



# 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=MjAyMTAzMjIwMTA1MjFfNTcwNjQ%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.

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# 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:

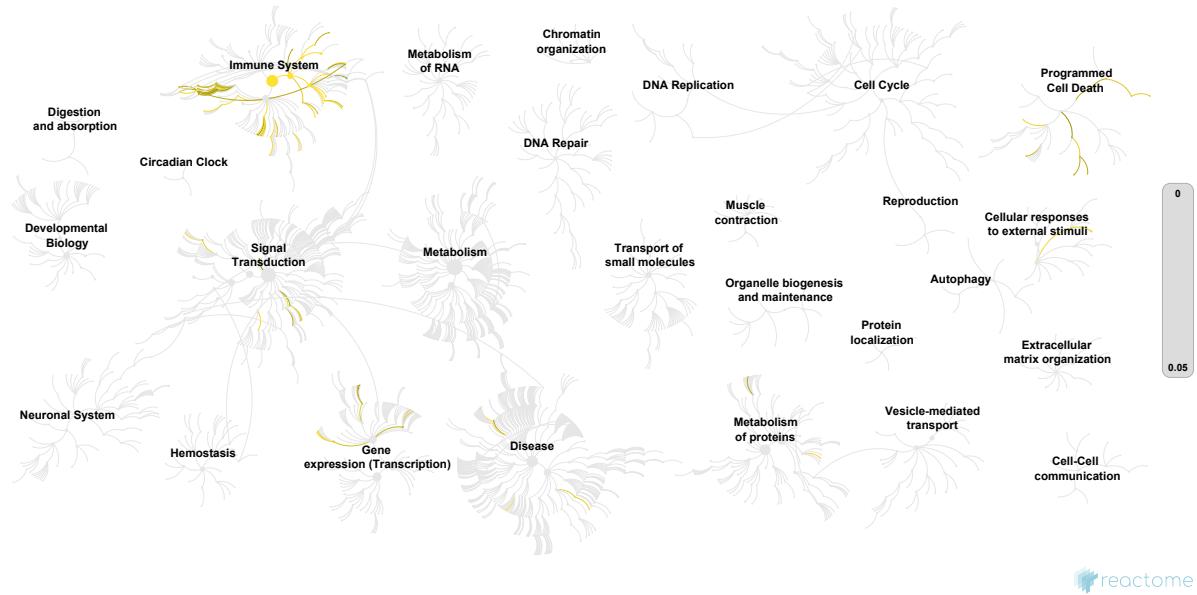
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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. ↗
- 354 out of 749 identifiers in the sample were found in Reactome, where 991 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 MjAyMTAzMjIwMTA1MjFfNTcwNjQ%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	43 / 86	0.006	1.11e-16	4.07e-14	13 / 15	0.001
Signaling by Interleukins	102 / 647	0.044	1.11e-16	4.07e-14	253 / 493	0.037
Cytokine Signaling in Immune system	162 / 1,108	0.075	1.11e-16	4.07e-14	343 / 687	0.052
Interleukin-4 and Interleukin-13 signaling	43 / 216	0.015	1.64e-11	4.51e-09	10 / 47	0.004
Interferon Signaling	54 / 401	0.027	4.46e-08	9.80e-06	41 / 69	0.005
Chemokine receptors bind chemokines	16 / 57	0.004	5.48e-07	1.00e-04	10 / 19	0.001
Interferon alpha/beta signaling	31 / 191	0.013	8.79e-07	1.38e-04	16 / 22	0.002
Interferon gamma signaling	33 / 255	0.017	3.97e-05	0.005	5 / 16	0.001
Immune System	208 / 2,713	0.184	4.32e-05	0.005	608 / 1,593	0.12
Interleukin-1 processing	5 / 8	5.43e-04	1.35e-04	0.015	2 / 5	3.78e-04
DDX58/IFIH1-mediated induction of interferon-alpha/beta	16 / 96	0.007	2.78e-04	0.028	37 / 46	0.003
STAT5 activation downstream of FLT3 ITD mutants	7 / 21	0.001	3.10e-04	0.028	13 / 14	0.001
Interleukin-7 signaling	9 / 36	0.002	3.73e-04	0.029	21 / 26	0.002
Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways	13 / 70	0.005	3.75e-04	0.029	27 / 46	0.003
Interleukin-6 family signaling	8 / 31	0.002	6.36e-04	0.046	27 / 34	0.003
Inflammasomes	8 / 33	0.002	9.46e-04	0.064	17 / 28	0.002
RIP-mediated NFkB activation via ZBP1	6 / 19	0.001	0.001	0.066	4 / 4	3.02e-04
NF-kB activation through FADD/RIP-1 pathway mediated by caspase-8 and -10	5 / 13	8.83e-04	0.001	0.066	5 / 5	3.78e-04
Ovarian tumor domain proteases	9 / 43	0.003	0.001	0.066	7 / 14	0.001
FOXO-mediated transcription of cell cycle genes	7 / 27	0.002	0.001	0.066	19 / 22	0.002
TRAIL signaling	4 / 8	5.43e-04	0.001	0.066	6 / 6	4.54e-04
IkB variant leads to EDA-ID	4 / 8	5.43e-04	0.001	0.066	2 / 2	1.51e-04
CLEC7A/inflammasome pathway	4 / 8	5.43e-04	0.001	0.066	2 / 4	3.02e-04
Toll Like Receptor 3 (TLR3) Cascade	15 / 102	0.007	0.001	0.066	38 / 61	0.005

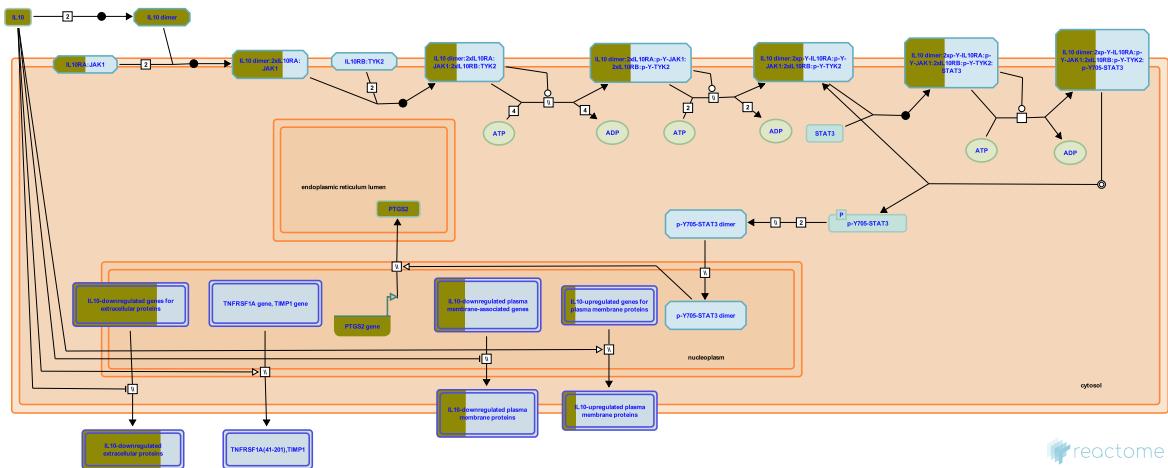
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
RAF-independent MAPK1/3 activation	7 / 28	0.002	0.002	0.072	4 / 12	9.07e-04

\* 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

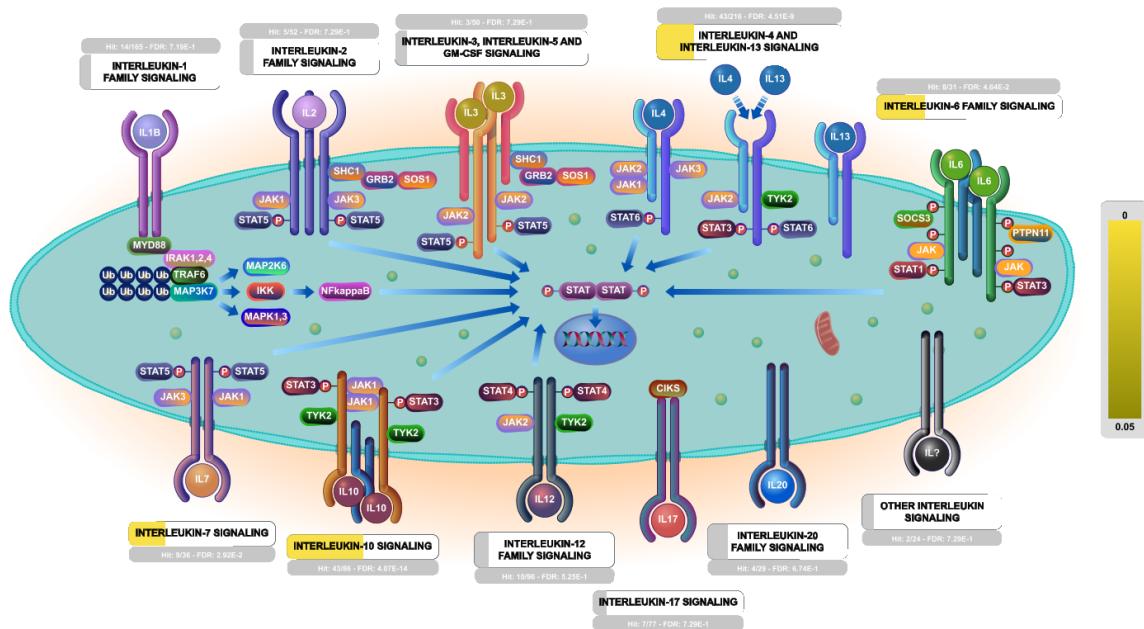
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ENSG00000275302	ENSG00000275302	ENSG00000277632	ENSG00000277632		

## 2. 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

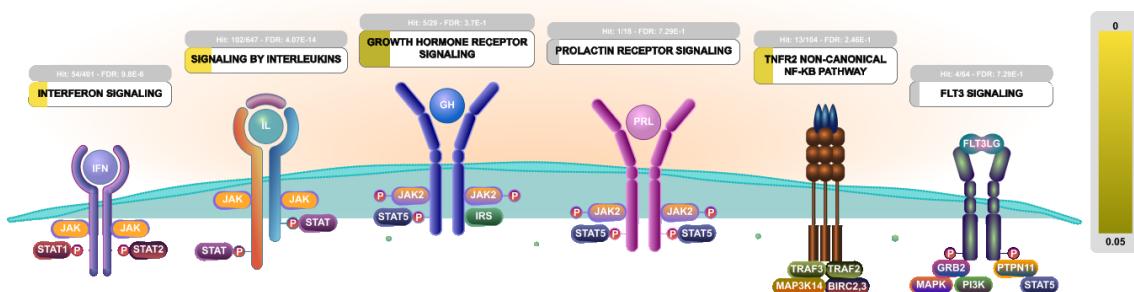
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2009-11-27	Created	Jupe S
2010-05-17	Reviewed	Pinteaux E
2010-05-17	Authored	Ray KP
2010-05-26	Edited	Jupe S
2020-11-20	Modified	Shorser S

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### 3. 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

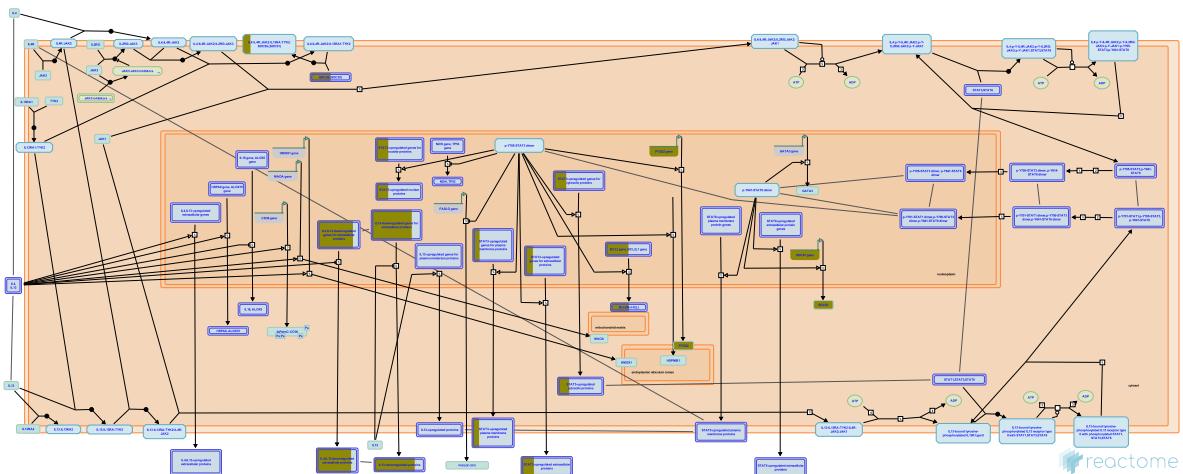
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#### 4. Interleukin-4 and Interleukin-13 signaling (R-HSA-6785807)



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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2015-07-01	Created	Jupe S
2016-09-02	Edited	Jupe S
2016-09-02	Reviewed	Leibovich SJ

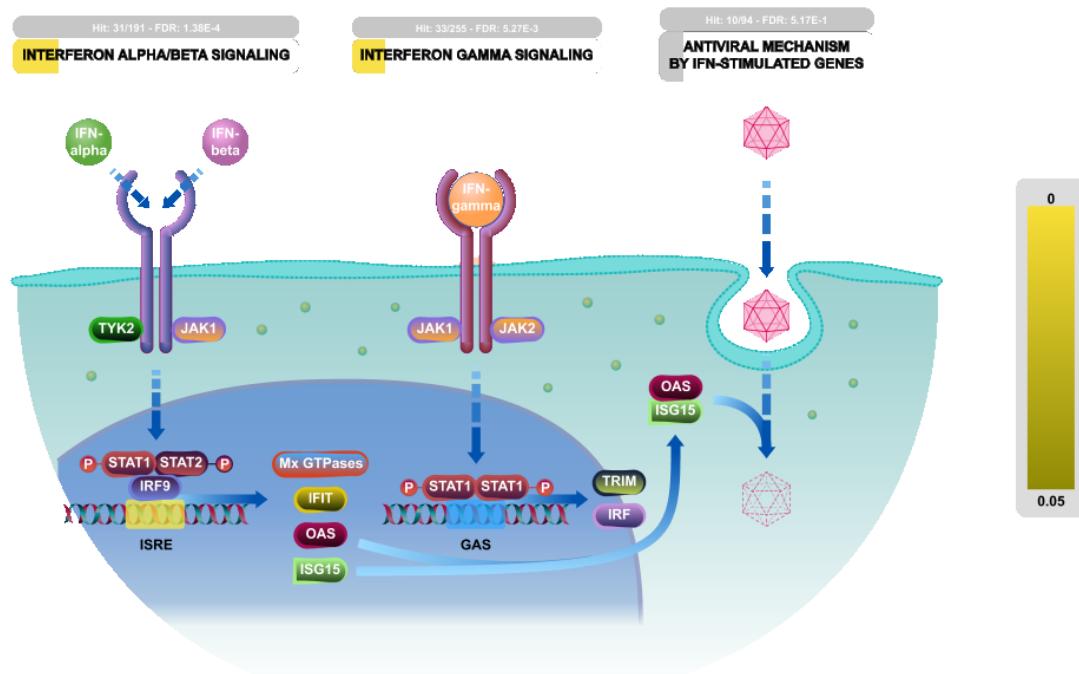
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2020-11-24	Modified	Shorser S

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## 5. Interferon Signaling (R-HSA-913531)



Interferons (IFNs) are cytokines that play a central role in initiating immune responses, especially antiviral and antitumor effects. There are three types of IFNs: Type I (IFN-alpha, -beta and others, such as omega, epsilon, and kappa), Type II (IFN-gamma) and Type III (IFN-lambda). In this module we are mainly focusing on type I IFNs alpha and beta and type II IFN-gamma. Both type I and type II IFNs exert their actions through cognate receptor complexes, IFNAR and IFNGR respectively, present on cell surface membranes. Type I IFNs are broadly expressed heterodimeric receptors composed of the IFNAR1 and IFNAR2 subunits, while the type II IFN receptor consists of IFNGR1 and IFNGR2. Type III interferon lambda has three members: lambda1 (IL-29), lambda2 (IL-28A), and lambda3 (IL-28B) respectively. IFN-lambda signaling is initiated through unique heterodimeric receptor composed of IFN-LR1/IF-28Ralpha and IL10R2 chains.

Type I IFNs typically recruit JAK1 and TYK2 proteins to transduce their signals to STAT1 and 2; in combination with IRF9 (IFN-regulatory factor 9), these proteins form the heterotrimeric complex ISGF3. In nucleus ISGF3 binds to IFN-stimulated response elements (ISRE) to promote gene induction.

Type II IFNs in turn rely upon the activation of JAKs 1 and 2 and STAT1. Once activated, STAT1 dimerizes to form the transcriptional regulator GAF (IFNG activated factor) and this binds to the IFNG activated sequence (GAS) elements and initiate the transcription of IFNG-responsive genes.

Like type I IFNs, IFN-lambda recruits TYK2 and JAK1 kinases and then promote the phosphorylation of STAT1/2, and induce the ISRE3 complex formation.

## References

Plataniias LC (2005). Mechanisms of type-I- and type-II-interferon-mediated signalling. Nat Rev Immunol, 5, 375-86. [View](#)

Gough DJ, Levy DE, Johnstone RW & Clarke CJ (2008). IFNgamma signaling-does it mean JAK-STAT?. *Cytokine Growth Factor Rev*, 19, 383-94. [🔗](#)

Schroder K, Hertzog PJ, Ravasi T & Hume DA (2004). Interferon-gamma: an overview of signals, mechanisms and functions. *J Leukoc Biol*, 75, 163-89. [🔗](#)

Bonjardim CA, Ferreira PC & Kroon EG (2009). Interferons: signaling, antiviral and viral evasion. *Immunol Lett*, 122, 1-11. [🔗](#)

Uddin S & Plataniias LC (2004). Mechanisms of type-I interferon signal transduction. *J Biochem Mol Biol*, 37, 635-41. [🔗](#)

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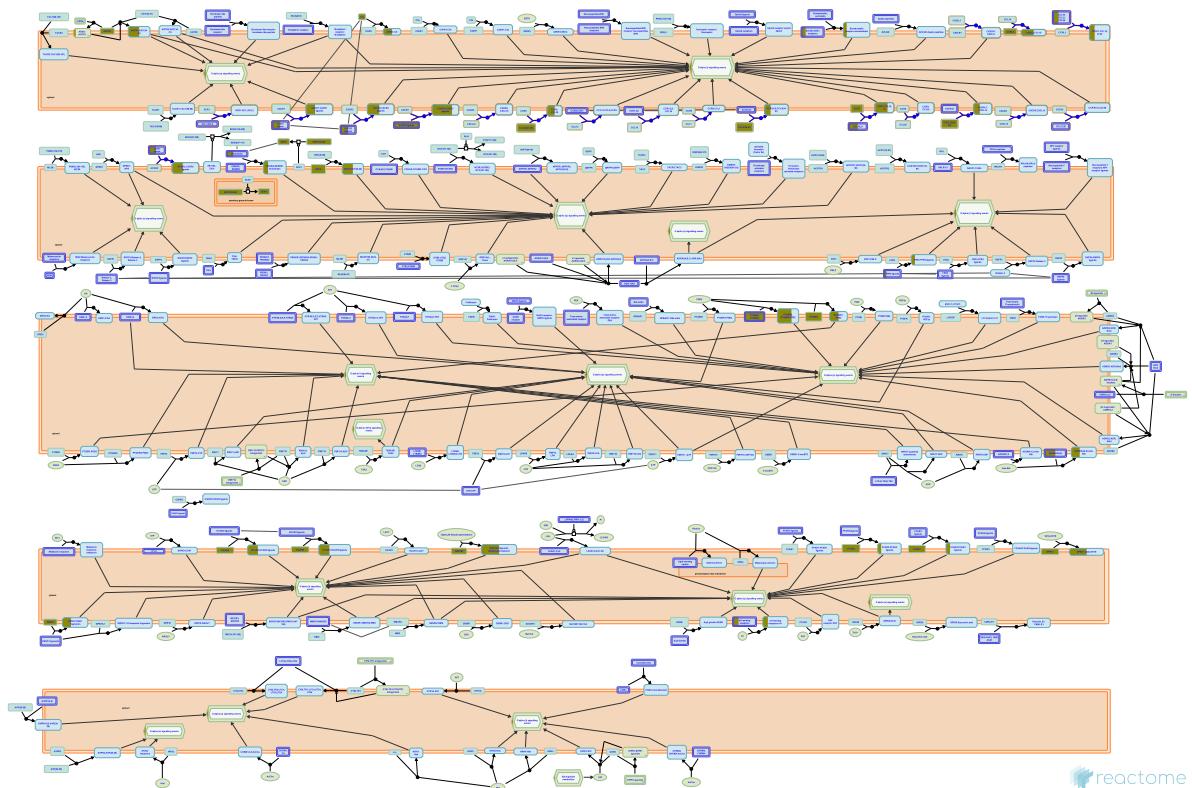
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2010-07-16	Created	Garapati P V
2010-08-17	Reviewed	Abdul-Sater AA, Schindler C
2020-11-20	Modified	Shorser S

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## 6. 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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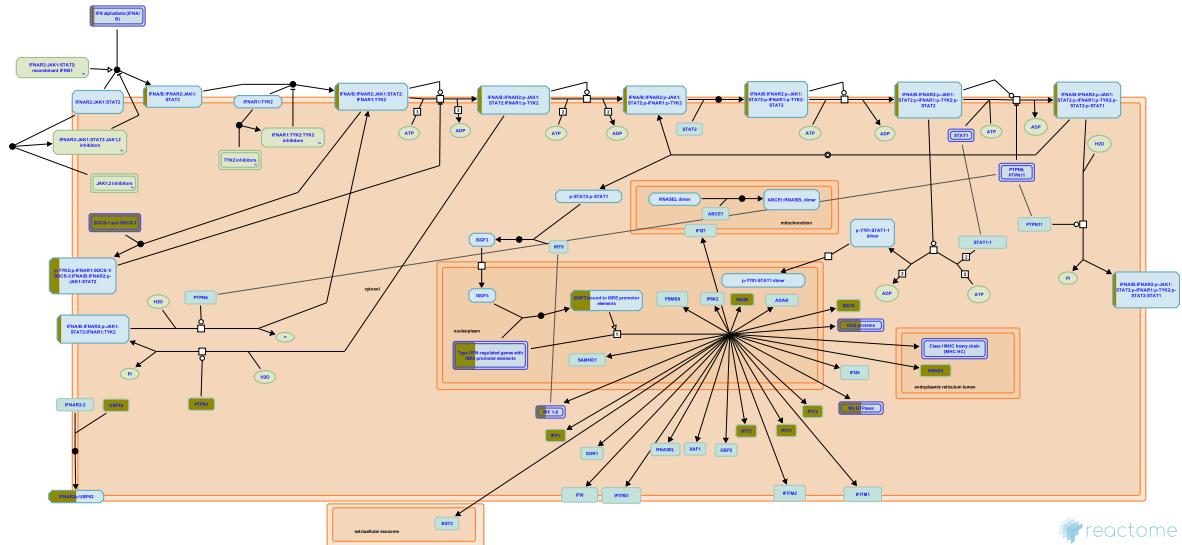
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## 7. Interferon alpha/beta signaling (R-HSA-909733)



Type I interferons (IFNs) are composed of various genes including IFN alpha (IFNA), beta (IFNB), omega, epsilon, and kappa. In humans the IFNA genes are composed of more than 13 subfamily genes, whereas there is only one IFNB gene. The large family of IFNA/B proteins all bind to a single receptor which is composed of two distinct chains: IFNAR1 and IFNAR2. The IFNA/B stimulation of the IFNA receptor complex leads to the formation of two transcriptional activator complexes: IFNA-activated-factor (AAF), which is a homodimer of STAT1 and IFN-stimulated gene factor 3 (ISGF3), which comprises STAT1, STAT2 and a member of the IRF family, IRF9/P48. AAF mediates activation of the IRF-1 gene by binding to GAS (IFNG-activated site), whereas ISGF3 activates several IFN-inducible genes including IRF3 and IRF7.

## References

- Uzé G, Schreiber G, Piehler J & Pellegrini S (2007). The receptor of the type I interferon family. *Curr Top Microbiol Immunol*, 316, 71-95. [🔗](#)
- Gauzzi MC, Velazquez L, McKendry R, Mogensen KE, Fellous M & Pellegrini S (1996). Interferon-alpha-dependent activation of Tyk2 requires phosphorylation of positive regulatory tyrosines by another kinase. *J Biol Chem*, 271, 20494-500. [🔗](#)
- Yan H, Krishnan K, Greenlund AC, Gupta S, Lim JT, Schreiber RD, ... Krolewski JJ (1996). Phosphorylated interferon-alpha receptor 1 subunit (IFNaR1) acts as a docking site for the latent form of the 113 kDa STAT2 protein. *EMBO J*, 15, 1064-74. [🔗](#)
- Li X, Leung S, Qureshi S, Darnell JE Jr & Stark GR (1996). Formation of STAT1-STAT2 heterodimers and their role in the activation of IRF-1 gene transcription by interferon-alpha. *J Biol Chem*, 271, 5790-4. [🔗](#)

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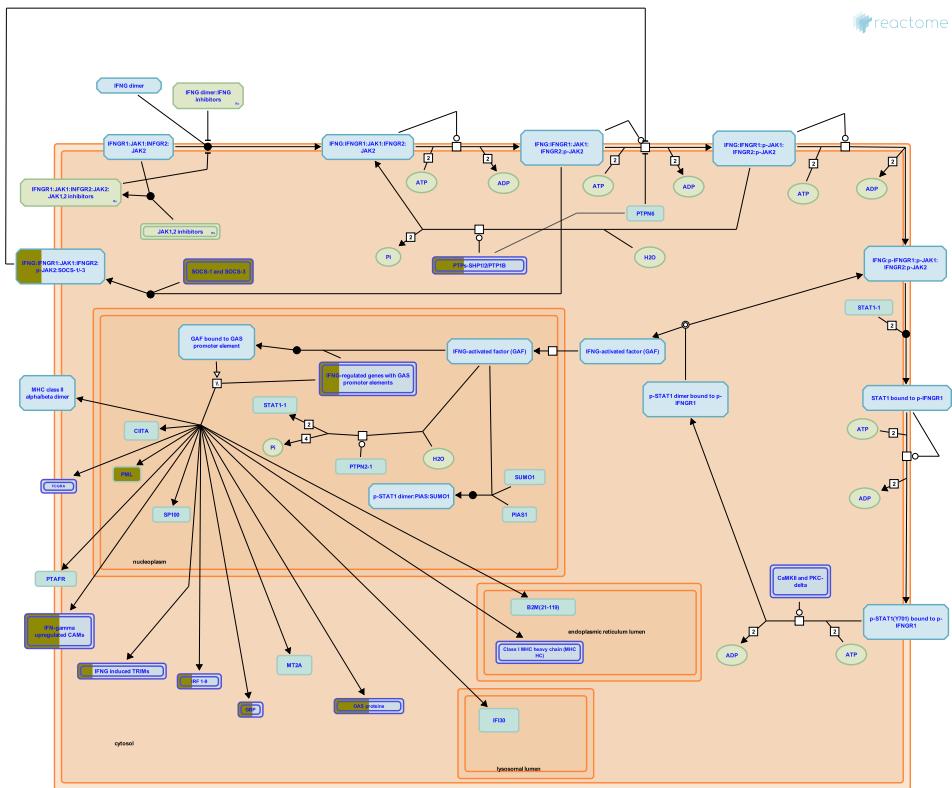
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## 8. Interferon gamma signaling (R-HSA-877300)



Interferon-gamma (IFN-gamma) belongs to the type II interferon family and is secreted by activated immune cells—primarily T and NK cells, but also B-cells and APC. IFNG exerts its effect on cells by interacting with the specific IFN-gamma receptor (IFNGR). IFNGR consists of two chains, namely IFN $\gamma$ R1 (also known as the IFN $\gamma$ R alpha chain) and IFN $\gamma$ R2 (also known as the IFN $\gamma$ R beta chain). IFN $\gamma$ R1 is the ligand binding receptor and is required but not sufficient for signal transduction, whereas IFN $\gamma$ R2 do not bind IFNG independently but mainly plays a role in IFNG signaling and is generally the limiting factor in IFNG responsiveness. Both IFN $\gamma$ R chains lack intrinsic kinase/phosphatase activity and thus rely on other signaling proteins like Janus-activated kinase 1 (JAK1), JAK2 and Signal transducer and activator of transcription 1 (STAT1) for signal transduction. IFN $\gamma$ R complex in its resting state is a preformed tetramer and upon IFNG association undergoes a conformational change. This conformational change induces the phosphorylation and activation of JAK1, JAK2, and STAT1 which in turn induces genes containing the gamma-interferon activation sequence (GAS) in the promoter.

## References

- Gough DJ, Levy DE, Johnstone RW & Clarke CJ (2008). IFNgamma signaling—does it mean JAK-STAT?. *Cytokine Growth Factor Rev*, 19, 383-94. [🔗](#)
- Pestka S, Kotenko SV, Muthukumaran G, Izotova LS, Cook JR & Garotta G (1997). The interferon gamma (IFN-gamma) receptor: a paradigm for the multichain cytokine receptor. *Cytokine Growth Factor Rev*, 8, 189-206. [🔗](#)
- Bach EA, Aguet M & Schreiber RD (1997). The IFN gamma receptor: a paradigm for cytokine receptor signaling. *Annu Rev Immunol*, 15, 563-91. [🔗](#)
- Schroder K, Hertzog PJ, Ravasi T & Hume DA (2004). Interferon-gamma: an overview of signals, mechanisms and functions. *J Leukoc Biol*, 75, 163-89. [🔗](#)

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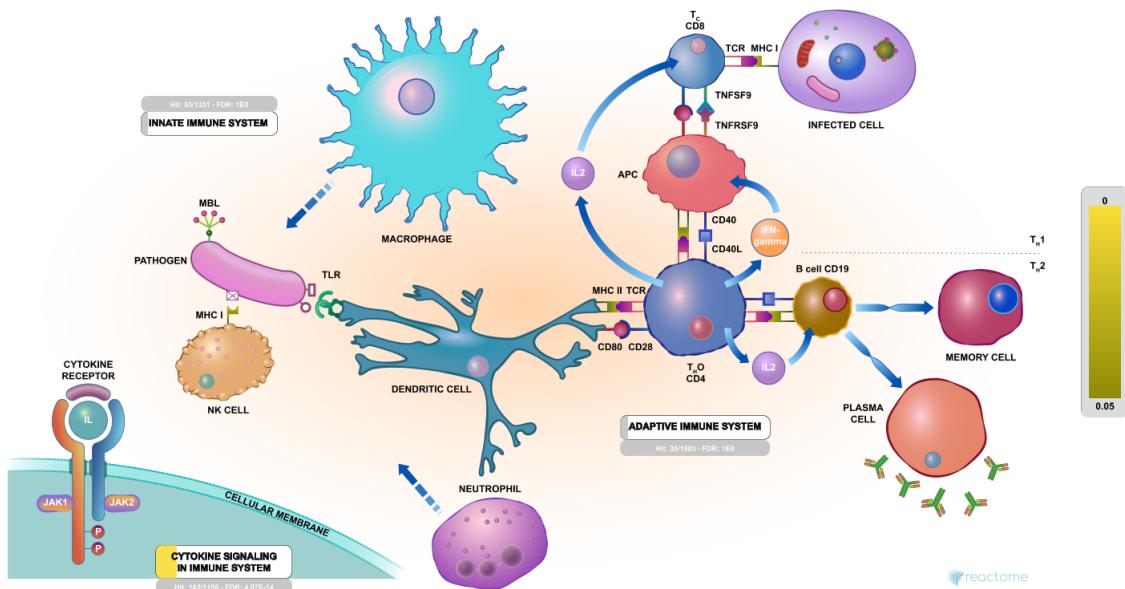
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## 9. Immune System (R-HSA-168256)



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

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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
2020-11-20	Modified	Shorser S

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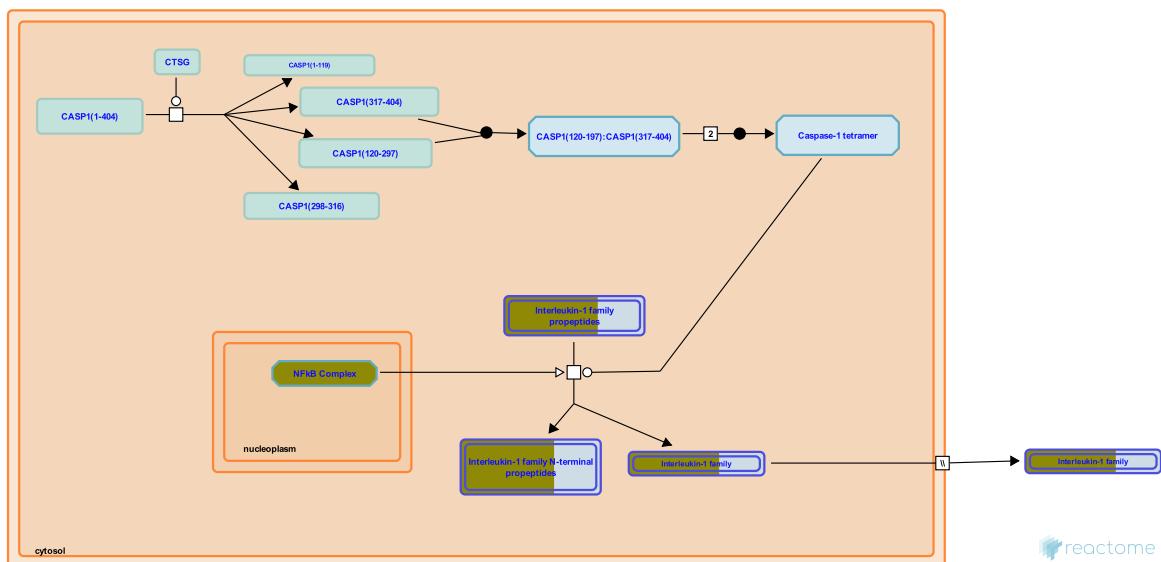
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## 10. Interleukin-1 processing (R-HSA-448706)



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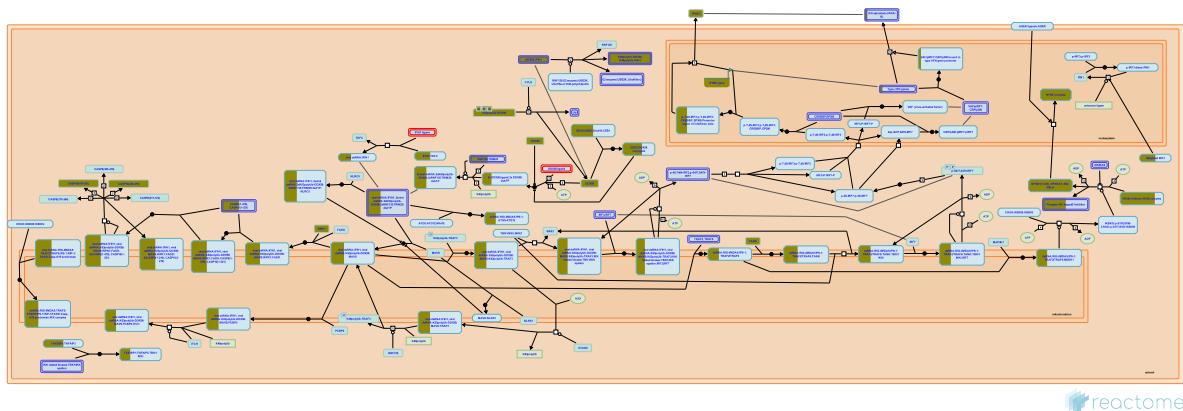
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2010-05-17	Authored	Ray KP
2010-08-06	Edited	Jupe S

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

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## 11. DDX58/IFIH1-mediated induction of interferon-alpha/beta (R-HSA-168928)



**Cellular compartments:** mitochondrial outer membrane.

RIG-I-like helicases (RLHs) the retinoic acid inducible gene-I (RIG-I) and melanoma differentiation associated gene 5 (MDA5) are RNA helicases that recognize viral RNA present within the cytoplasm. Functionally RIG-I and MDA5 positively regulate the IFN genes in a similar fashion, however they differ in their response to different viral species. RIG-I is essential for detecting influenza virus, Sendai virus, VSV and Japanese encephalitis virus (JEV), whereas MDA5 is essential in sensing encephalomyocarditis virus (EMCV), Mengo virus and Theiler's virus, all of which belong to the picornavirus family. RIG-I and MDA5 signalling results in the activation of IKK epsilon and (TKK binding kinase 1) TBK1, two serine/threonine kinases that phosphorylate interferon regulatory factor 3 and 7 (IRF3 and IRF7). Upon phosphorylation, IRF3 and IRF7 translocate to the nucleus and subsequently induce interferon alpha (IFNA) and interferon beta (IFNB) gene transcription.

## References

- Honda K, Yanai H, Takaoka A & Taniguchi T (2005). Regulation of the type I IFN induction: a current view. *Int Immunol*, 17, 1367-78. [🔗](#)
- Loo YM, Fornek J, Crochet N, Bajwa G, Perwitasari O, Martinez-Sobrido L, ... Gale M Jr (2008). Distinct RIG-I and MDA5 signaling by RNA viruses in innate immunity. *J Virol*, 82, 335-45. [🔗](#)
- Bowie AG & Unterholzner L (2008). Viral evasion and subversion of pattern-recognition receptor signalling. *Nat Rev Immunol*, 8, 911-22. [🔗](#)
- Yoneyama M & Fujita T (2008). Structural mechanism of RNA recognition by the RIG-I-like receptors. *Immunity*, 29, 178-81. [🔗](#)
- Yoneyama M & Fujita T (2007). RIG-I family RNA helicases: cytoplasmic sensor for antiviral innate immunity. *Cytokine Growth Factor Rev*, 18, 545-51. [🔗](#)

## Edit history

Date	Action	Author
2005-11-22	Created	de Bono B
2010-08-02	Edited	Garapati P V
2010-08-02	Authored	Garapati P V
2010-10-30	Reviewed	Akira S, Kawai T
2020-11-20	Modified	Shorser S

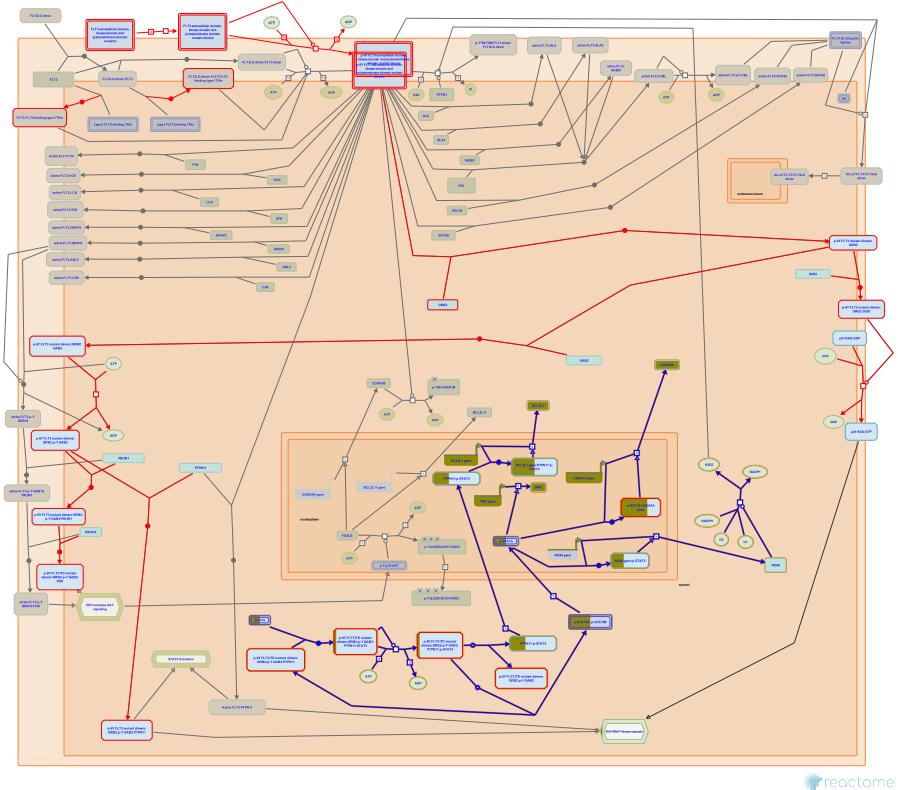
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## 12. STAT5 activation downstream of FLT3 ITD mutants ([R-HSA-9702518](#))



**Diseases:** cancer.

STAT5 signaling appears to be preferentially activated downstream of FLT3 ITD mutants relative to the wild-type or FLT3 TKD mutants, although this is subject to some debate (Choudhary et al, 2005; Reindl et al, 2006; Bagrintseva et al, 2005; Grundler et al, 2003; Choudhary et al, 2007; Marshall et al, 2018; reviewed in Choudhary et al, 2005). STAT5 activation contributes to oncogenesis by promoting the transcription of a number of factors involved in regulating cell cycle progression, proliferation and apoptosis, among others (Kim et al, 2005; Nabinger et al, 2013; Takahashi et al, 2004; Godfrey et al, 2012; Hayakawa et al, 2000; reviewed in Murphy and Rani, 2015).

## References

- Choudhary C, Schwäble J, Brandts C, Tickenbrock L, Sargin B, Kindler T, ... Serve H (2005). AML-associated Flt3 kinase domain mutations show signal transduction differences compared with Flt3 ITD mutations, 106, 265-73. [🔗](#)
- Reindl C, Bagrintseva K, Vempati S, Schnittger S, Ellwart JW, Wenig K, ... Spiekermann K (2006). Point mutations in the juxtamembrane domain of FLT3 define a new class of activating mutations in AML. Blood, 107, 3700-7. [🔗](#)
- Bagrintseva K, Geisenhof S, Kern R, Eichenlaub S, Reindl C, Ellwart JW, ... Spiekermann K (2005). FLT3-ITD-TKD dual mutants associated with AML confer resistance to FLT3 PTK inhibitors and cytotoxic agents by overexpression of Bcl-x(L). Blood, 105, 3679-85. [🔗](#)
- Grundler R, Miethling C, Thiede C, Peschel C & Duyster J (2005). FLT3-ITD and tyrosine kinase domain mutants induce 2 distinct phenotypes in a murine bone marrow transplantation model, 105, 4792-9. [🔗](#)

Choudhary C, Brandts C, Schwäble J, Tickenbrock L, Sargin B, Ueker A, ... Serve H (2007). Activation mechanisms of STAT5 by oncogenic Flt3-ITD. *Blood*, 110, 370-4. [🔗](#)

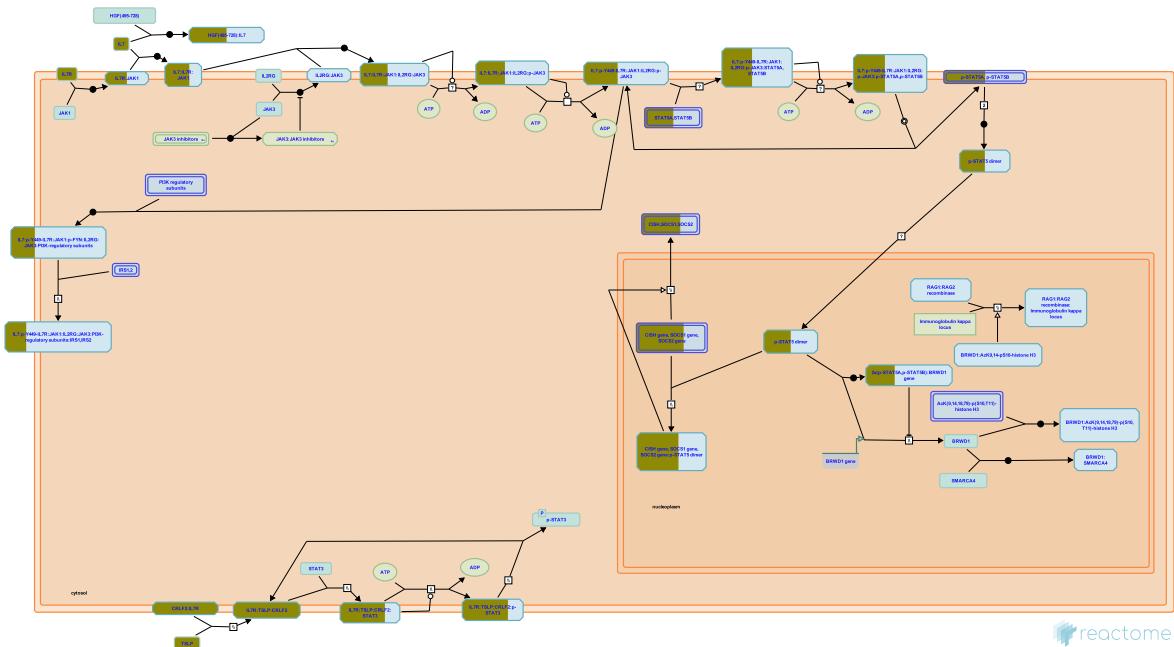
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2020-11-06	Authored	Rothfels K
2020-11-24	Modified	Shorser S

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### 13. Interleukin-7 signaling (R-HSA-1266695)



Interleukin-7 (IL7) is produced primarily by T zone fibroblastic reticular cells found in lymphoid organs, and also expressed by non-hematopoietic stromal cells present in other tissues including the skin, intestine and liver. It is an essential survival factor for lymphocytes, playing a key anti-apoptotic role in T-cell development, as well as mediating peripheral T-cell maintenance and proliferation. This dual function is reflected in a dose-response relationship that distinguishes the survival function from the proliferative activity; low doses of IL7 (<1 ng/ml) sustain only survival, higher doses (>1 ng/ml) promote survival and cell cycling (Kittipatarin et al. 2006, Swainson et al. 2007).

The IL7 receptor is a heterodimeric complex of the common cytokine-receptor gamma chain (IL2RG, CD132, or Gc) and the IL7-receptor alpha chain (IL7R, IL7RA, CD127). Both chains are members of the type 1 cytokine family. Neither chain is unique to the IL7 receptor as IL7R is utilized by the receptor for thymic stromal lymphopoitin (TSLP) while IL2RG is shared with the receptors for IL2, IL4, IL9, IL15 and IL21. IL2RG consists of a single transmembrane region and a 240aa extracellular region that includes a fibronectin type III (FNIII) domain thought to be involved in receptor complex formation. It is expressed on most lymphocyte populations. Null mutations of IL2RG in humans cause X-linked severe combined immunodeficiency (X-SCID), which has a phenotype of severely reduced T-cell and natural killer (NK) cell populations, but normal numbers of B cells. In addition to reduced T- and NK-cell numbers, Il2rg knockout mice also have dramatically reduced B-cell populations suggesting that Il2rg is more critical for B-cell development in mice than in humans. Patients with severe combined immunodeficiency (SCID) phenotype due to IL7R mutations (see Puel & Leonard 2000), or a partial deficiency of IL7R (Roifman et al. 2000) have markedly reduced circulating T cells, but normal levels of peripheral blood B cells and NK cells, similar to the phenotype of IL2RG mutations, highlighting a requirement for IL7 in T cell lymphopoiesis. It has been suggested that IL7 is essential for murine, but not human B cell development, but recent studies indicate that IL7 is essential for human B cell production from adult bone marrow and that IL7-induced expansion of the progenitor B cell compartment is increasingly critical for human B cell production during later stages of development (Parrish et al. 2009).

IL7 has been shown to induce rapid and dose-dependent tyrosine phosphorylation of JAKs 1 and 3, and concomitantly tyrosine phosphorylation and DNA-binding activity of STAT5a/b (Foxwell et al. 1995). IL7R was shown to directly induce the activation of JAKs and STATs by van der Plas et al. (1996). Jak1 and Jak3 knockout mice displayed severely impaired thymic development, further supporting their importance in IL7 signaling (Rodig et al. 1998, Nosaka et al. 1995).

The role of STAT5 in IL7 signaling has been studied largely in mouse models. Tyr449 in the cytoplasmic domain of IL7RA is required for T-cell development in vivo and activation of JAK/STAT5 and PI3k/Akt pathways (Jiang et al. 2004, Pallard et al. 1999). T-cells from an IL7R Y449F knock-in mouse did not activate STAT5 (Osbourne et al. 2007), indicating that IL7 regulates STAT5 activity via this key tyrosine residue. STAT5 seems to enhance proliferation of multiple cell lineages in mouse models but it remains unclear whether STAT5 is required solely for survival signaling or also for the induction of proliferative activity (Kittipatarin & Khaled, 2007).

The model for IL7 receptor signaling is believed to resemble that of other Gc family cytokines, based on detailed studies of the IL2 receptor, where IL2RB binds constitutively to JAK1 while JAK3 is pre-associated uniquely with the IL2RG chain. Extending this model to IL7 suggests a similar series of events: IL7R constitutively associated with JAK1 binds IL7, the resulting trimer recruits IL2RG:JAK3, bringing JAK1 and JAK3 into proximity. The association of both chains of the IL7 receptor orients the cytoplasmic domains of the receptor chains so that their associated kinases (Janus and phosphatidylinositol 3-kinases) can phosphorylate sequence elements on the cytoplasmic domains (Jiang et al. 2005). JAKs have low intrinsic enzymatic activity, but after mutual phosphorylation acquire much higher activity, leading to phosphorylation of the critical Y449 site on IL7R. This site binds STAT5 and possibly other signaling adapters, they in turn become phosphorylated by JAK1 and/or JAK3. Phosphorylated STATs translocate to the nucleus and trigger the transcriptional events of their target genes.

The role of the PI3K/AKT pathway in IL7 signaling is controversial. It is a potential T-cell survival pathway because in many cell types PI3K signaling regulates diverse cellular functions such as cell cycle progression, transcription, and metabolism. The ERK/MAPK pathway does not appear to be involved in IL7 signaling (Crawley et al. 1996).

It is not clear how IL7 influences cell proliferation. In the absence of a proliferative signal such as IL7 or IL3, dependent lymphocytes arrest in the G0/G1 phase of the cell cycle. To exit this phase, cells typically activate specific G1 Cyclin-dependent kinases/cyclins and down regulate cell cycle inhibitors such as Cyclin-dependent kinase inhibitor 1B (Cdkn1b or p27kip1). There is indirect evidence suggesting a possible role for IL7 stimulated activation of PI3K/AKT signaling, obtained from transformed cell lines and thymocytes, but not confirmed by observations using primary T-cells (Kittipatarin & Khaled, 2007). IL7 withdrawal results in G1/S cell cycle arrest and is correlated with loss of cdk2 activity (Geiselhart et al. 2001), both events which are known to be regulated by the dephosphorylating activity of Cdc25A. Expression of a p38 MAPK-resistant Cdc25A mutant in an IL-7-dependent T-cell line as well as in peripheral, primary T-cells was sufficient to sustain cell survival and promote cell cycling for several days in the absence of IL7 (Khaled et al. 2005). Cdkn1b is a member of the CIP/KIP family of cyclin-dependent cell cycle inhibitors (CKIs) that negatively regulates the G1/S transition. In IL7 dependent T-cells, the expression of Cdkn1b was sufficient to cause G1 arrest in the presence of IL7. Withdrawal of IL7 induced the upregulation of Cdkn1b and arrested cells in G1 while siRNA knockout of Cdkn1b enhanced cell cycle progression. However, adoptive transfer of Cdkn1b-deficient lymphocytes into IL7 deficient mice indicated that loss of Cdkn1b could only partially compensate for the IL7 signal needed by T-cells to expand in a lymphopenic environment (Li et al. 2006), so though Cdkn1b may be involved in negative regulation of the cell cycle through an effect on cdk2 activity, its absence is not sufficient to fully induce cell cycling under lymphopenic conditions.

## References

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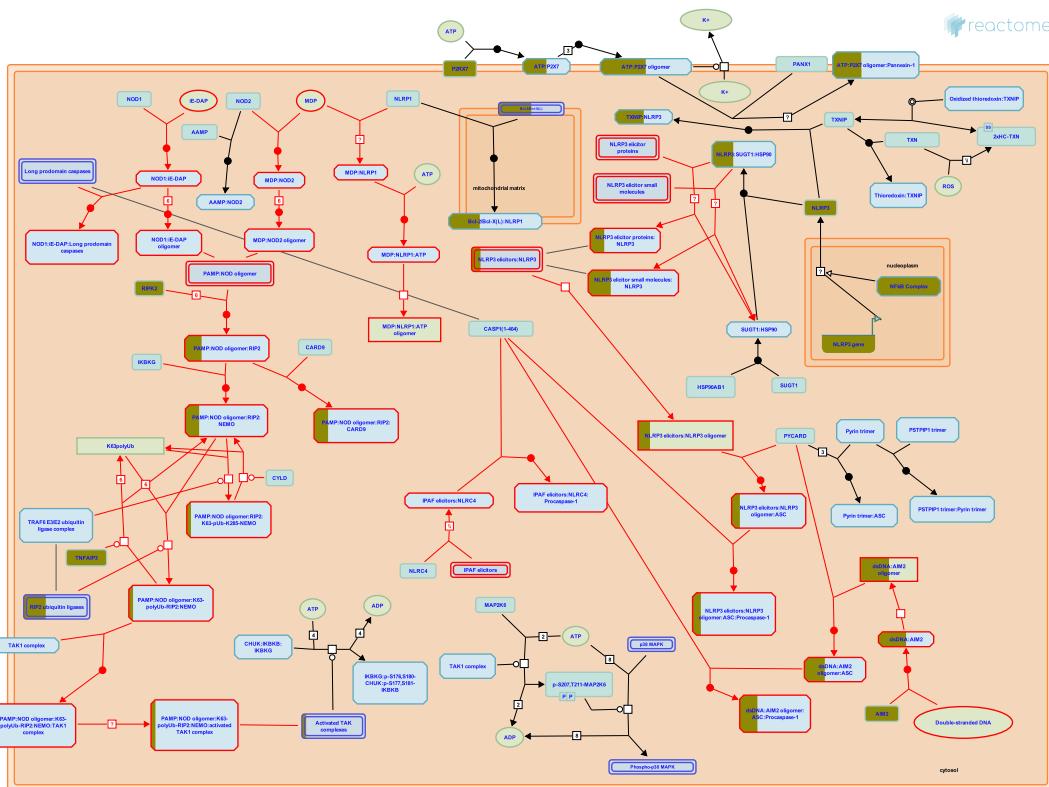
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2016-03-23	Edited	Orlic-Milacic M
2016-05-11	Revised	Mandal M
2017-07-26	Reviewed	Kumar U
2017-08-21	Reviewed	Goronzy JJ
2020-11-20	Modified	Shorser S

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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 & Tschoopp, 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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Date	Action	Author
2005-11-17	Created	Gillespie ME
2010-04-22	Authored	Jupe S
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

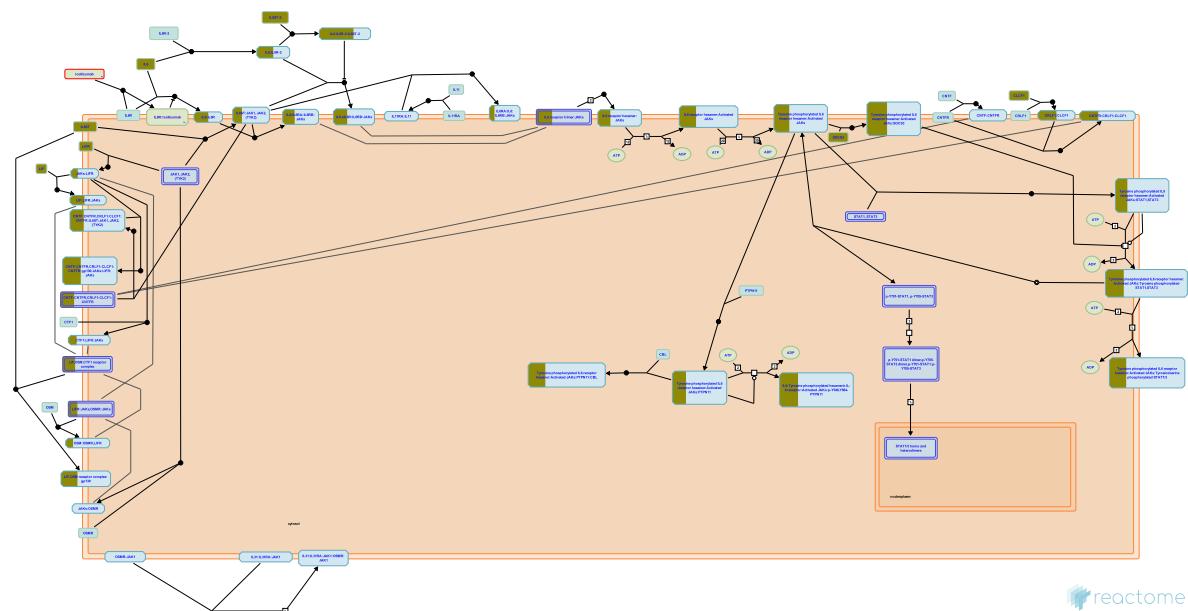
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## 15. Interleukin-6 family signaling (R-HSA-6783589)



**Cellular compartments:** plasma membrane, extracellular region.

The interleukin-6 (IL6) family of cytokines includes IL6, IL11, IL27, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin 1 and 2 (CT-1) and cardiotrophin-like cytokine (CLC) (Heinrich et al. 2003, Pflanz et al. 2002). The latest addition to this family is IL31, discovered in 2004 (Dillon et al. 2004). The family is defined largely by the shared use of the common signal transducing receptor Interleukin-6 receptor subunit beta (IL6ST, gp130). The IL31 receptor uniquely does not include this subunit, instead it uses the related IL31RA. The members of the IL6 family share very low sequence homology but are structurally highly related, forming anti-parallel four-helix bundles with a characteristic “up-up-down-down” topology (Rozwarski et al. 1994, Cornelissen et al. 2012).

Although each member of the IL6 family signals through a distinct receptor complex, their underlying signaling mechanisms are similar. Assembly of the receptor complex is followed by activation of receptor-associated Janus kinases (JAKs), believed to be constitutively associated with the receptor subunits. Activation of JAKs initiates downstream cytoplasmic signaling cascades that involve recruitment and phosphorylation of transcription factors of the Signal transducer and activator of transcription (STAT) family, which dimerize and translocate to the nucleus where they bind enhancer elements of target genes leading to transcriptional activation (Nakashima & Taga 1998).

Negative regulators of IL6 signaling include Suppressor of cytokine signals (SOCS) family members and PTPN11 (SHP-2).

IL6 is a pleiotropic cytokine with roles in processes including immune regulation, hematopoiesis, inflammation, oncogenesis, metabolic control and sleep.

IL6 and IL11 bind their corresponding specific receptors IL6R and IL11R respectively, resulting in dimeric complexes that subsequently associate with IL6ST, leading to IL6ST homodimer formation (in a hexameric or higher order complex) and signal initiation. IL6R alpha exists in transmembrane and soluble forms. The transmembrane form is mainly expressed by hepatocytes, neutrophils, monocytes/macrophages, and some lymphocytes. Soluble forms of IL6R (sIL6R) are also expressed by these cells. Two major mechanisms for the production of sIL6R have been proposed. Alternative splicing generates a transcript lacking the transmembrane domain by using splicing donor and acceptor sites that flank the transmembrane domain coding region. This also introduces a frameshift leading to the incorporation of 10 additional amino acids at the C terminus of sIL6R. A second mechanism for the generation of sIL6R is the proteolytic cleavage or 'shedding' of membrane-bound IL-6R. Two proteases ADAM10 and ADAM17 are thought to contribute to this (Briso et al. 2008). sIL6R can bind IL6 and stimulate cells that express gp130 but not IL6R alpha, a process that is termed trans-signaling. This explains why many cells, including hematopoietic progenitor cells, neuronal cells, endothelial cells, smooth muscle cells, and embryonic stem cells, do not respond to IL6 alone, but show a remarkable response to IL6/sIL6R. It is clear that the trans-signaling pathway is responsible for the pro-inflammatory activities of IL6 whereas the membrane bound receptor governs regenerative and anti-inflammatory IL6 activities

LIF, CNTF, OSM, CTF1, CRLF1 and CLCF1 signal via IL6ST:LIFR heterodimeric receptor complexes (Taga & Kishimoto 1997, Mousa & Bakhet 2013). OSM signals via a receptor complex consisting of IL6ST and OSMR. These cytokines play important roles in the regulation of complex cellular processes such as gene activation, proliferation and differentiation (Heinrich et al. 1998).

Antibodies have been developed to inhibit IL6 activity for the treatment of inflammatory diseases (Kopf et al. 2010).

## References

- Taga T & Kishimoto T (1997). Gp130 and the interleukin-6 family of cytokines. *Annu. Rev. Immunol.*, 15, 797-819. [🔗](#)
- Taga T (1996). Gp130, a shared signal transducing receptor component for hematopoietic and neuropoietic cytokines. *J. Neurochem.*, 67, 1-10. [🔗](#)
- Kishimoto T, Akira S, Narazaki M & Taga T (1995). Interleukin-6 family of cytokines and gp130. *Blood*, 86, 1243-54. [🔗](#)
- Heinrich PC, Behrmann I, Müller-Newen G, Schaper F & Graeve L (1998). Interleukin-6-type cytokine signalling through the gp130/Jak/STAT pathway. *Biochem. J.*, 334, 297-314. [🔗](#)
- Nakashima K & Taga T (1998). gp130 and the IL-6 family of cytokines: signaling mechanisms and thrombopoietic activities. *Semin. Hematol.*, 35, 210-21. [🔗](#)

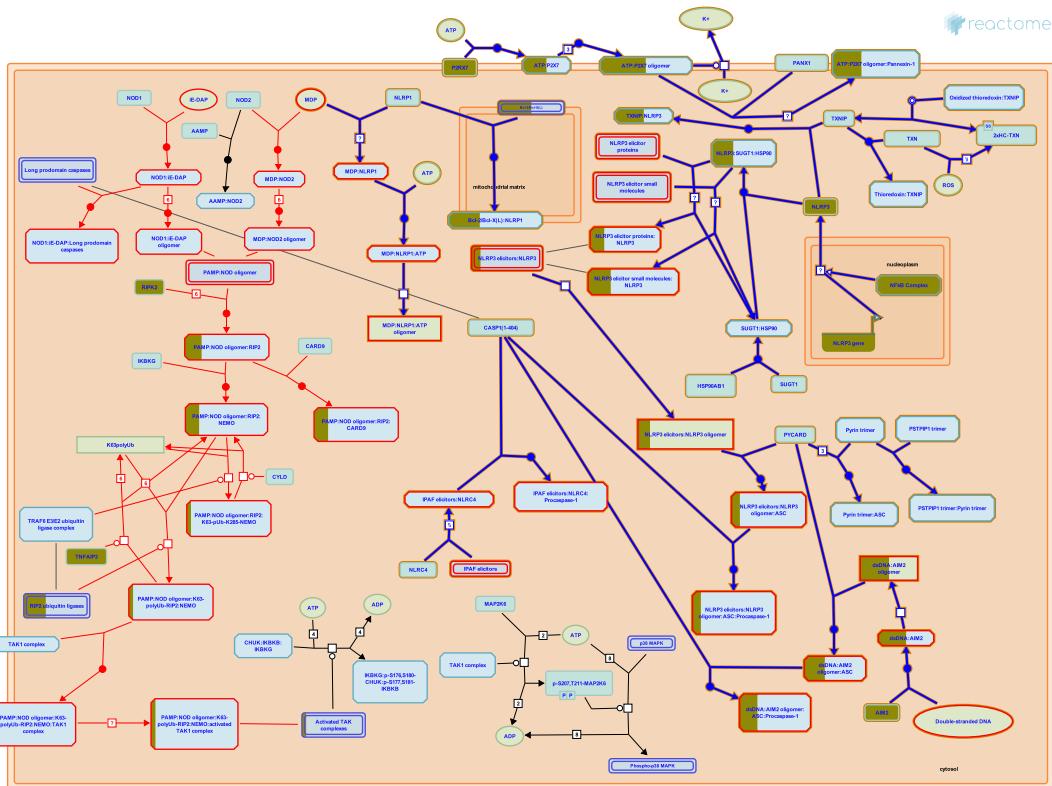
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## 16. Inflammasomes (R-HSA-622312)



**Cellular compartments:** cytosol.

In contrast to NOD1/2 some NLRPs function as large macromolecular complexes called 'Inflammasomes'. These multiprotein platforms control activation of the cysteinyl aspartate protease caspase-1 and thereby the subsequent cleavage of pro-interleukin 1B (pro-IL1B) into the active proinflammatory cytokine IL1B. Activation of caspase-1 is essential for production of IL1B and IL18, which respectively bind and activate the IL1 receptor (IL1R) and IL18 receptor (IL18R) complexes. IL1R and IL18R activate NF $\kappa$ B and other signaling cascades.

As the activation of inflammasomes leads to caspase-1 activation, inflammasomes can be considered an upstream step of the IL1R and IL18R signaling cascades, linking intracellular pathogen sensing to immune response pathways mediated by Toll-Like Receptors (TLRs). Monocytes and macrophages do not express pro-IL1B until stimulated, typically by TLRs (Franchi et al. 2009). The resulting pro-IL1B is not converted to IL1B unless a second stimulus activates an inflammasome. This requirement for two distinct stimuli allows tight regulation of IL1B/IL18 production, necessary because excessive IL-1B production is associated with numerous inflammatory diseases such as gout and rheumatoid arthritis (Masters et al. 2009).

There are at least four subtypes of the inflammasome, characterized by the NLRP. In addition the protein AIM2 can form an inflammasome. All activate caspase-1. NLRP1 (NALP1), NLRP3 (Cryopyrin, NALP3), IPAF (CARD12, NLRC4) and AIM2 inflammasomes all have clear physiological roles in vivo. NLRP2, NLRP6, NLRP7, NLRP10 and NLRP12 have been demonstrated to modulate caspase-1 activity in vitro but the significance of this is unclear (Mariathasan and Monack, 2007).

NLRP3 and AIM2 bind the protein 'apoptosis-associated speck-like protein containing a CARD' (ASC, also called PYCARD), via a PYD-PYD domain interaction. This in turn recruits procaspase-1 through a CARD-CARD interaction. NLRP1 and IPAF contain CARD domains and can bind procaspase-1 directly, though both are stimulated by ASC. Oligomerization of NLRPs is believed to bring procaspases into close proximity, leading to 'induced proximity' auto-activation (Boatright et al. 2003). This leads to formation of the active caspase tetramer. NLRPs are generally considered to be cytoplasmic proteins, but there is evidence for cytoplasmic-nuclear shuttling of the family member CIITA (LeibundGut-Landmann et al. 2004) and tissue/cell dependent NALP1 expression in the nucleus of neurons and lymphocytes (Kummer et al. 2007); the significance of this remains unclear.

## References

Lamkanfi M & Dixit VM (2009). Inflammasomes: guardians of cytosolic sanctity. Immunol Rev, 227, 95-105. [🔗](#)

Schroder K & Tschoopp J (2010). The inflammasomes. Cell, 140, 821-32. [🔗](#)

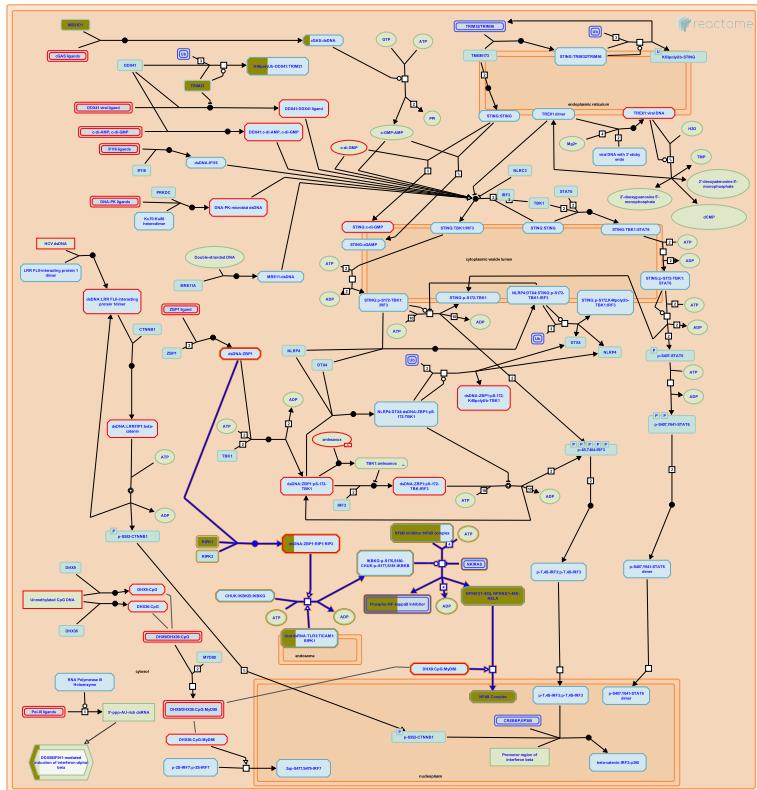
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2011-06-06	Reviewed	Rittinger K, Wong E
2020-11-20	Modified	Shorser S

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ENSG00000173039	Q04206				
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## 17. RIP-mediated NF $\kappa$ B activation via ZBP1 (R-HSA-1810476)



**Cellular compartments:** cytosol.

Overexpression of human or murine ZBP1 (DAI) in human embryonic kidney 293T cells (HEK293T) activated NF- $\kappa$ B-dependent promoter in a dose-dependent manner. Two RHIM-containing kinases RIP1 and RIP3 are implicated in ZBP1-induced NF $\kappa$ B activation (Rebsamen M et al 2009; Kaiser WJ et al 2008).

## References

Rebsamen M, Heinz LX, Meylan E, Michallet MC, Schroder K, Hofmann K, ... Tschopp J (2009). DAI/ZBP1 recruits RIP1 and RIP3 through RIP homotypic interaction motifs to activate NF- $\kappa$ B. *EMBO Rep*, 10, 916-22. [\[CrossRef\]](#)

Kaiser WJ, Upton JW & Mocarski ES (2008). Receptor-interacting protein homotypic interaction motif-dependent control of NF- $\kappa$ B activation via the DNA-dependent activator of IFN regulatory factors. *J Immunol*, 181, 6427-34. [\[CrossRef\]](#)

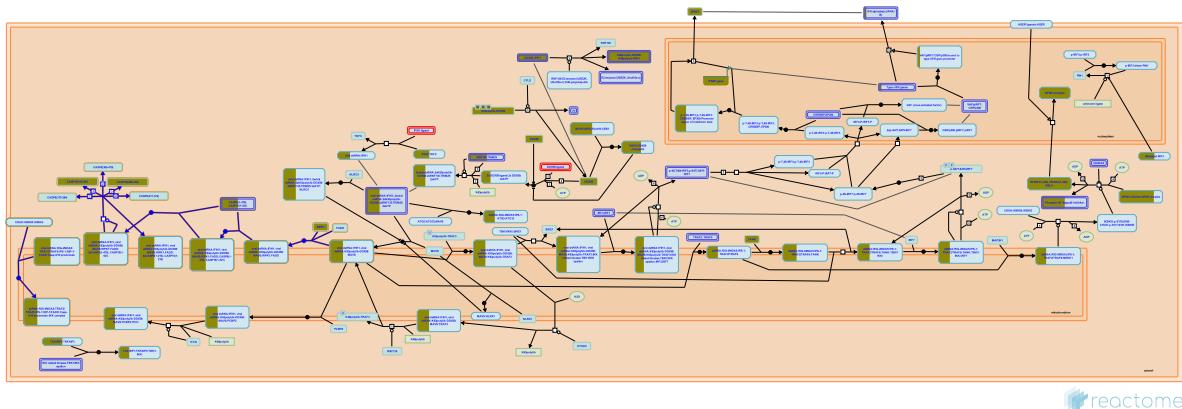
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2011-10-25	Created	Shamovsky V
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ENSG00000127666	Q8IUC6	ENSG00000137275	Q13546	ENSG00000173039	Q04206

## 18. NF-kB activation through FADD/RIP-1 pathway mediated by caspase-8 and -10 (R-HSA-933543)



reactome

**Cellular compartments:** mitochondrial outer membrane.

Fas-AssociatedDeathDomain (FADD) and receptor interacting protein 1 (RIP1) are death domain containing molecules that interact with the C-terminal portion of IPS-1 and induce NF-kB through interaction and activation of initiator caspases (caspase-8 and -10). Caspases are usually involved in apoptosis and inflammation but they also exhibit nonapoptotic functions. These nonapoptotic caspase functions involve prodomain-mediated activation of NF-kB. Processed caspases (caspase-8/10) encoding the DED (death effector domain) strongly activate NF-kB. The exact mechanism by which caspases mediate NF-kB activation is unclear, but the prodomains of caspase-8/10 may act as a scaffolding and allow the recruitment of the IKK complex in association with other signaling molecules.

## References

- Takahashi K, Kawai T, Kumar H, Sato S, Yonehara S & Akira S (2006). Roles of caspase-8 and caspase-10 in innate immune responses to double-stranded RNA. *J Immunol*, 176, 4520-4. [🔗](#)
- Shikama Y, Yamada M & Miyashita T (2003). Caspase-8 and caspase-10 activate NF-kappaB through RIP, NIK and IKKalpha kinases. *Eur J Immunol*, 33, 1998-2006. [🔗](#)
- Lamkanfi M, Declercq W, Vanden Berghe T & Vandenebeele P (2006). Caspases leave the beaten track: caspase-mediated activation of NF-kappaB. *J Cell Biol*, 173, 165-71. [🔗](#)
- Kawai T, Takahashi K, Sato S, Coban C, Kumar H, Kato H, ... Takeuchi O (2005). IPS-1, an adaptor triggering RIG-I- and Mda5-mediated type I interferon induction. *Nat Immunol*, 6, 981-8. [🔗](#)

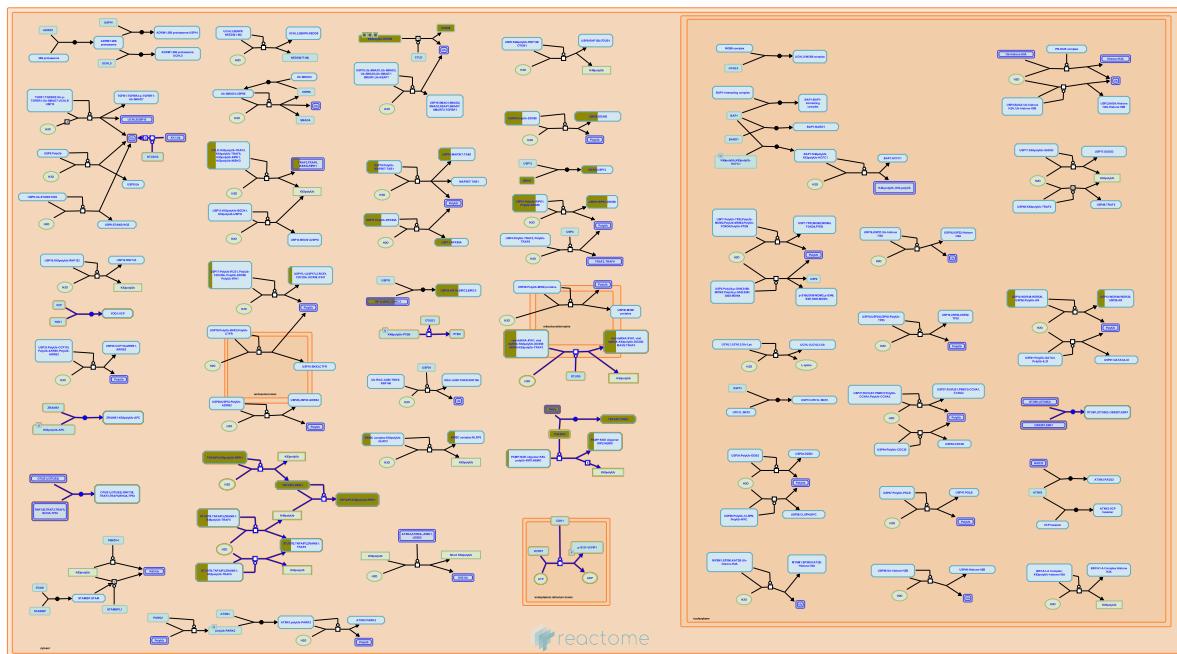
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ENSG0000121060	Q14258	ENSG0000137275	Q13546		

## 19. Ovarian tumor domain proteases (R-HSA-5689896)



Humans have 16 Ovarian tumour domain (OTU) family DUBs that can be evolutionarily divided into three classes, the OTUs, the Otubains (OTUBs), and the A20-like OTUs (Komander et al. 2009).

OTU family DUBs can be highly selective in the type of ubiquitin crosslinks they cleave. OTUB1 is specific for K48-linked chains, whereas OTUB2 can cleave K11, K63 and K48-linked poly-Ub (Wang et al. 2009, Edelmann et al. 2009, Mevissen et al. 2013). A20 prefers K48-linked chains, Cezanne is specific for K11-linked chains, and TRABID acts on both K29, K33 and K63-linked poly-Ub (Licchesi et al. 2011, Komander & Barford 2008, Bremm et al. 2010, Mevissen et al. 2013). The active site of the OTU domain contains an unusual loop not seen in other thiol-DUBs and can lack an obvious catalytic Asp/Asn (Komander & Barford 2009, Messick et al. 2008, Lin et al. 2008). A20 and OTUB1 have an unusual mode of activity, binding directly to E2 enzymes (Nakada et al. 2010, Wertz et al. 2004).

## References

Mevissen TE, Hospenthal MK, Geurink PP, Elliott PR, Akutsu M, Arnaudo N, ... Komander D (2013). OTU deubiquitinases reveal mechanisms of linkage specificity and enable ubiquitin chain restriction analysis. *Cell*, 154, 169-84. [View](#)

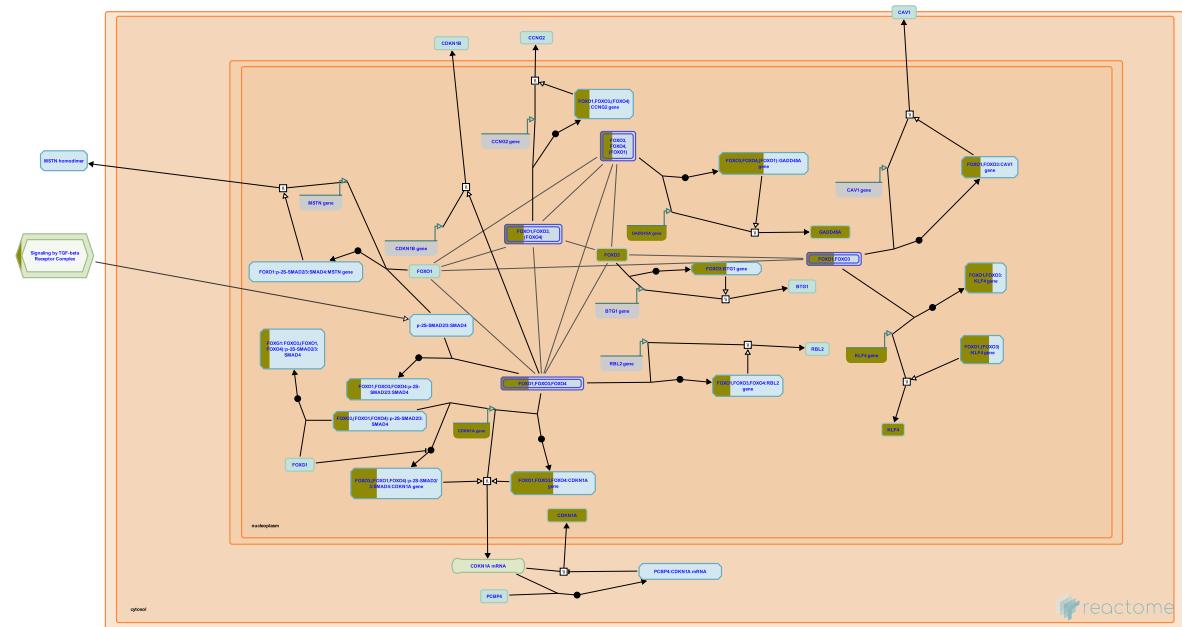
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ENSG0000137275	Q13546	ENSG0000145901	Q15025	ENSG0000168884	Q8NFZ5

## 20. FOXO-mediated transcription of cell cycle genes (R-HSA-9617828)



FOXO transcription factors induce expression of several genes that negatively regulate proliferation of different cell types, such as erythroid progenitors (Bakker et al. 2004, Wang et al. 2015) and neuroepithelial progenitor cells in the telencephalon (Seoane et al. 2004).

Transcription of cyclin-dependent kinase (CDK) inhibitors CDKN1A (p21Cip1) is directly stimulated by FOXO1, FOXO3 and FOXO4 (Seoane et al. 2004, Tinkum et al. 2013). FOXO transcription factors can cooperate with the SMAD2/3:SMAD4 complex to induce CDKN1A transcription in response to TGF-beta signaling (Seoane et al. 2004).

FOXO transcription factors FOXO1, FOXO3 and FOXO4 stimulate transcription of the CDKN1B (p27Kip1) gene, but direct binding of FOXOs to the CDKN1B gene locus has not been demonstrated (Dijkers et al. 2000, Medema et al. 2000, Lees et al. 2008).

FOXO3 and FOXO4, and possibly FOXO1, directly stimulate transcription of the GADD45A gene (Tran et al. 2002, Furukawa Hibi et al. 2002, Hughes et al. 2011, Sengupta et al. 2011, Ju et al. 2014).

Transcription of the retinoblastoma family protein RBL2 (p130), involved in the maintenance of quiescent (G0) state, is directly stimulated by FOXO1, FOXO3 and FOXO4 (Kops et al. 2002, Chen et al. 2006).

Transcription of the anti-proliferative protein CCNG2 is directly stimulated by FOXO1 and FOXO3, and possibly FOXO4 (Martinez Gac et al. 2004, Chen et al. 2006). Transcription of the anti-proliferative protein BTG1 is directly stimulated by FOXO3 (Bakker et al. 2004, Bakker et al. 2007, Wang et al. 2015).

Transcription of CAV1, encoding caveolin-1, involved in negative regulation of growth factor receptor signaling and establishment of quiescent cell phenotype, is directly stimulated by FOXO1 and FOXO3 (van den Heuvel et al. 2005, Roy et al. 2008, Nho et al. 2013, Sisci et al. 2013).

FOXO1 and FOXO3 promote transcription of the KLF4 gene, encoding a transcription factor Krueppel-like factor 4, which inhibits proliferation of mouse B cells (Yusuf et al. 2008).

FOXO1, together with the p-2S-SMAD2/3:SMAD4 complex, stimulates transcription of the MSTN gene, encoding myostatin, a TGF-beta family member that stimulates differentiation of myoblasts (Allen and Unterman 2007).

## References

- Bakker WJ, van Dijk TB, Parren-van Amelsvoort M, Kolbus A, Yamamoto K, Steinlein P, ... von Lindern M (2007). Differential regulation of Foxo3a target genes in erythropoiesis. *Mol. Cell. Biol.*, 27, 3839-3854. [🔗](#)
- Bakker WJ, Blázquez-Domingo M, Kolbus A, Besooyen J, Steinlein P, Beug H, ... van Dijk TB (2004). FoxO3a regulates erythroid differentiation and induces BTG1, an activator of protein arginine methyl transferase 1. *J. Cell Biol.*, 164, 175-84. [🔗](#)
- Chen J, Yusuf I, Andersen HM & Fruman DA (2006). FOXO transcription factors cooperate with delta EF1 to activate growth suppressive genes in B lymphocytes. *J. Immunol.*, 176, 2711-21. [🔗](#)
- Martínez-Gac L, Marqués M, García Z, Campanero MR & Carrera AC (2004). Control of cyclin G2 mRNA expression by forkhead transcription factors: novel mechanism for cell cycle control by phosphoinositide 3-kinase and forkhead. *Mol. Cell. Biol.*, 24, 2181-9. [🔗](#)
- Medema RH, Kops GJ, Bos JL & Burgering BM (2000). AFX-like Forkhead transcription factors mediate cell-cycle regulation by Ras and PKB through p27kip1. *Nature*, 404, 782-7. [🔗](#)

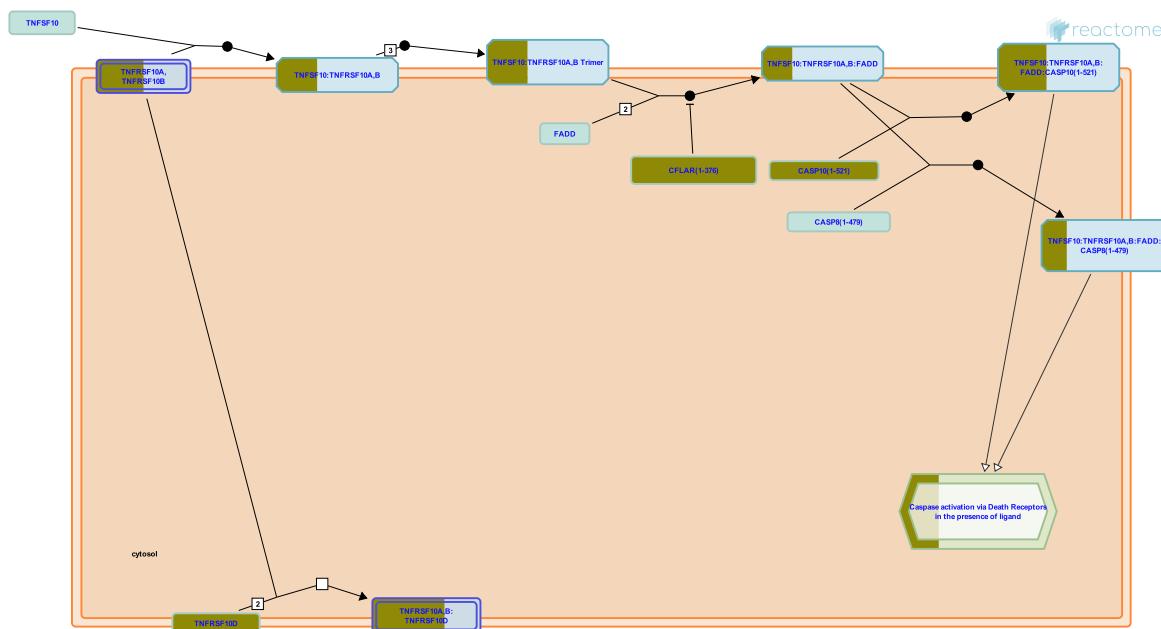
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## 21. TRAIL signaling (R-HSA-75158)



Tumor necrosis factor-related apoptosis-inducing ligand or Apo 2 ligand (TRAIL/Apo2L) is a member of the tumor necrosis factor (TNF) family. This group of apoptosis induction pathways all work through protein interactions mediated by the intracellular death domain (DD), encoded within the cytoplasmic domain of the receptor. TRAIL selectively induces apoptosis through its interaction with the Fas-associated death domain protein (FADD) and caspase-8/10 (Wang S & el-Deiry WS 2003; Sprick MR et al. 2002). TRAIL and its receptors, TRAIL-R1 and TRAIL-R2, were shown to be rapidly endocytosed via clathrin-dependent and -independent manner in human Burkitt's lymphoma B cells (BJAB) (Kohlhaas SL et al. 2007). However, FADD and caspase-8 were able to bind TRAIL-R1/R2 in TRAIL-stimulated BJAB cells at 4<sup>o</sup>C (at which membrane trafficking is inhibited), suggesting that the endocytosis was not required for an assembly of the functional TRAIL DISC complex. Moreover, blocking of clathrin-dependent endocytosis did not interfere with the capacity of TRAIL to promote apoptosis (Kohlhaas SL et al. 2007).

## References

Wang S & el-Deiry WS (2003). TRAIL and apoptosis induction by TNF-family death receptors. *Oncogene*, 22, 8628-33. [View](#)

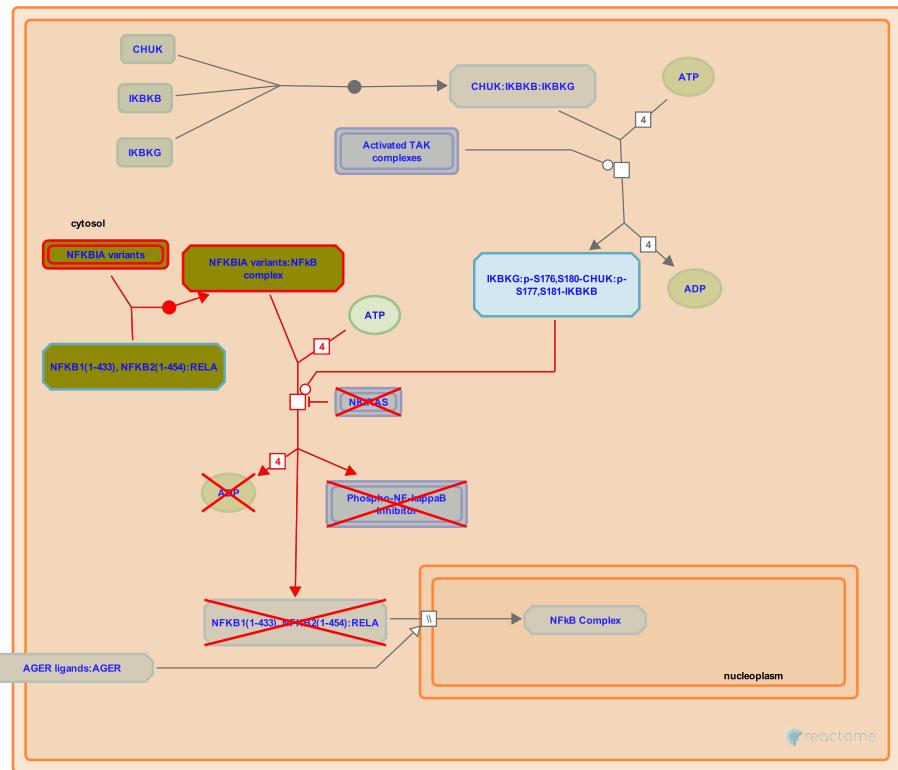
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## 22. IkBA variant leads to EDA-ID (R-HSA-5603029)



**Diseases:** primary immunodeficiency disease.

The nuclear factor kappa B (NF $\kappa$ B) family of transcription factors is kept inactive in the cytoplasm by the inhibitor of kappa B (IkB) family members IKBA (IkB alpha, NFKBIA), IKBB (IkB beta, NFKBIB) and IKBE (IkB epsilon, NFKBIE) (Oeckinghaus A and Ghosh S 2009). Multiple stimuli such as inflammatory cytokines, microbial products or various types of stress activate NF $\kappa$ B signaling leading to stimuli-induced phosphorylation of IkB molecule (Scherer DC et al. 1995; Alkalay I et al. 1995; Lawrence T 2009; Hoesel B and Schmid JA 2013). The phosphorylation of IkB proteins triggers their polyubiquitination and subsequent degradation by 26S proteasome, allowing free NF $\kappa$ B dimer to translocate to the nucleus where it directs the expression of target genes. Studies have identified an autosomal dominant form of ectodermal dysplasia with immunodeficiency (AD-EDA-ID) caused by a hypermorphic heterozygous mutation of NFKBIA/IKBA gene. The IKBA defects prevent the phosphorylation and degradation of IKBA protein resulting in gain-of-function condition with the enhanced inhibitory capacity of IKBA in sequestering NF $\kappa$ B dimers in the cytoplasm (Courtois G et al. 2003; Lopes-Granados E et al. 2008; Schimke LF et al. 2013).

## References

- Schimke LF, Rieber N, Rylaarsdam S, Cabral-Marques O, Hubbard N, Puel A, ... Torgerson TR (2013). A novel gain-of-function IKBA mutation underlies ectodermal dysplasia with immunodeficiency and polyendocrinopathy. *J. Clin. Immunol.*, 33, 1088-99. [🔗](#)
- Lopez-Granados E, Keenan JE, Kinney MC, Leo H, Jain N, Ma CA, ... Jain A (2008). A novel mutation in NFKBIA/IKBA results in a degradation-resistant N-truncated protein and is associated with ectodermal dysplasia with immunodeficiency. *Hum. Mutat.*, 29, 861-8. [🔗](#)

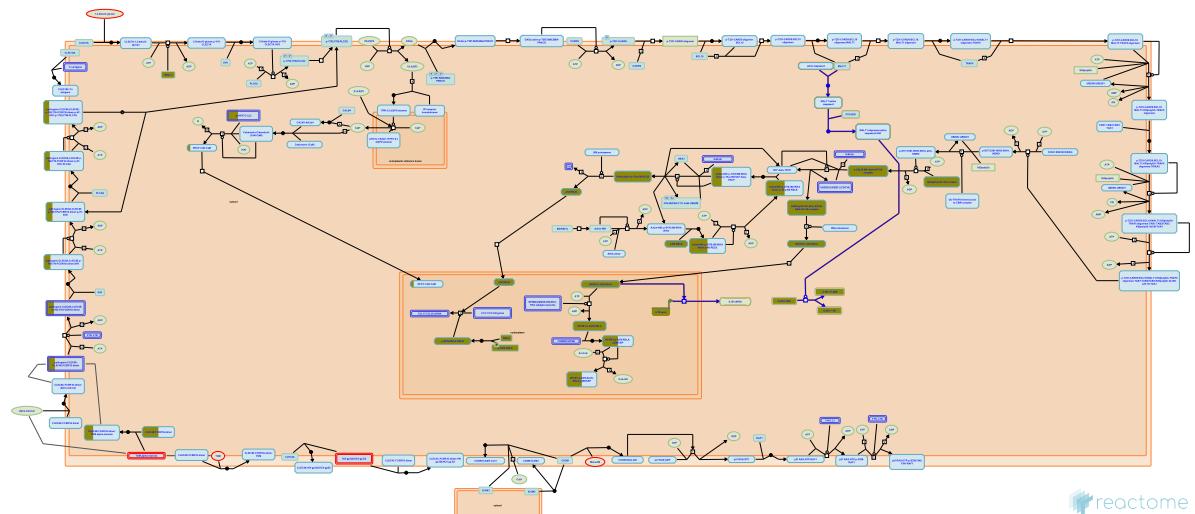
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ENSG00000109320	P19838	ENSG00000173039	Q04206

## 23. CLEC7A/inflammasome pathway (R-HSA-5660668)



**Cellular compartments:** plasma membrane, cytosol.

Antifungal immunity through the induction of T-helper 17 cells (TH17) responses requires the production of mature, active interleukin-1beta (IL1B). CLEC7A (dectin-1) through the SYK route induces activation of NF- $\kappa$ B and transcription of the gene encoding pro-IL1B via the CARD9-BCL10-MALT1 complex as well as the formation and activation of a MALT1-caspase-8-ASC complex that mediated the processing of pro-IL1B. The inactive precursor pro-IL1B has to be processed into mature bioactive form of IL1B and is usually mediated by inflammatory cysteine protease caspase-1. Gringhuis et al. showed that CLEC7A mediated processing of IL1B occurs through two distinct mechanisms: CLEC7A triggering induced a primary noncanonical caspase-8 inflammasome for pro-IL1B processing that was independent of caspase-1 activity, whereas some fungi triggered a second additional mechanism that required activation of the NLRP3/caspase 1 inflammasome. Unlike the canonical caspase-1 inflammasome, CLEC7A mediated noncanonical caspase-8-dependent inflammasome is independent of pathogen internalization. CLEC7A/inflammasome pathway enables the host immune system to mount a protective TH17 response against fungi and bacterial infection (Gringhuis et al. 2012, Cheng et al. 2011).

## References

- Gringhuis SI, Kaptein TM, Wevers BA, Theelen B, van der Vlist M, Boekhout T & Geijtenbeek TB (2012). Dectin-1 is an extracellular pathogen sensor for the induction and processing of IL-1 $\beta$  via a noncanonical caspase-8 inflammasome. *Nat. Immunol.*, 13, 246-54. [\[CrossRef\]](#)
- Cheng SC, van de Veerdonk FL, Lenardon M, Stoffels M, Plantinga T, Smeekens S, ... Netea MG (2011). The dectin-1/inflammasome pathway is responsible for the induction of protective T-helper 17 responses that discriminate between yeasts and hyphae of *Candida albicans*. *J. Leukoc. Biol.*, 90, 357-66. [\[CrossRef\]](#)

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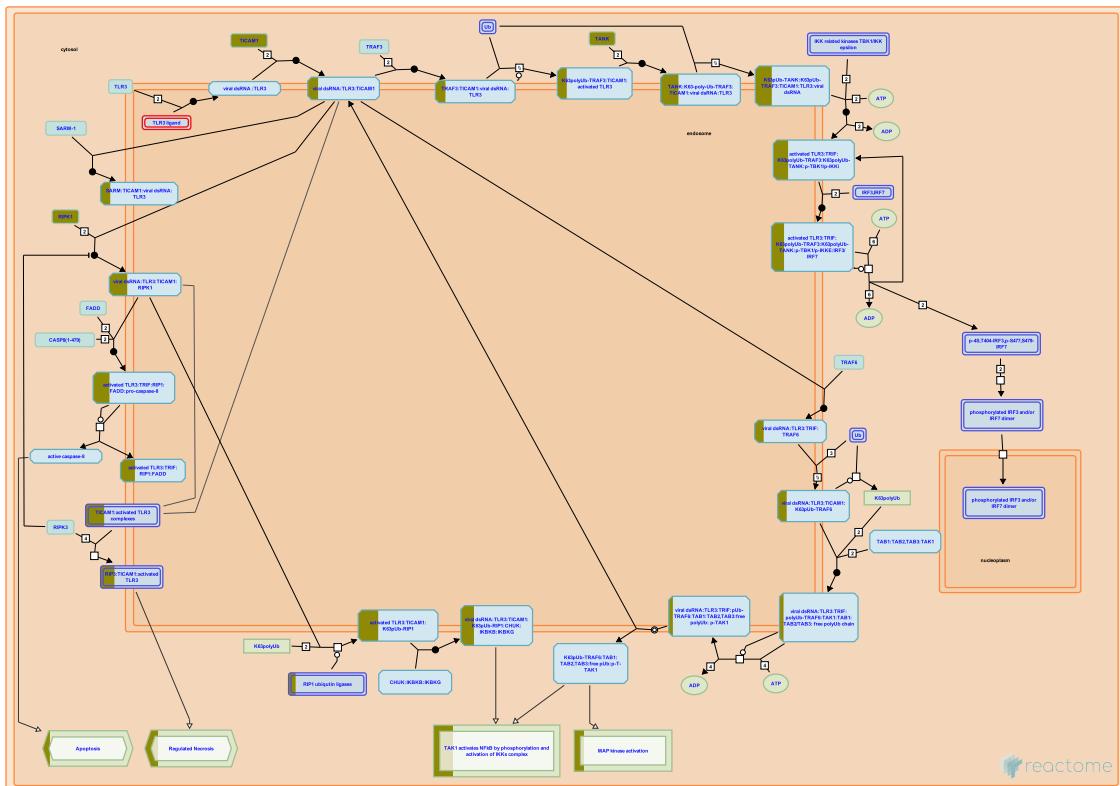
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2020-11-24	Modified	Shorser S

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## 24. 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-kappaB 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. [🔗](#)
- Sen GC & Sarkar SN (2005). Transcriptional signaling by double-stranded RNA: role of TLR3. *Cytokine Growth Factor Rev*, 16, 1-14. [🔗](#)
- 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. [🔗](#)

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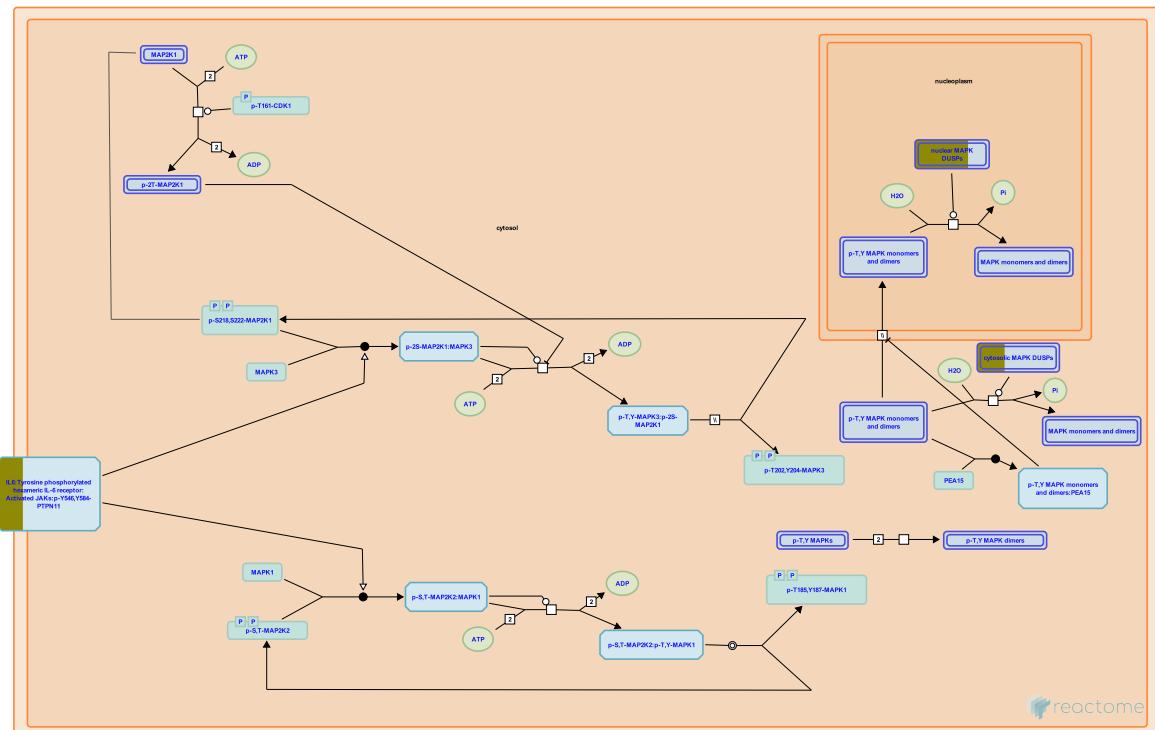
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2005-11-10	Created	Gillespie ME
2006-04-24	Reviewed	Gay NJ
2009-09-29	Revised	Shamovsky V

Date	Action	Author
2011-08-12	Edited	Shamovsky V
2020-11-24	Modified	Shorser S

### Entities found in this pathway (15)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ENSG0000023445	Q13489	ENSG0000034152	P46734	ENSG0000077150	Q00653
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ENSG0000109320	P19838	ENSG0000110330	Q13490	ENSG0000127666	Q8IUC6
ENSG0000134070	O43187	ENSG0000136560	Q92844	ENSG0000137275	Q13546
ENSG0000143479	P49137	ENSG0000168884	Q8NFZ5	ENSG0000173039	Q04206

## 25. 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. [🔗](#)

## Edit history

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

## Entities found in this pathway (7)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ENSG00000111266	Q9BY84	ENSG00000120129	P28562	ENSG00000134352	P40189-1
ENSG00000136244	P05231	ENSG00000138166	Q16690	ENSG00000158050	Q05923
ENSG00000184545	Q13202				

## 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.

### Entities (354)

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ENSG00000026751	Q9NQ25	ENSG00000034152	P46734	ENSG00000043462	Q13094
ENSG00000047365	Q8WZ64	ENSG00000049130	P21583-1	ENSG00000049249	Q07011
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ENSG00000072364	Q9UHB7	ENSG00000073756	P35354	ENSG00000076554	P55327
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ENSG00000086061	P31689	ENSG00000086062	P15291	ENSG00000086544	P27987, Q96DU7
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ENSG00000101017	P25942-1	ENSG00000101333	Q15147	ENSG00000101384	P78504
ENSG00000102554	Q13887	ENSG00000103168	Q15572	ENSG00000103257	Q01650
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## 7. Identifiers not found

These 395 identifiers were not found neither mapped to any entity in Reactome.

ENSG0000005889 ENSG0000008118 ENSG0000010818 ENSG0000013588 ENSG0000020577 ENSG0000042062 ENSG0000054598 ENSG00000059728 ENSG0000066697 ENSG0000075426 ENSG0000078081 ENSG0000078804 ENSG0000085185 ENSG0000085511 ENSG00000089351 ENSG0000099860 ENSG0000101825 ENSG0000102794 ENSG0000102921 ENSG0000103241 ENSG0000106125 ENSG00000108700 ENSG0000110422 ENSG0000110848 ENSG0000111860 ENSG0000111913 ENSG0000112149 ENSG0000112245 ENSG00000114529 ENSG0000114784 ENSG0000116044 ENSG0000116285 ENSG0000117036 ENSG0000117090 ENSG0000118263 ENSG00000119138 ENSG0000119862 ENSG0000119866 ENSG0000121101 ENSG0000121577 ENSG0000122035 ENSG0000122591 ENSG00000124201 ENSG0000124479 ENSG0000126003 ENSG0000126778 ENSG0000128284 ENSG0000128335 ENSG0000128710 ENSG00000131669 ENSG0000132823 ENSG0000132975 ENSG0000133069 ENSG0000133874 ENSG0000134326 ENSG0000135373 ENSG00000136048 ENSG0000136630 ENSG0000137094 ENSG0000137449 ENSG0000137507 ENSG0000137571 ENSG0000137747 ENSG00000137936 ENSG0000137965 ENSG0000138670 ENSG0000138771 ENSG0000140379 ENSG0000140511 ENSG0000144655 ENSG00000144824 ENSG0000146278 ENSG0000146776 ENSG0000146839 ENSG0000147324 ENSG0000149289 ENSG0000150510 ENSG00000152784 ENSG0000153993 ENSG0000154099 ENSG0000154548 ENSG0000154640 ENSG0000154642 ENSG0000155307 ENSG00000156273 ENSG0000156875 ENSG0000157111 ENSG0000157654 ENSG0000158615 ENSG0000162616 ENSG0000162783 ENSG00000163659 ENSG0000163673 ENSG0000163874 ENSG0000164188 ENSG0000164236 ENSG0000164543 ENSG0000164920 ENSG00000164949 ENSG0000165259 ENSG0000165312 ENSG0000165379 ENSG0000165694 ENSG0000165997 ENSG0000166002 ENSG00000166881 ENSG0000167034 ENSG0000167693 ENSG0000167874 ENSG0000168062 ENSG0000168334 ENSG0000168955 ENSG00000169504 ENSG0000170542 ENSG0000171811 ENSG0000172403 ENSG0000172738 ENSG0000172986 ENSG0000173451 ENSG00000173926 ENSG0000175155 ENSG0000175183 ENSG0000175895 ENSG0000176046 ENSG0000177311 ENSG0000178033 ENSG00000178860 ENSG0000179165 ENSG0000179428 ENSG0000179431 ENSG0000179604 ENSG0000180316 ENSG0000180828 ENSG00000182253 ENSG0000182575 ENSG0000184226 ENSG0000184602 ENSG0000185112 ENSG0000185215 ENSG0000185433 ENSG00000187479 ENSG0000188396 ENSG0000188886 ENSG0000189067 ENSG0000196449 ENSG0000196843 ENSG0000197415 ENSG00000198133 ENSG0000198355 ENSG0000198535 ENSG0000198604 ENSG0000198839 ENSG0000203364 ENSG0000204261 ENSG00000205189 ENSG0000205502 ENSG0000213443 ENSG0000213516 ENSG0000214289 ENSG0000214900 ENSG0000218565 ENSG00000219565 ENSG0000221949 ENSG0000221963 ENSG0000222041 ENSG0000222043 ENSG0000223552 ENSG0000223711 ENSG00000224093 ENSG0000224875 ENSG0000225492 ENSG0000225626 ENSG0000225792 ENSG0000225886 ENSG0000225889 ENSG00000226012 ENSG0000226081 ENSG0000226312 ENSG0000226380 ENSG0000227018 ENSG0000227199 ENSG0000227908 ENSG00000228988 ENSG0000229619 ENSG0000229644 ENSG0000229664 ENSG0000229781 ENSG0000230638 ENSG0000230641 ENSG00000230844 ENSG0000230943 ENSG0000231123 ENSG0000231233 ENSG0000231560 ENSG0000231574 ENSG0000231808 ENSG00000232043 ENSG0000232118 ENSG0000232133 ENSG0000232194 ENSG0000232517 ENSG0000232615 ENSG0000232618 ENSG00000232713 ENSG0000232927 ENSG0000233138 ENSG0000234191 ENSG0000234431 ENSG0000234511 ENSG0000234883 ENSG00000235700 ENSG0000236056 ENSG0000236213 ENSG0000236276 ENSG0000236304 ENSG0000236345 ENSG0000236530 ENSG00000236739 ENSG0000236914 ENSG0000236939 ENSG0000237372 ENSG0000237499 ENSG0000237513 ENSG0000237522 ENSG00000237732 ENSG0000237892 ENSG0000237931 ENSG0000239569 ENSG0000240050 ENSG0000240296 ENSG0000240445 ENSG00000241280 ENSG0000241978 ENSG0000242113 ENSG0000242258 ENSG0000244676 ENSG0000244953 ENSG0000245080 ENSG00000245651 ENSG0000246214 ENSG0000249138 ENSG0000249173 ENSG0000249252 ENSG0000249738 ENSG0000250274 ENSG00000250602 ENSG0000250889 ENSG0000250929 ENSG0000251136 ENSG0000251139 ENSG0000251194 ENSG0000251196 ENSG00000251323 ENSG0000251393 ENSG0000251867 ENSG0000251922 ENSG0000253213 ENSG0000253372 ENSG0000253535 ENSG00000254102 ENSG0000254281 ENSG0000254287 ENSG0000254531 ENSG0000254612 ENSG0000254959 ENSG0000255282 ENSG00000255363 ENSG0000255389 ENSG0000255443 ENSG0000255521 ENSG0000255605 ENSG0000255750 ENSG0000255874 ENSG00000256167 ENSG0000256249 ENSG0000256268 ENSG0000257202 ENSG0000257242 ENSG0000258572 ENSG0000258738 ENSG00000258922 ENSG0000259075 ENSG0000259326 ENSG0000259834 ENSG0000260231 ENSG0000260244 ENSG0000260360 ENSG00000260583 ENSG0000260898 ENSG0000261097 ENSG0000261267 ENSG0000261504 ENSG0000261604 ENSG0000261618 ENSG00000262211 ENSG0000264501 ENSG0000266094 ENSG0000266698 ENSG0000266708 ENSG0000266709 ENSG0000266947 ENSG00000266978 ENSG0000267034 ENSG0000267325 ENSG0000267365 ENSG0000267520 ENSG0000267607 ENSG0000267712 ENSG00000269680 ENSG0000269826 ENSG0000269906 ENSG0000270008 ENSG0000270390 ENSG0000270607 ENSG0000270792 ENSG00000271856 ENSG0000272264 ENSG0000272273 ENSG0000272841 ENSG0000272986 ENSG0000273129 ENSG0000273320 ENSG00000273320

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