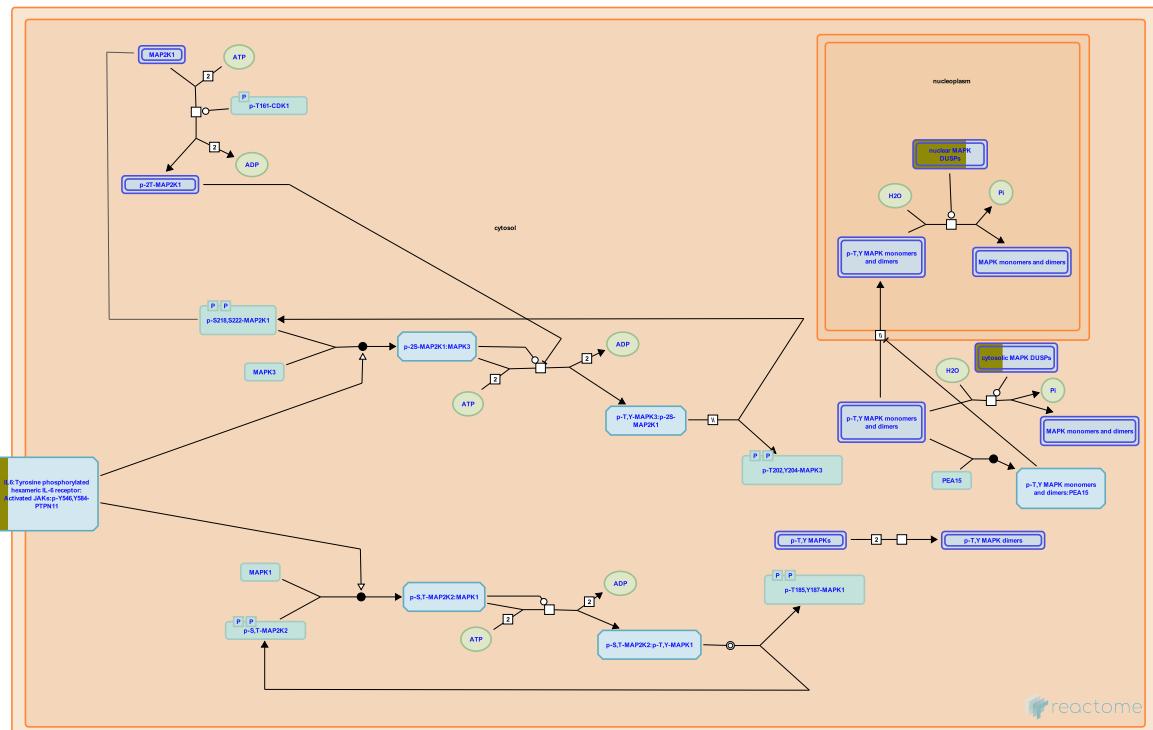
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2020-11-20	Modified	Shorser S

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## 21. RAF-independent MAPK1/3 activation (R-HSA-112409)



**Cellular compartments:** cytosol, nucleoplasm.

Depending upon the stimulus and cell type mitogen-activated protein kinases (MAPK) signaling pathway can transmit signals to regulate many different biological processes by virtue of their ability to target multiple effector proteins (Kyriakis JM & Avruch J 2012; Yoon and Seger 2006; Shaul YD & Seger R 2007; Arthur JS & Ley SC 2013). In particular, the extracellular signal-regulated kinases MAPK3(ERK1) and MAPK1 (ERK2) are involved in diverse cellular processes such as proliferation, differentiation, regulation of inflammatory responses, cytoskeletal remodeling, cell motility and invasion through the increase of matrix metalloproteinase production (Viala E & Pouyssegur J 2004; Hsu MC et al. 2006; Dawson CW et al. 2008; Kuriakose T et al. 2014). The canonical RAF:MAP2K:MAPK1/3 cascade is stimulated by various extracellular stimuli including hormones, cytokines, growth factors, heat shock and UV irradiation triggering the GEF-mediated activation of RAS at the plasma membrane and leading to the activation of the RAF MAP3 kinases. However, many physiological and pathological stimuli have been found to activate MAPK1/3 independently of RAF and RAS (Dawson CW et al. 2008; Wang J et al. 2009; Kuriakose T et al. 2014). For example, AMP-activated protein kinase (AMPK), but not RAF1, was reported to regulate MAP2K1/2 and MAPK1/3 (MEK and ERK) activation in rat hepatoma H4IIE and human erythroleukemia K562 cells in response to autophagy stimuli (Wang J et al. 2009). Tumor progression locus 2 (TPL2, also known as MAP3K8 and COT) is another MAP3 kinase which promotes MAPK1/3 (ERK)-regulated immune responses downstream of toll-like receptors (TLR), TNF receptor and IL1beta signaling pathways (Gantke T et al. 2011).

In response to stimuli the cell surface receptors transmit signals inducing MAP3 kinases, e.g., TPL2, MEKK1, which in turn phosphorylate MAP2Ks (MEK1/2). MAP2K then phosphorylate and activate the MAPK1/3 (ERK1 and ERK2 MAPKs). Activated MAPK1/3 phosphorylate and regulate the activities of an ever growing pool of substrates that are estimated to comprise over 160 proteins (Yoon and Seger 2006). The majority of ERK substrates are nuclear proteins, but others are found in the cytoplasm and other organelles. Activated MAPK1/3 can translocate to the nucleus, where they phosphorylate and regulate various transcription factors, such as Ets family transcription factors (e.g., ELK1), ultimately leading to changes in gene expression (Zuber J et al. 2000).

## References

- Arthur JS & Ley SC (2013). Mitogen-activated protein kinases in innate immunity. *Nat. Rev. Immunol.*, 13, 679-92. [🔗](#)
- Roskoski R Jr (2012). ERK1/2 MAP kinases: structure, function, and regulation. *Pharmacol. Res.*, 66, 105-43. [🔗](#)
- Gantke T, Sriskantharajah S & Ley SC (2011). Regulation and function of TPL-2, an I?B kinase-regulated MAP kinase kinase kinase. *Cell Res.*, 21, 131-45. [🔗](#)

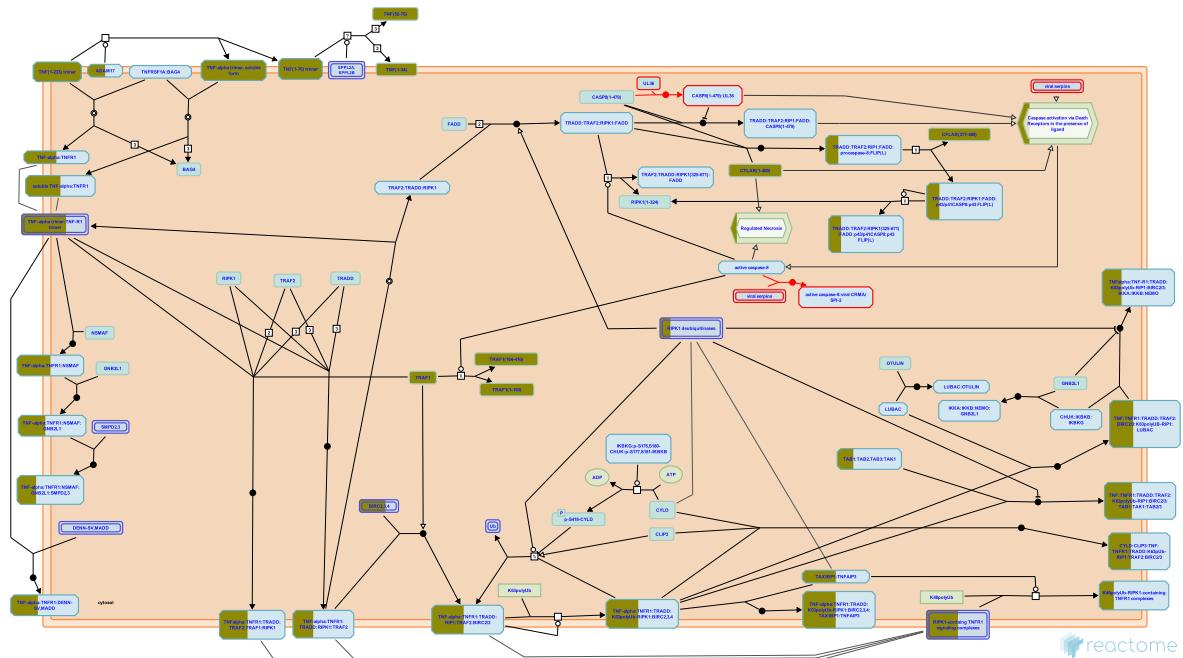
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Date	Action	Author
2004-04-29	Created	Charalambous M
2007-11-08	Reviewed	Greene LA
2020-11-24	Modified	Shorser S

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ENSG00000111266	Q9BY84	ENSG00000120129	P28562	ENSG00000136244	P05231
ENSG00000138166	Q16690	ENSG00000158050	Q05923	ENSG00000184545	Q13202

## 22. TNF signaling (R-HSA-75893)



The inflammatory cytokine tumor necrosis factor alpha (TNF-alpha) is expressed in immune and nonimmune cell types including macrophages, T cells, mast cells, granulocytes, natural killer (NK) cells, fibroblasts, neurons, keratinocytes and smooth muscle cells as a response to tissue injury or upon immune responses to pathogenic stimuli (Köck A. et al. 1990; Dubravec DB et al. 1990; Walsh LJ et al. 1991; te Velde AA et al. 1990; Imaizumi T et al. 2000). TNF-alpha interacts with two receptors, namely TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2). Activation of TNFR1 can trigger multiple signal transduction pathways inducing inflammation, proliferation, survival or cell death (Ward C et al. 1999; Micheau O and Tschoop J 2003; Widera D et al. 2006). Whether a TNF-alpha-stimulated cell will survive or die is dependent on autocrine/paracrine signals, and on the cellular context.

TNF binding to TNFR1 results initially in the formation of complex I that consists of TNFR1, TRADD (TNFR1-associated death domain), TRAF2 (TNF receptor associated factor-2), RIPK1 (receptor-interacting serin/threonine protein kinase 1), and E3 ubiquitin ligases BIRC2,BIRC3 (cIAP1/2,cellular inhibitor of apoptosis) and LUBAC (Micheau O and Tschoopp J 2003). The conjugation of ubiquitin chains by BIRC2/3 and LUBAC (composed of HOIP, HOIL-1 and SHARPIN ) to RIPK1 allows further recruitment and activation of the TAK1 (also known as mitogen-activated protein kinase kinase kinase 7 (MAP3K7)) complex and IB kinase (IKK) complex. TAK1 and IKK phosphorylate RIPK1 to limit its cytotoxic activity and activate both nuclear factor kappaB and mitogenactivated protein (MAP) kinase signaling pathways promoting cell survival by induction of anti-apoptotic proteins such as BIRC, cellular FLICE (FADD-like IL-1-converting enzyme)-like inhibitory protein (cFLIP) and secretion of pro-inflammatory cytokines (TNF and IL-6). When the survival pathway is inhibited, the TRADD:TRAF2:RIPK1 detaches from the membrane-bound TNFR1 signaling complex and recruits Fas-associated death domain-containing protein (FADD) and procaspase-8 (also known as complex II). Once recruited to FADD, multiple procaspase-8 molecules interact via their tandem death-effector domains( DED), thereby facilitating both proximity-induced dimerization and proteolytic cleavage of procaspase-8, which are required for initiation of apoptotic cell death (Hughes MA et al. 2009; Oberst A et al. 2010). When caspase activity is inhibited under certain pathophysiological conditions (e.g. caspase-8 inhibitory proteins such as CrmA and VICA after infection with cowpox virus or CMV) or by pharmacological agents, deubiquitinated RIPK1 is physically and functionally engaged by its homolog RIPK3 leading to formation of the necrosome, a necroptosis-inducing complex consisting of RIPK1 and RIPK3 (Tewari M & Dixit VM 1995; Fliss PM & Brune W 2012; Sawai H 2013; Moquin DM et al. 2013; Kalai M et al. 2002; Cho YS et al. 2009, He S et al. 2009, Zhang DW et al., 2009). Within the complex II procaspase-8 can also form heterodimers with cFLIP isoforms, FLIP long (L) and FLIP short (S), which are encoded by the NFkappaB target gene CFLAR (Irmler M et al. 1997; Boatright KM et al. 2004; Yu JW et al. 2009; Pop C et al. 2011). FLIP(S) appears to act purely as an antagonist of caspase-8 activity blocking apoptotic but promoting necroptotic cell death (Feoktistova et al. 2011). The regulatory function of FLIP(L) has been found to differ depending on its expression levels. FLIP(L) was shown to inhibit death receptor (DR)-mediated apoptosis only when expressed at high levels, while low cell levels of FLIP(L) enhanced DR signaling to apoptosis (Boatright KM et al. 2004; Okano H et al. 2003; Yerbes R et al. 2011; Yu JW et al. 2009; Hughes MA et al. 2016). In addition, caspase-8:FLIP(L) heterodimer activity within the TRADD:TRAF2:RIPK1:FADD:CASP8:FLIP(L) complex allowed cleavage of RIPK1 to cause the dissociation of the TRADD:TRAF2:RIP1:FADD:CASP8, thereby inhibiting RIPK1-mediated necroptosis (Feoktistova et al. 2011, 2012). TNF-alpha can also activate sphingomyelinase (SMASE, such as SMPD2,3) proteins to catalyze hydrolysis of sphingomyeline into ceramide (Adam D et al.1996; Adam-Klages S et al. 1998; Ségui B et al. 2001). Activation of neutral SMPD2,3 leads to an accumulation of ceramide at the cell surface and has proinflammatory effects. However, TNF can also activate the pro-apoptotic acidic SMASE via caspase-8 mediated activation of caspase-7 which in turn proteolytically cleaves and activates the 72kDa pro-A-SMase form (Edelmann B et al. 2011). Ceramide induces anti-proliferative and pro-apoptotic responses. Further, ceramide can be converted by ceramidase into sphingosine, which in turn is phosphorylated by sphingosine kinase into sphingosine-1-phosphate (S1P). S1P exerts the opposite biological effects to ceramide by activating cytoprotective signaling to promote cell growth counteracting the apoptotic stimuli (Cuvillier O et al. 1996). Thus, TNF-alpha-induced TNFR1 activation leads to divergent intracellular signaling networks with extensive cross-talk between the pro-apoptotic/necroptotic pathway, and the other NFkappaB, and MAPK pathways providing highly specific cell responses initiated by various types of stimuli.

## References

Chen G & Goeddel DV (2002). TNF-R1 signaling: a beautiful pathway. Science, 296, 1634-5. [🔗](#)

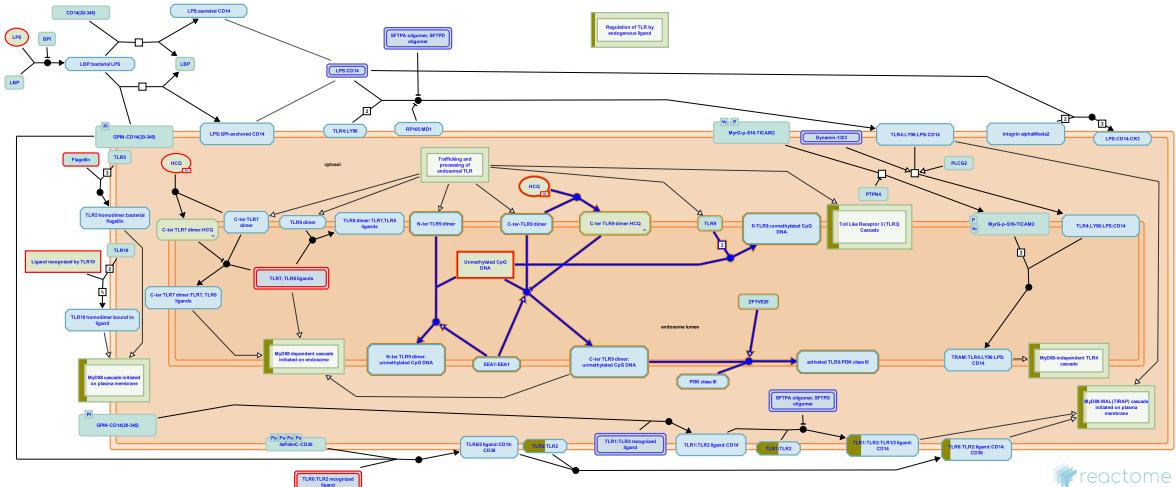
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2004-01-28	Created	Tschopp J
2004-08-25	Authored	Gillespie ME
2013-05-22	Reviewed	Pop C, Salvesen GS
2013-05-28	Revised	Shamovsky V
2015-05-12	Edited	Shamovsky V
2015-08-25	Reviewed	Wajant H
2020-11-24	Modified	Shorser S

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ENSG00000151694	P78536	ENSG00000232810	P01375		

## 23. Toll Like Receptor 9 (TLR9) Cascade (R-HSA-168138)



**Cellular compartments:** cytosol, endosome membrane, nucleoplasm.

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.

## References

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

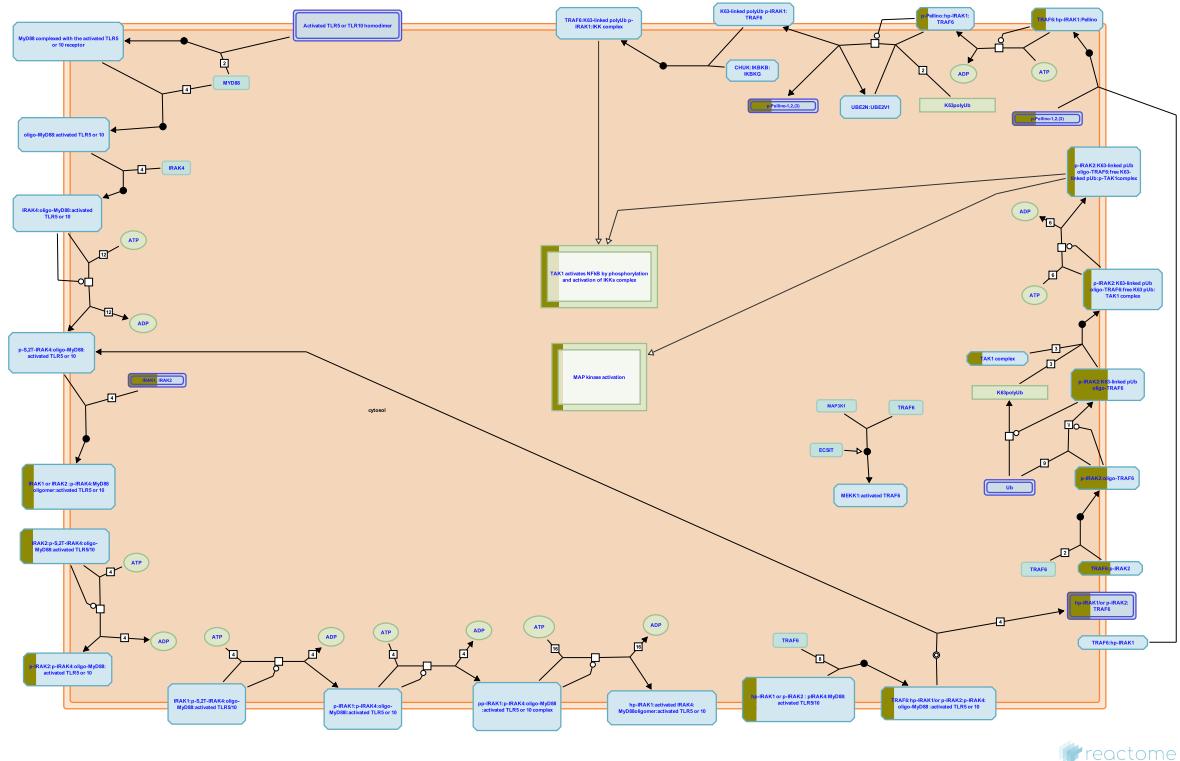
## Edit history

Date	Action	Author
2005-11-10	Authored	Luo F
2005-11-10	Created	Gillespie ME
2006-10-31	Reviewed	Gale M Jr
2010-09-22	Revised	Shamovsky V
2010-10-29	Reviewed	Gillespie ME
2010-11-15	Edited	Shamovsky V
2020-11-24	Modified	Shorser S

## Entities found in this pathway (12)

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ENSG0000109320	P19838	ENSG0000127666	Q8IUC6	ENSG0000134070	O43187
ENSG0000143479	P49137	ENSG0000168884	Q8NFZ5	ENSG0000197329	Q96FA3

## 24. MyD88 cascade initiated on plasma membrane (R-HSA-975871)



Mammalian myeloid differentiation factor 88 (MyD88) is Toll/interleukin (IL)-1 (TIR)-domain containing adapter protein which plays crucial role in TLR signaling. All TLRs, with only one exception of TLR3, can initiate downstream signaling through MyD88. In the MyD88 - dependent pathway, once the adaptor is bound to TLR it leads to recruitment of IL1 receptor associated kinase family IRAK which is followed by activation of tumour necrosis factor receptor-associated factor 6 (TRAF6). TRAF6 is an ubiquitin E3 ligase which in turn induces TGF-beta activating kinase 1 (TAK1) auto phosphorylation. Once activated TAK1 can ultimately mediate the induction of the transcription factor NF-κB or the mitogen-activated protein kinases (MAPK), such as JNK, p38 and ERK. This results in the translocation of the activated NF-κB and MAPKs to the nucleus and the initiation of appropriate gene transcription leading to the production of many proinflammatory cytokines and antimicrobial peptides.

## References

Hasan U, Chaffois C, Gaillard C, Saulnier V, Merck E, Tancredi S, ... Bates EE (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. [🔗](#)

Zhang Z, Louboutin JP, Weiner DJ, Goldberg JB & Wilson JM (2005). Human airway epithelial cells sense *Pseudomonas aeruginosa* infection via recognition of flagellin by Toll-like receptor 5. *Infect Immun*, 73, 7151-60. [🔗](#)

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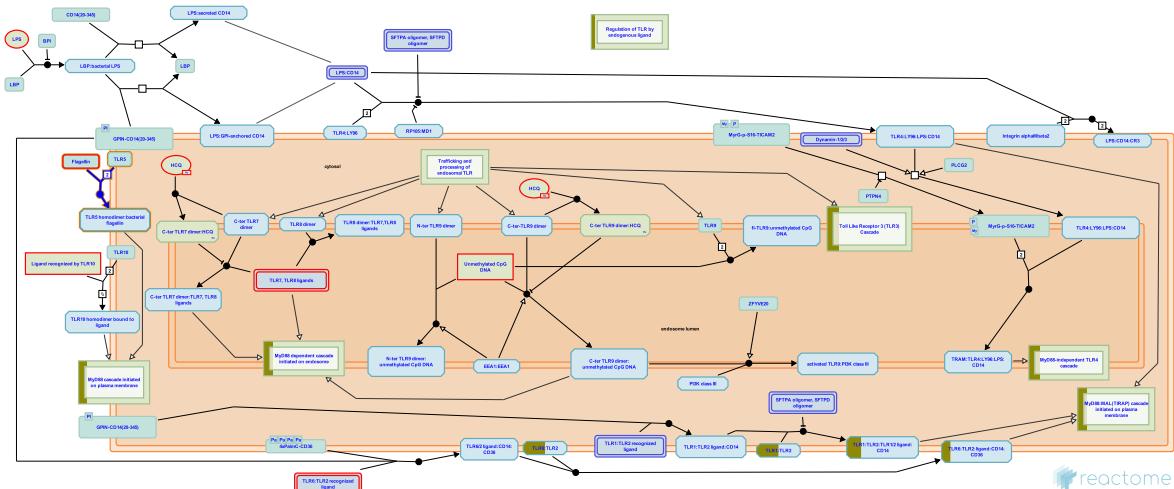
Date	Action	Author
2010-10-06	Authored	Shamovsky V
2010-10-06	Created	Shamovsky V

Date	Action	Author
2011-02-10	Reviewed	Gillespie ME
2011-08-04	Reviewed	Li L
2011-08-12	Edited	Shamovsky V
2020-11-24	Modified	Shorser S

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ENSG00000109320	P19838	ENSG00000134070	O43187	ENSG00000143479	P49137
ENSG00000168884	Q8NFZ5	ENSG00000197329	Q96FA3		

## 25. Toll Like Receptor 5 (TLR5) Cascade (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).

## References

- Hayashi F, Smith KD, Ozinsky A, Hawn TR, Yi EC, Goodlett DR, ... Aderem A (2001). The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5. *Nature*, 410, 1099-103. [🔗](#)
- Gewirtz AT, Navas TA, Lyons S, Godowski PJ & Madara JL (2001). Cutting edge: bacterial flagellin activates basolaterally expressed TLR5 to induce epithelial proinflammatory gene expression. *J Immunol*, 167, 1882-5. [🔗](#)
- Paul W (2003). *Innate Immune System, Fundamental Immunology*, 497-518.

## Edit history

Date	Action	Author
2005-11-10	Authored	Luo F
2005-11-10	Created	Gillespie ME
2006-10-31	Reviewed	Gale M Jr
2011-02-10	Reviewed	Gillespie ME
2011-08-12	Edited	Shamovsky V
2020-11-24	Modified	Shorser S

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ENSG0000168884	Q8NFZ5	ENSG0000197329	Q96FA3		

## 6. Identifiers found

Below is a list of the input identifiers that have been found or mapped to an equivalent element in Reactome, classified by resource.

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## 7. Identifiers not found

These 234 identifiers were not found neither mapped to any entity in Reactome.

ENSG0000005889 ENSG0000010818 ENSG0000050344 ENSG0000066697 ENSG0000067082 ENSG0000078081 ENSG0000078804 ENSG0000085511 ENSG0000089351 ENSG0000092345 ENSG0000099860 ENSG0000101331 ENSG0000102096 ENSG0000102794 ENSG00000108700 ENSG0000110848 ENSG0000111860 ENSG0000112149 ENSG0000113369 ENSG0000113742 ENSG0000114784 ENSG00000116044 ENSG0000117036 ENSG0000118263 ENSG0000119698 ENSG0000122035 ENSG0000124201 ENSG0000126003 ENSG00000132975 ENSG0000135604 ENSG0000136048 ENSG0000137460 ENSG0000137571 ENSG0000137757 ENSG0000138670 ENSG00000140379 ENSG0000144233 ENSG0000144655 ENSG0000144802 ENSG0000145911 ENSG0000146278 ENSG0000146839 ENSG00000149557 ENSG0000152229 ENSG0000154099 ENSG0000154548 ENSG0000154640 ENSG0000155324 ENSG0000156273 ENSG00000159200 ENSG0000162783 ENSG0000163121 ENSG0000163545 ENSG0000163673 ENSG0000163874 ENSG0000164188 ENSG00000165312 ENSG0000165694 ENSG0000165997 ENSG0000166016 ENSG0000166920 ENSG0000167034 ENSG0000167693 ENSG00000168955 ENSG0000168994 ENSG0000169155 ENSG0000169504 ENSG0000170542 ENSG0000171811 ENSG0000173451 ENSG00000177045 ENSG0000177311 ENSG0000178803 ENSG0000178860 ENSG0000179165 ENSG0000179428 ENSG0000179431 ENSG00000179833 ENSG0000180316 ENSG0000181026 ENSG0000181649 ENSG0000184602 ENSG0000185215 ENSG0000185433 ENSG00000187231 ENSG0000187479 ENSG0000188396 ENSG0000188613 ENSG0000188886 ENSG0000189067 ENSG0000196449 ENSG00000197536 ENSG0000198355 ENSG0000203364 ENSG0000205189 ENSG0000205502 ENSG0000205856 ENSG0000213516 ENSG00000217801 ENSG0000221949 ENSG0000222043 ENSG0000223911 ENSG0000224080 ENSG0000224776 ENSG0000225626 ENSG00000226239 ENSG0000226312 ENSG0000226380 ENSG0000228509 ENSG0000228804 ENSG0000228988 ENSG0000229271 ENSG00000229781 ENSG0000230638 ENSG0000230641 ENSG0000230647 ENSG0000230943 ENSG0000231233 ENSG0000231560 ENSG00000231856 ENSG0000232043 ENSG0000232133 ENSG0000232194 ENSG0000232517 ENSG0000232702 ENSG0000232927 ENSG00000234191 ENSG0000234431 ENSG0000234456 ENSG0000234511 ENSG0000234883 ENSG0000235217 ENSG0000236591 ENSG00000237372 ENSG0000237499 ENSG0000237892 ENSG0000237931 ENSG0000241280 ENSG0000244953 ENSG0000249138 ENSG00000249738 ENSG0000250602 ENSG0000250889 ENSG0000251136 ENSG0000251196 ENSG0000251230 ENSG0000251867 ENSG00000253522 ENSG0000253535 ENSG0000254281 ENSG0000255282 ENSG0000255355 ENSG0000255363 ENSG0000255443 ENSG00000255874 ENSG0000255929 ENSG0000256249 ENSG0000257202 ENSG0000257242 ENSG0000258555 ENSG0000258724 ENSG00000258922 ENSG0000259075 ENSG0000259326 ENSG0000259342 ENSG0000259605 ENSG0000259834 ENSG0000260196 ENSG00000261618 ENSG0000264501 ENSG0000266094 ENSG0000266698 ENSG0000266709 ENSG0000266978 ENSG0000267520 ENSG00000267712 ENSG0000267737 ENSG0000269680 ENSG0000269826 ENSG0000269906 ENSG0000270390 ENSG0000271614 ENSG00000272273 ENSG0000273320 ENSG0000273344 ENSG0000273604 ENSG0000274215 ENSG0000274767 ENSG0000275688 ENSG00000276418 ENSG0000276753 ENSG0000277089 ENSG0000277604 ENSG0000277895 ENSG0000277969 ENSG0000279095 ENSG00000279862 ENSG0000280303 ENSG0000281376 ENSG0000282221 ENSG0000283724 ENSG0000283904 ENSG0000284386 ENSG00000284486 ENSG0000284633