



Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 78 on 02/12/2021. The web link to these results is:

<https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMTEyMDIwNDUxMTdfOTk2Nw%3D%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:

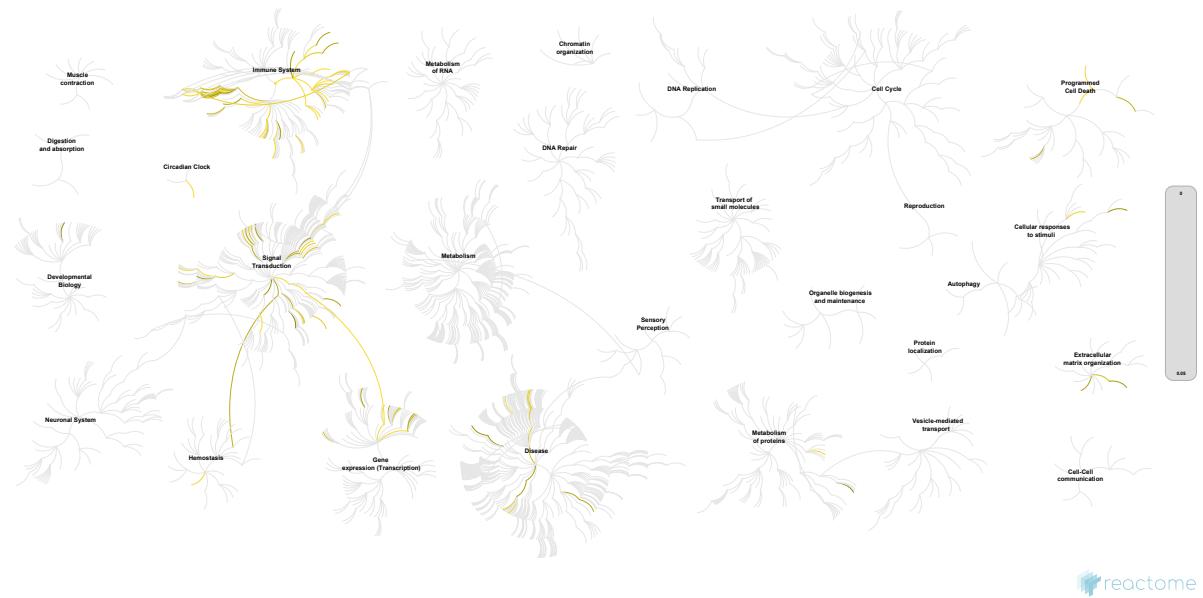
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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. ↗
- 333 out of 506 identifiers in the sample were found in Reactome, where 962 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 MjAyMTEyMDIwNDUxMTdfOTk2Nw%3D%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	48 / 86	0.006	1.11e-16	2.89e-14	13 / 15	0.001
Cytokine Signaling in Immune system	138 / 1,092	0.077	1.11e-16	2.89e-14	338 / 708	0.052
Signaling by Interleukins	94 / 643	0.045	1.11e-16	2.89e-14	234 / 493	0.036
Interleukin-4 and Interleukin-13 signaling	43 / 211	0.015	1.11e-16	2.89e-14	11 / 47	0.003
Immune System	180 / 2,684	0.188	2.09e-10	4.35e-08	609 / 1,623	0.12
Chemokine receptors bind chemokines	16 / 57	0.004	7.13e-09	1.23e-06	8 / 19	0.001
TNFR2 non-canonical NF- κ B pathway	16 / 104	0.007	1.71e-05	0.003	30 / 43	0.003
Interferon alpha/beta signaling	22 / 186	0.013	2.87e-05	0.004	15 / 22	0.002
TNFs bind their physiological receptors	8 / 30	0.002	5.93e-05	0.007	8 / 13	9.58e-04
TNF receptor superfamily (TNFSF) members mediating non-canonical NF- κ B pathway	6 / 17	0.001	1.12e-04	0.012	8 / 12	8.84e-04
BMAL1:CLOCK,NPAS2 activates circadian gene expression	9 / 43	0.003	1.29e-04	0.012	9 / 20	0.001
Interleukin-1 processing	5 / 12	8.41e-04	1.97e-04	0.017	2 / 5	3.68e-04
Regulated Necrosis	11 / 77	0.005	6.30e-04	0.05	18 / 57	0.004
NGF-stimulated transcription	9 / 56	0.004	8.58e-04	0.061	14 / 37	0.003
Transcriptional activity of SMAD2/SMAD3:SMAD4 heterotrimer	9 / 57	0.004	9.69e-04	0.061	15 / 44	0.003
Interleukin-1 family signaling	17 / 167	0.012	0.001	0.061	50 / 80	0.006
Interferon Signaling	31 / 394	0.028	0.001	0.061	37 / 69	0.005
TRAF3-dependent IRF activation pathway	5 / 18	0.001	0.001	0.061	8 / 11	8.10e-04
Inactivation of CSF3 (G-CSF) signaling	6 / 27	0.002	0.001	0.061	9 / 9	6.63e-04
Nuclear events stimulated by ALK signaling in cancer	6 / 27	0.002	0.001	0.061	5 / 9	6.63e-04
Interleukin-18 signaling	4 / 11	7.71e-04	0.001	0.061	4 / 4	2.95e-04
SMAD2/SMAD3:SMAD4 heterotrimer regulates transcription	7 / 38	0.003	0.001	0.061	10 / 19	0.001
RAF-independent MAPK1/3 activation	6 / 28	0.002	0.002	0.061	4 / 12	8.84e-04

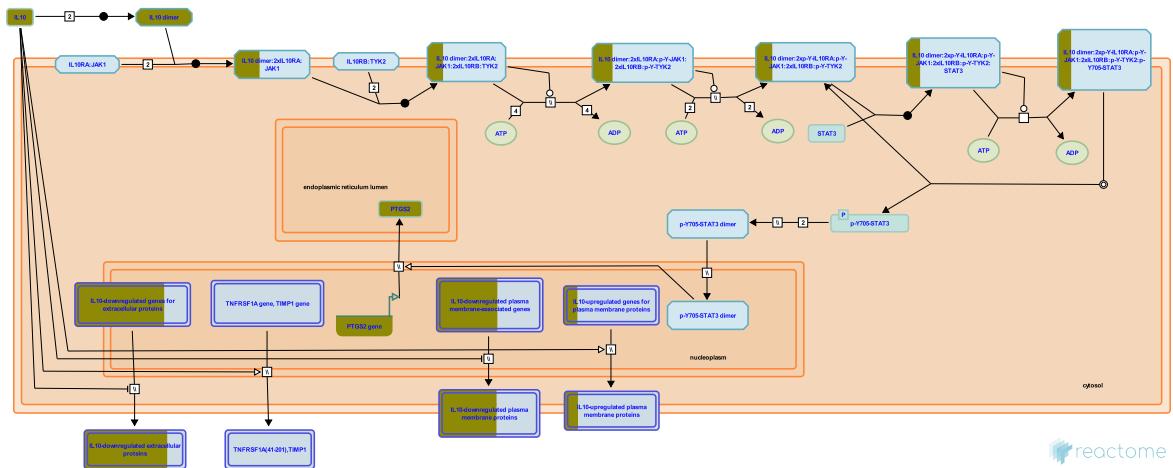
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
RIP-mediated NFkB activation via ZBP1	5 / 19	0.001	0.002	0.061	3 / 4	2.95e-04
Peptide ligand-binding receptors	19 / 203	0.014	0.002	0.061	14 / 77	0.006

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

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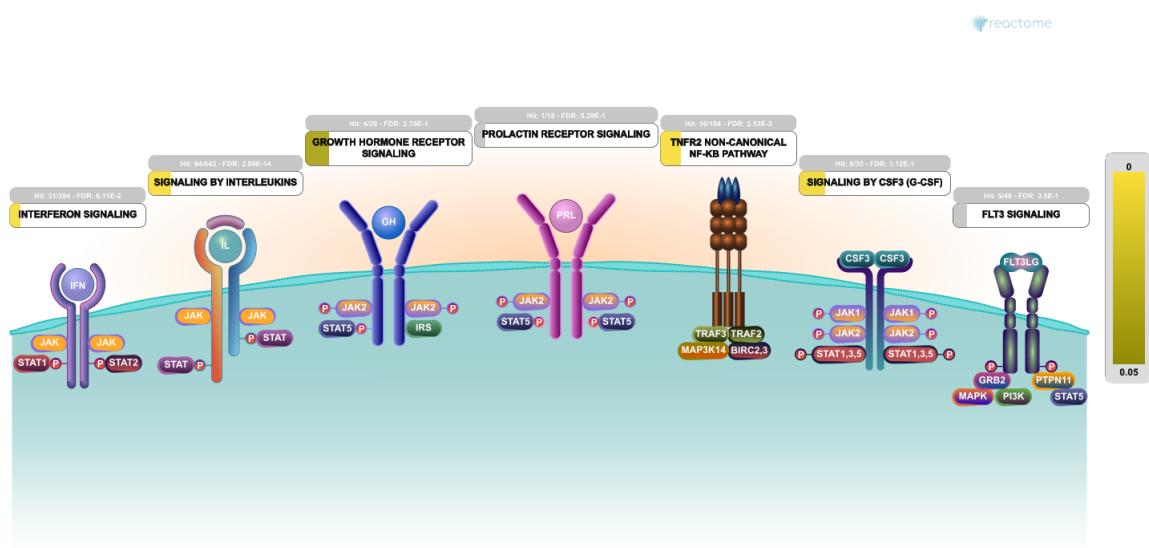
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2015-06-17	Created	Jupe S
2016-09-05	Reviewed	Meldal BH
2016-11-14	Edited	Jupe S
2021-09-20	Modified	Weiser JD

25 submitted entities found in this pathway, mapping to 49 Reactome entities

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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

Feldmann M & Oppenheim J (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>

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

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

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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
2021-09-10	Modified	Weiser JD

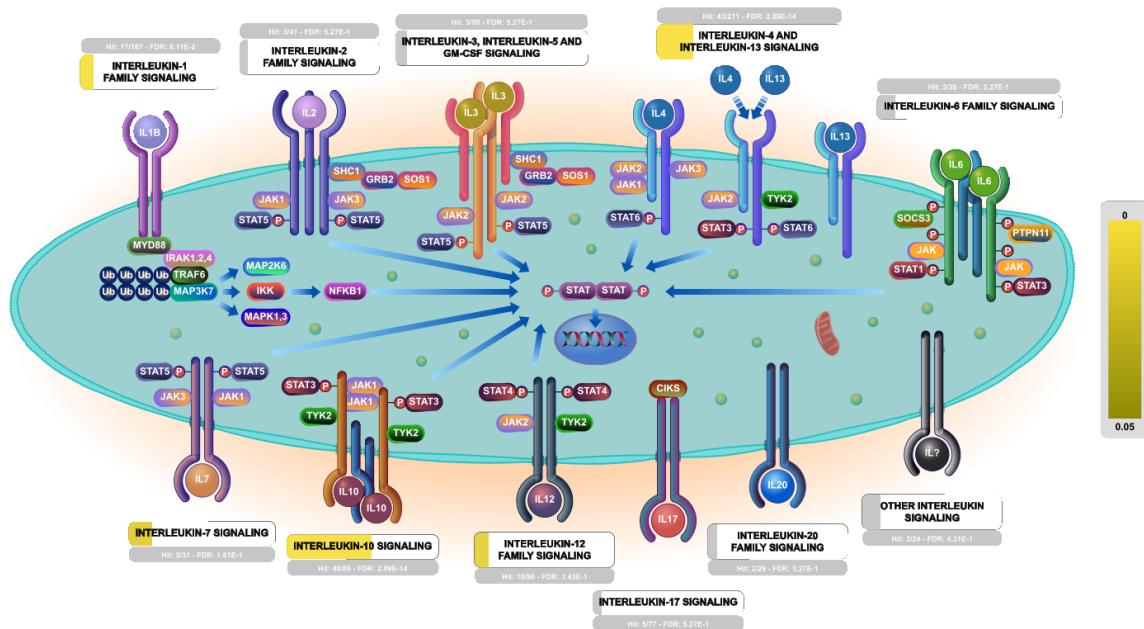
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3. Signaling by Interleukins (R-HSA-449147)



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

- Dinarello CA (2009). Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol*, 27, 519-50. [🔗](#)
- Komlosi Z, Kucuksezer UC, Frei R, Huitema C, Garbani M, Pezer M, ... Eiwegger T (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. [🔗](#)
- Vosshenrich CA & Di Santo JP (2002). Interleukin signaling. *Curr Biol*, 12, R760-3. [🔗](#)

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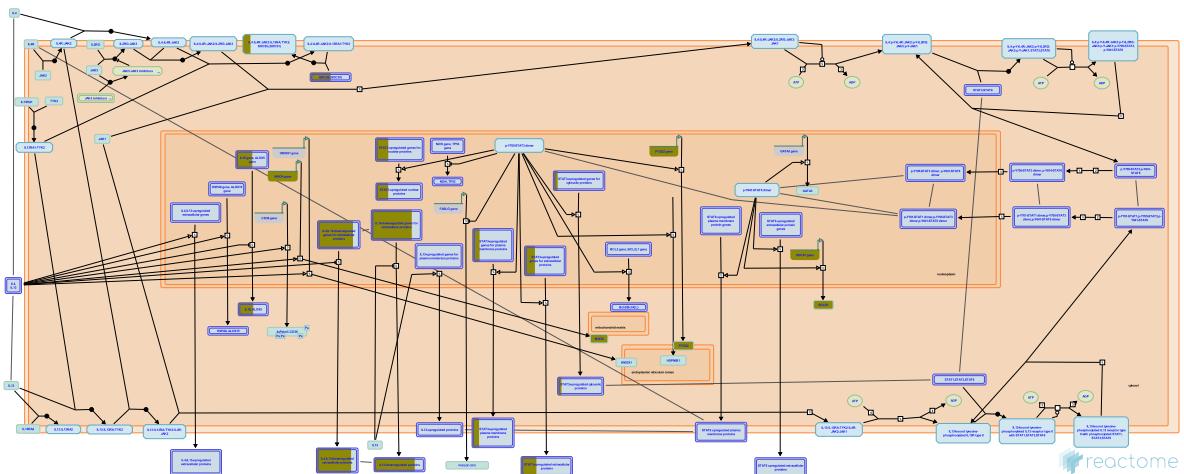
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2021-09-10	Modified	Weiser JD

56 submitted entities found in this pathway, mapping to 95 Reactome entities

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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).

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Date	Action	Author
2015-07-01	Authored	Jupe S
2015-07-01	Created	Jupe S
2016-09-02	Edited	Jupe S
2016-09-02	Reviewed	Leibovich SJ

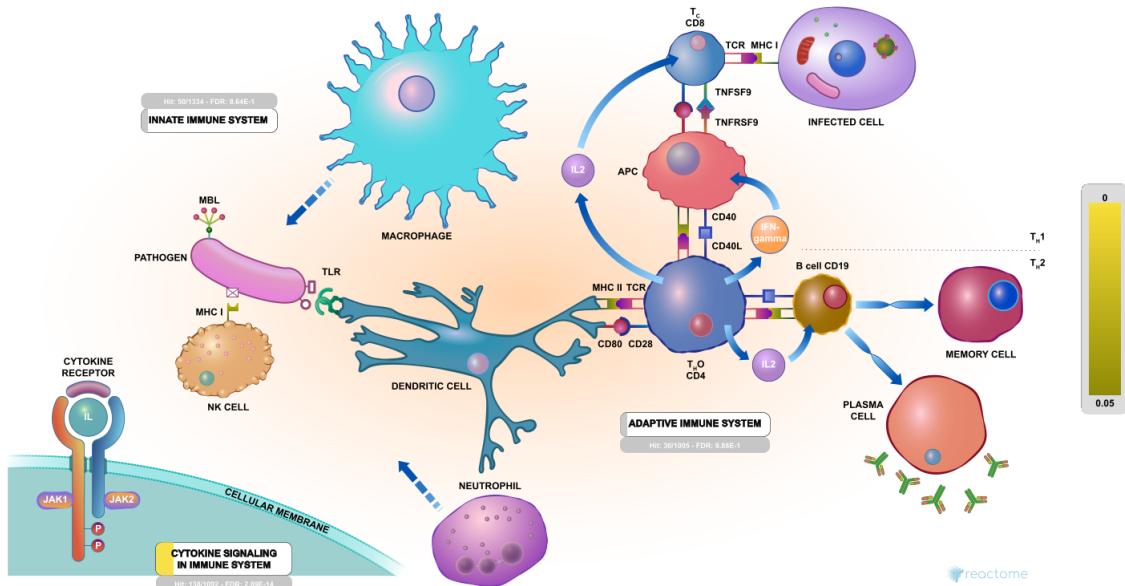
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2021-09-20	Modified	Weiser JD

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ENSG0000150782	ENSG0000150782	ENSG0000156127	ENSG0000156127	ENSG0000169429	ENSG0000169429
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ENSG0000189221	ENSG0000189221	ENSG0000196611	ENSG0000196611	ENSG0000232810	ENSG0000232810

5. 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
2021-09-10	Modified	Weiser JD

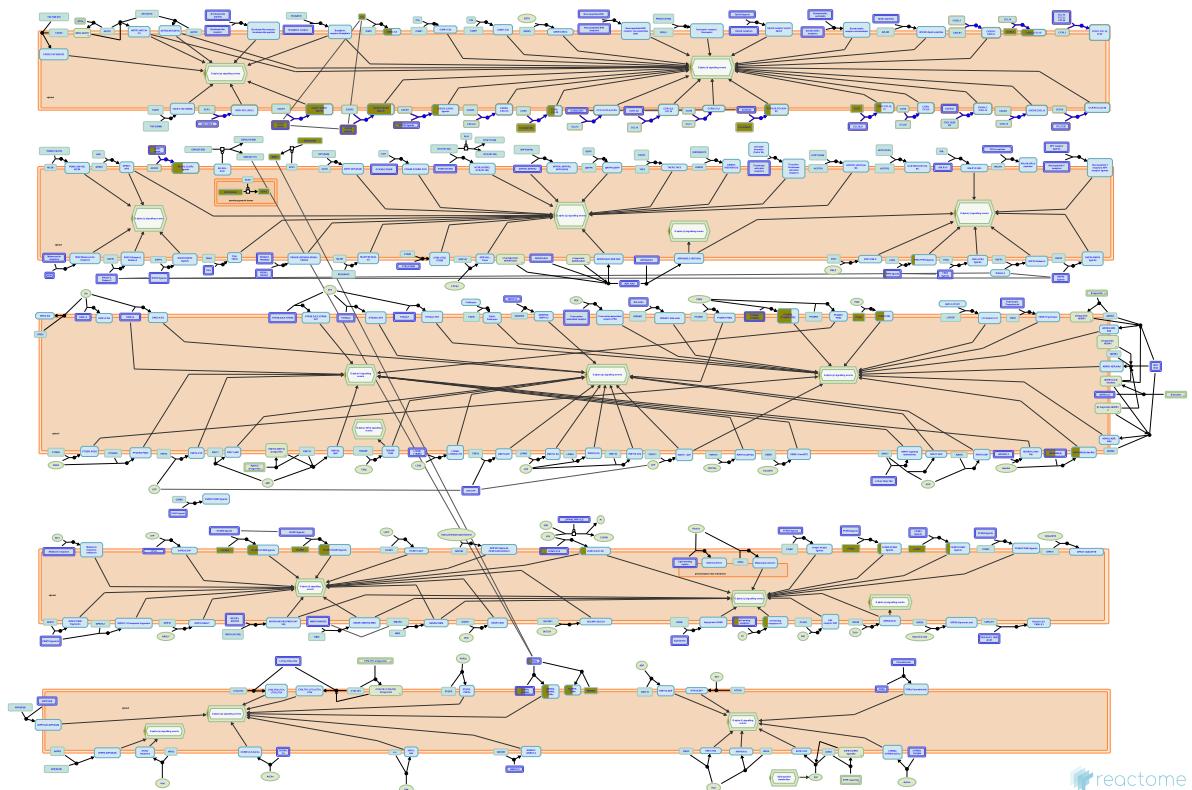
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6. Chemokine receptors bind chemokines (R-HSA-380108)



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.

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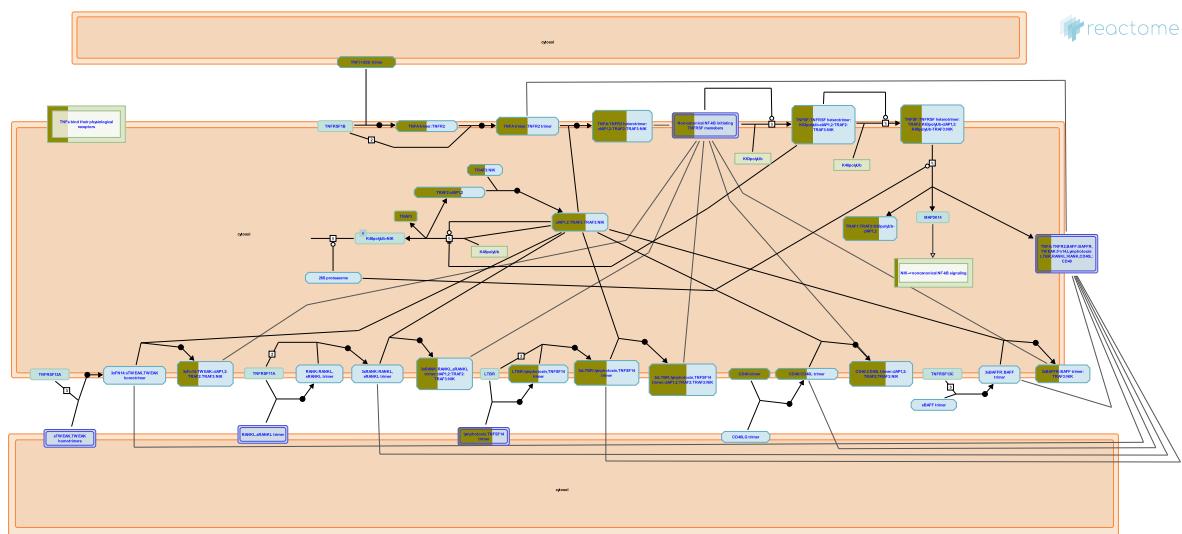
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2008-11-07	Authored	Jassal B
2008-11-07	Created	Jassal B
2021-09-10	Modified	Weiser JD

15 submitted entities found in this pathway, mapping to 18 Reactome entities

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7. TNFR2 non-canonical NF- κ B pathway (R-HSA-5668541)



Cellular compartments: nucleoplasm, plasma membrane.

Tumor necrosis factor-alpha (TNFA) exerts a wide range of biological effects through TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2). Under normal physiological conditions TNFR2 exhibits more restricted expression, being found on certain subpopulation of immune cells and few other cell types (Grell et al. 1995). TNFR1 mediated signalling pathways have been very well characterized but, TNFR2 has been much less well studied. TNFR1 upon activation by TNFA activates apoptosis through two pathways, involving the adaptor proteins TNFR1-associated death domain (TRADD) and fas-associated death domain (FADD). In contrast, TNFR2 signalling especially in highly activated T cells, induces cell survival pathways that can result in cell proliferation by activating transcription factor NF- κ B (nuclear factor- κ B) via the alternative non-canonical route. TNFR2 signalling seems to play an important role, in particular for the function of regulatory T cells. It offers protective roles in several disorders, including autoimmune diseases, heart diseases, demyelinating and neurodegenerative disorders and infectious diseases (Faustman & Davis 2010).

Activation of the non-canonical pathway by TNFR2 is mediated through a signalling complex that includes TNF receptor-associated factor (TRAF2 and TRAF3), cellular inhibitor of apoptosis (cIAP1 and cIAP2), and NF- κ B-inducing kinase (NIK). In this complex TRAF3 functions as a bridging factor between the cIAP1/2:TRAF2 complex and NIK. In resting cells cIAP1/2 in the signalling complex mediates K48-linked polyubiquitination of NIK and subsequent proteasomal degradation making NIK levels invisible. Upon TNFR2 stimulation, TRAF2 is recruited to the intracellular TRAF binding motif and this also indirectly recruits TRAF1 and cIAP1/2, as well as TRAF3 and NIK which are already bound to TRAF2 in unstimulated cells. TRAF2 mediates K63-linked ubiquitination of cIAP1/2 and this in turn mediates cIAP dependent K48-linked ubiquitination of TRAF3 leading to the proteasome-dependent degradation of the latter. As TRAF3 is degraded, NIK can no longer interact with TRAF1/2:cIAP complex. As a result NIK concentration in the cytosol increases and NIK gets stabilised and activated. Activated NIK phosphorylates IKK α , which in turn phosphorylates p100 (NF κ B2) subunit. Phosphorylated p100 is also ubiquitinated by the SCF-beta-TRCP ubiquitin ligase complex and is subsequently processed by the proteasome to p52, which is a transcriptionally competent NF- κ B subunit in conjunction with RelB (Petrus et al. 2011, Sun 2011, Vallabhapurapu & Karin 2009).

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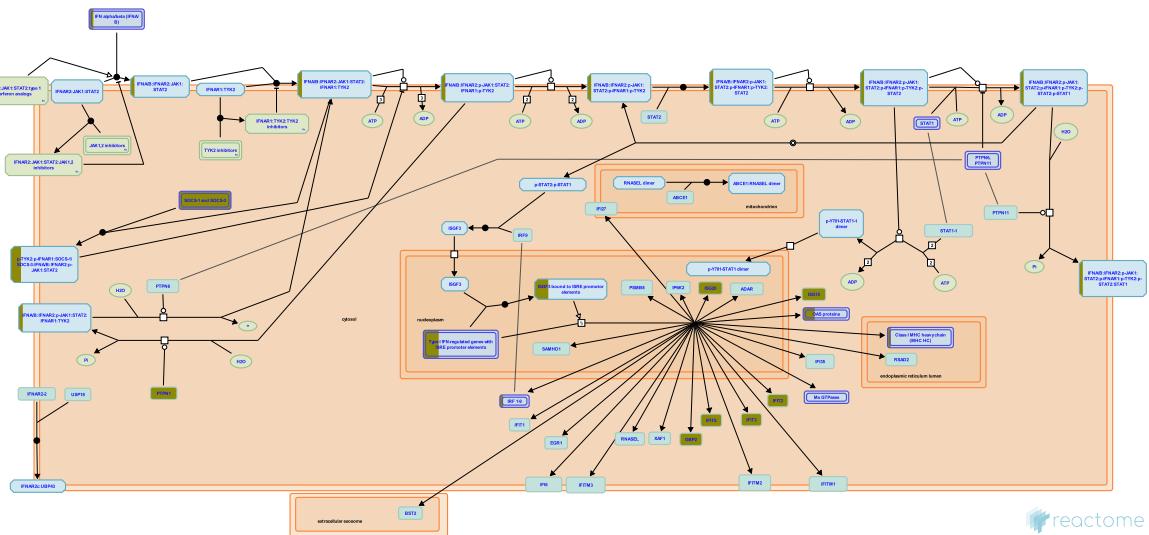
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2015-01-26	Authored	Garapati P V
2015-01-26	Created	Garapati P V
2015-05-12	Reviewed	Virgen-Slane R, Ware CF, Rajput A
2021-09-10	Modified	Weiser JD

15 submitted entities found in this pathway, mapping to 16 Reactome entities

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ENSG0000226979	P01374	ENSG0000227507	Q06643	ENSG0000232810	P01375

8. 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.

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2010-07-07	Edited	Garapati P V
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2010-08-17	Reviewed	Abdul-Sater AA, Schindler C

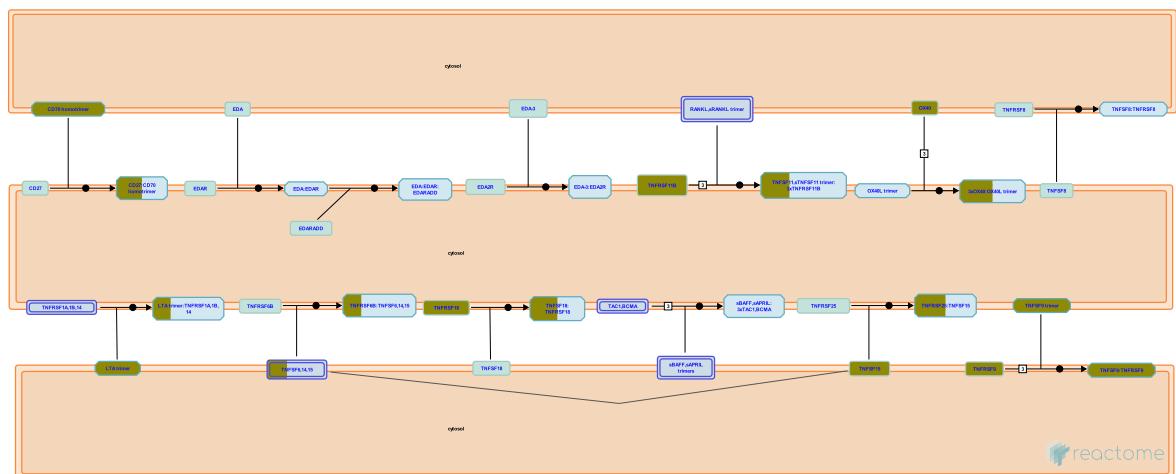
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2021-09-10	Modified	Weiser JD

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ENSG00000204642	P30511				

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ENSG00000172183	ENSG00000172183	ENSG00000187608	ENSG00000187608	ENSG00000204642	ENSG00000204642

9. TNFs bind their physiological receptors ([R-HSA-5669034](#))



Cellular compartments: plasma membrane.

Members of the tumour necrosis factor superfamily (TNFSF) and TNF receptor superfamily (TNFRSF) have crucial roles in both innate and adaptive immunity. These members are implicated in various acquired or genetic human diseases, ranging from septic shock to autoimmune disorders, allograft rejection and cancer (So et al. 2006).

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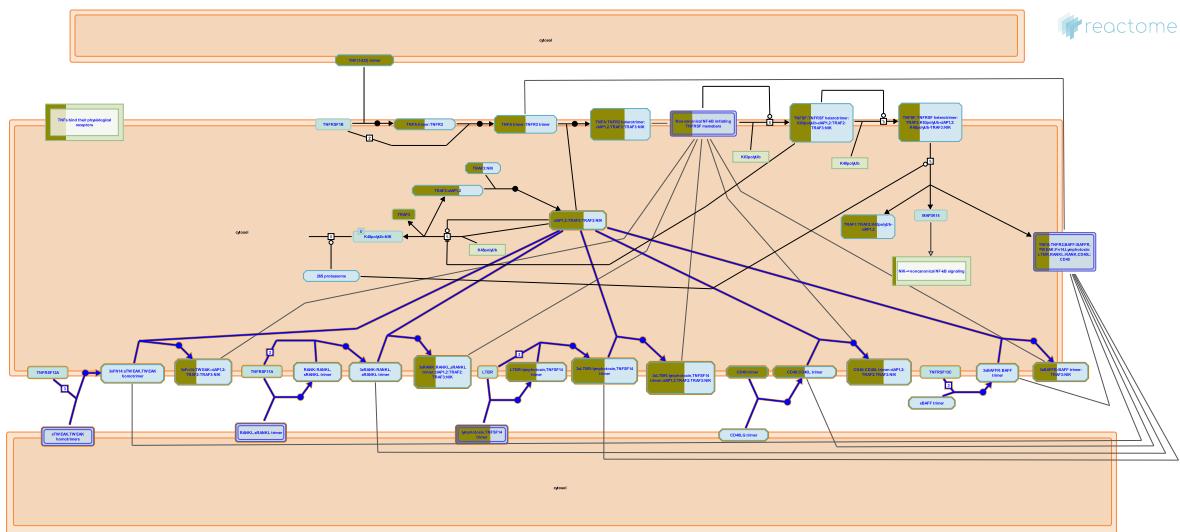
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2015-01-30	Created	Jassal B
2015-05-12	Reviewed	Virgen-Slane R, Ware CF, Rajput A
2021-09-10	Modified	Weiser JD

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ENSG0000186891	Q9Y5U5	ENSG0000226979	P01374		

10. TNF receptor superfamily (TNFSF) members mediating non-canonical NF- κ B pathway (R-HSA-5676594)



Cellular compartments: plasma membrane, extracellular region, cytosol.

Activation of NF- κ B is fundamental to signal transduction by members of the TNFRSF. Expression of NF- κ B target genes is essential for mounting innate immune responses to infectious microorganisms but is also important for the proper development and cellular compartmentalization of secondary lymphoid organs necessary to orchestrate an adaptive immune response.

NF- κ B transcription factor family is activated by two distinct pathways: the canonical pathway involving NF- κ B1 and the non-canonical pathway involving NF- κ B2. Unlike NF- κ B1 signalling, which can be activated by a wide variety of receptors, the NF- κ B2 pathway is typically activated by a subset of receptor and ligand pairs belonging to the tumor necrosis factor receptor (TNF) super family (TNFRSF) members. These members include TNFR2 (Rauert et al. 2010), B cell activating factor of the TNF family receptor (BAFFR also known as TNFRSF13C) (Kayagaki et al. 2002, CD40 (also known as TNFRSF5) (Coope et al. 2002), lymphotoxin beta-receptor (LTBR also known as TNFRSF3) (Dejardin et al. 2002), receptor activator for nuclear factor κ B (RANK also known as TNFRSF11A) (Novack et al. 2003), CD27 and Fibroblast growth factor-inducible immediate-early response protein 14 (FN14 also known as TNFRSF12A) etc. These receptors each mediate specific biological roles of the non-canonical NF- κ B. These non-canonical NF- κ B-stimulating receptors have one thing in common and is the presence of a TRAF-binding motif, which recruits different TNF receptor-associated factor (TRAF) members, particularly TRAF2 and TRAF3, to the receptor complex during ligand ligation (Grech et al. 2004, Bishop & Xie 2007). Receptor recruitment of these TRAF members leads to their degradation which is a critical step leading to the activation of NIK and induction of p100 processing (Sun 2011, 2012).

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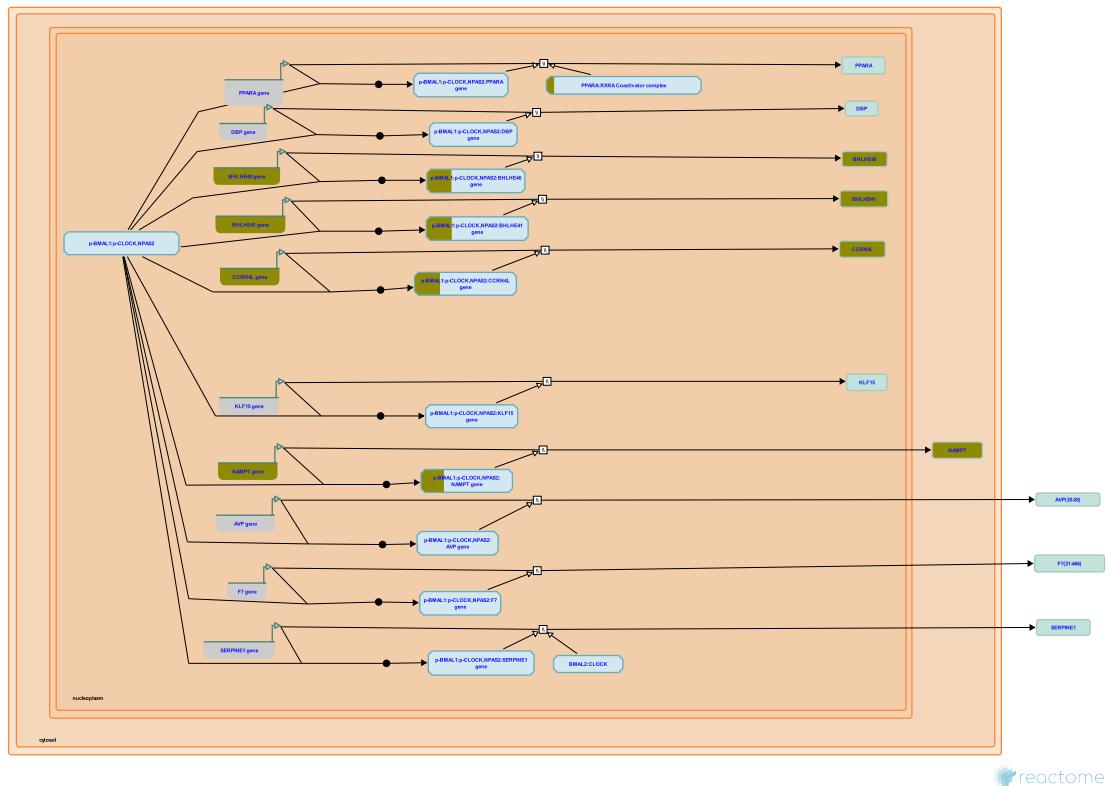
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Date	Action	Author
2015-01-26	Edited	Garapati P V
2015-01-26	Authored	Garapati P V
2015-02-20	Created	Garapati P V
2015-05-12	Reviewed	Virgen-Slane R, Ware CF, Rajput A
2021-09-10	Modified	Weiser JD

5 submitted entities found in this pathway, mapping to 6 Reactome entities

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ENSG00000023445	Q13489, Q13490	ENSG00000101017	P25942-1	ENSG00000131323	Q13114
ENSG00000226979	P01374	ENSG00000227507	Q06643		

11. BMAL1:CLOCK,NPAS2 activates circadian gene expression (R-HSA-1368108)



Cellular compartments: nucleoplasm, extracellular region, endoplasmic reticulum lumen, cytosol.

As inferred from mouse, BMAL1:CLOCK (ARNTL:CLOCK) and BMAL1:NPAS2 (ARNTL:NPAS2) heterodimers bind to sequence elements (E boxes) in the promoters of target genes and enhance transcription (Gekakis et al. 1998, reviewed in Munoz and Baler 2003).

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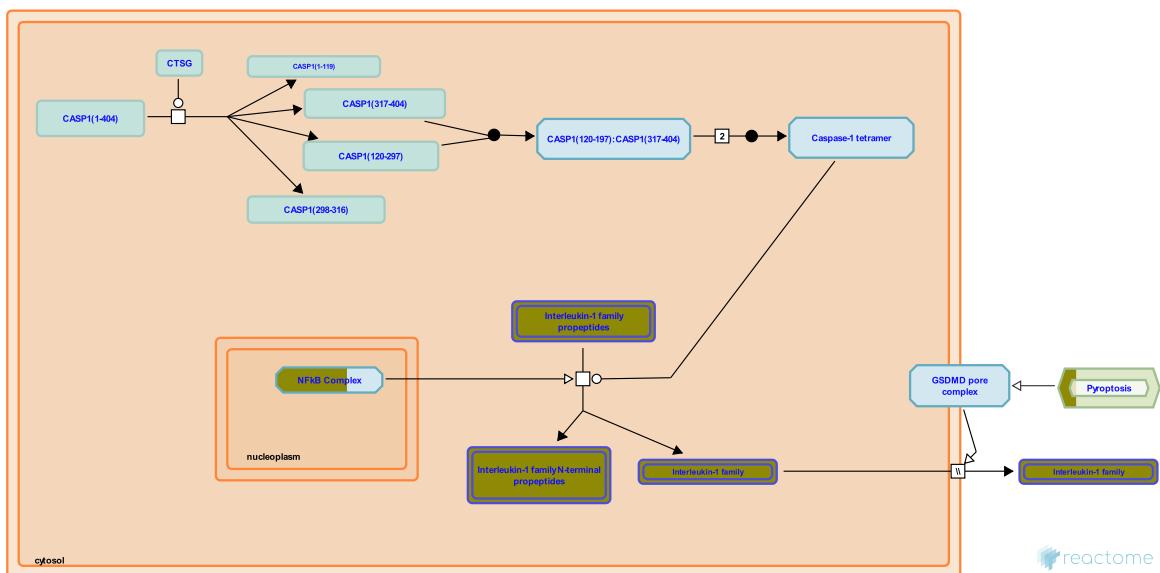
Date	Action	Author
2009-05-27	Reviewed	D'Eustachio P
2010-06-23	Reviewed	Hirota T, Delaunay F, Kay SA, Albrecht U
2011-06-22	Edited	May B
2011-06-22	Authored	May B
2011-06-30	Created	May B
2015-01-17	Revised	May B
2017-12-09	Modified	May B

5 submitted entities found in this pathway, mapping to 9 Reactome entities

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ENSG00000105835	P43490	ENSG00000123095	Q9C0J9	ENSG00000130589	Q9BYK8
ENSG00000134107	O14503	ENSG00000151014	Q9UK39		

Input	Ensembl Id	Input	Ensembl Id
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ENSG00000134107	ENSG00000134107	ENSG00000151014	ENSG00000151014

12. 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 potease 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

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

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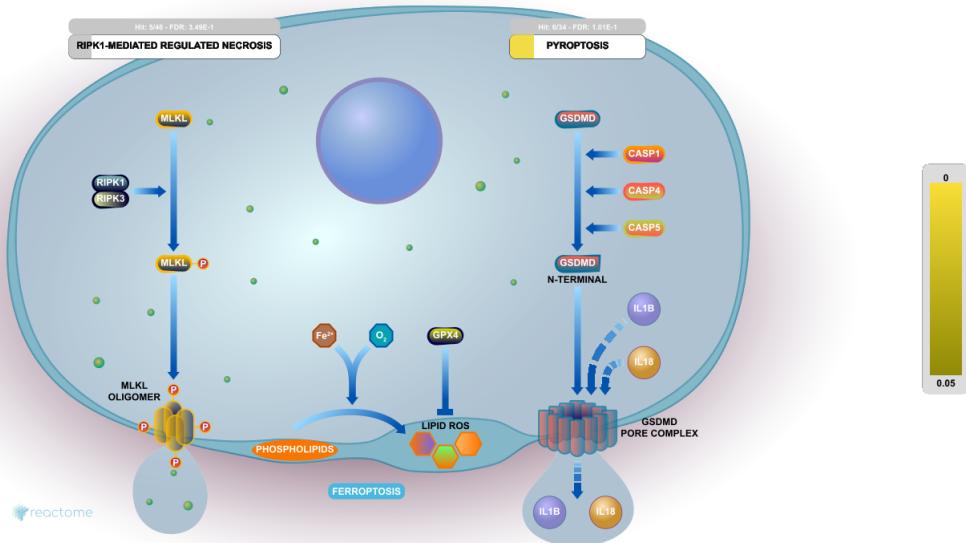
Date	Action	Author
2009-11-25	Created	Jupe S
2010-05-17	Authored	Ray KP
2010-08-06	Edited	Jupe S

Date	Action	Author
2010-09-06	Reviewed	Pinteaux E
2021-09-10	Modified	Weiser JD

5 submitted entities found in this pathway, mapping to 5 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ENSG0000077150	Q00653	ENSG0000109320	P19838	ENSG0000115008	P01583
ENSG0000125538	P01584	ENSG0000150782	Q14116		

13. Regulated Necrosis (R-HSA-5218859)



Necrosis has traditionally been considered as a passive, unregulated cell death. However, accumulating evidence suggests that necrosis, like apoptosis, can be executed by genetically controlled and highly regulated cellular process that is morphologically characterized by a loss of cell membrane integrity, intracellular organelles and/or the entire cell swelling (oncrosis) (Rello S et al. 2005; Galluzzi L et al. 2007; Berghe TV et al. 2014; Ros U et al. 2020). The morphological hallmarks of the necrotic death have been associated with different forms of programmed cell death including (but not limited to) parthanatos, necroptosis, glutamate-induced oxytosis, ferroptosis, inflammasome-mediated necrosis etc. Each of them can be triggered under certain pathophysiological conditions. For example UV, ROS or alkylating agents may induce poly(ADP-ribose) polymerase 1 (PARP1) hyperactivation (parthanatos), while tumor necrosis factor (TNF) or toll like receptor ligands (LPS and dsRNA) can trigger necrosome-mediated necroptosis. The initiation events, e.g., PARP1 hyperactivation, necrosome formation, activation of NADPH oxidases, in turn trigger one or several common intracellular signals such as NAD⁺ and ATP-depletion, enhanced Ca²⁺ influx, dysregulation of the redox status, increased production of reactive oxygen species (ROS) and the activity of phospholipases. These signals affect cellular organelles and membranes leading to osmotic swelling, massive energy depletion, lipid peroxidation and the loss of lysosomal membrane integrity. Different mechanisms of permeabilization have emerged depending on the cell death form. Pore formation by gasdermins (GSDMs) is a hallmark of pyroptosis, while mixed lineage kinase domain-like (MLKL) protein facilitates membrane permeabilization in necroptosis, and phospholipid peroxidation leads to membrane damage in ferroptosis. This diverse repertoire of mechanisms leading to membrane permeabilization contributes to define the specific inflammatory and immunological outcome of each type of regulated necrosis. Regulated or programmed necrosis eventually leads to cell lysis and release of cytoplasmic content into the extracellular region that is often associated with a tissue damage resulting in an intense inflammatory response.

The Reactome module describes necroptosis and pyroptosis.

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Nikoletopoulou V, Tavernarakis N, Palikaras K & Markaki M (2013). Crosstalk between apoptosis, necrosis and autophagy. *Biochim. Biophys. Acta*, 1833, 3448-59. [\[View\]](#)

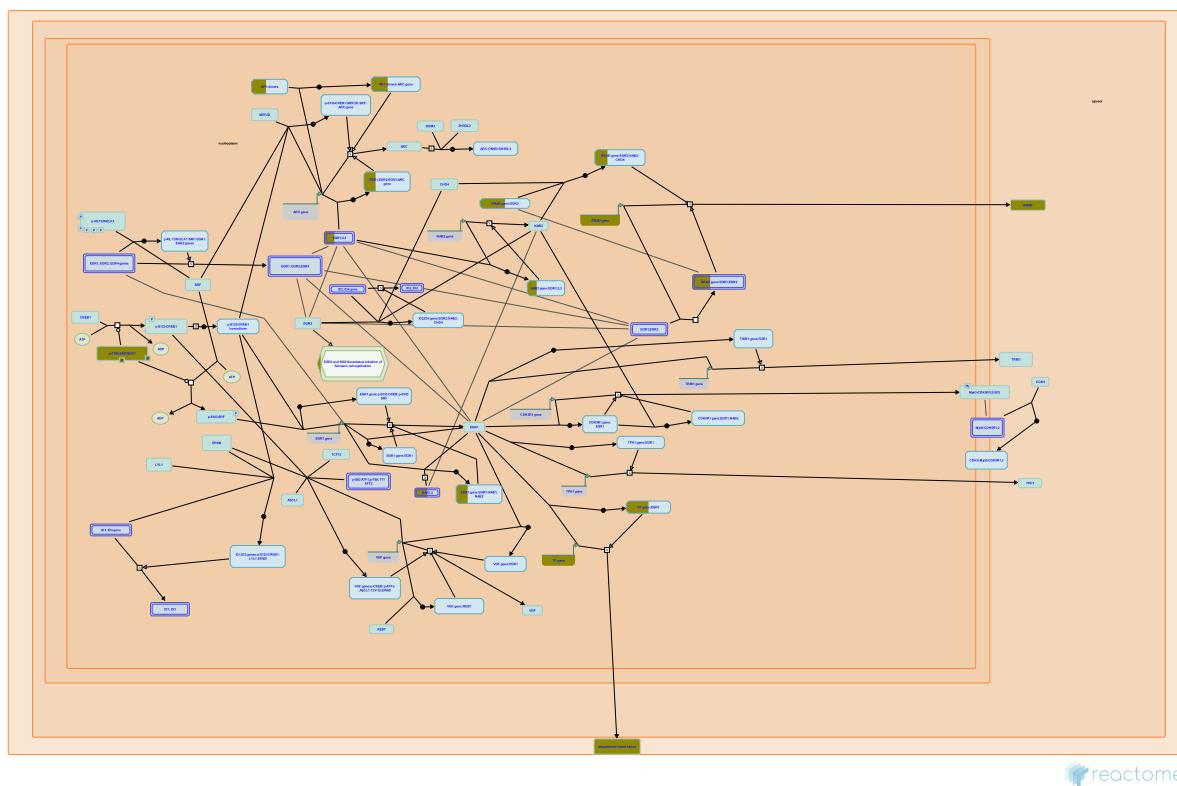
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Date	Action	Author
2013-12-20	Authored	Shamovsky V
2013-12-20	Created	Shamovsky V
2014-10-31	Reviewed	Gillespie ME
2015-02-10	Edited	Shamovsky V
2015-02-15	Reviewed	Chan FK
2021-09-10	Modified	Weiser JD

8 submitted entities found in this pathway, mapping to 11 Reactome entities

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ENSG00000003402	O15519-1, O15519-2	ENSG00000023445	Q13489, Q13490	ENSG00000105928	O60443
ENSG00000115008	P01583	ENSG00000125347	P10914	ENSG00000125538	P01584
ENSG00000150782	Q14116	ENSG00000197329	Q96FA3		
Input			Ensembl Id		
ENSG00000105928			ENSG00000105928		

14. NGF-stimulated transcription (R-HSA-9031628)



NGF stimulation induces expression of a wide array of transcriptional targets. In rat PC12 cells, a common model for NGF signaling, stimulation with NGF causes cells to exit the cell cycle and undergo a differentiation program leading to neurite outgrowth. This program is driven by the expression of immediate early genes (IEGs), which frequently encode transcription factors regulating the activity of NGF-specific delayed response genes (reviewed in Sheng and Greenberg, 1990; Flavell and Greenberg, 2008; Santiago and Bashaw, 2014).

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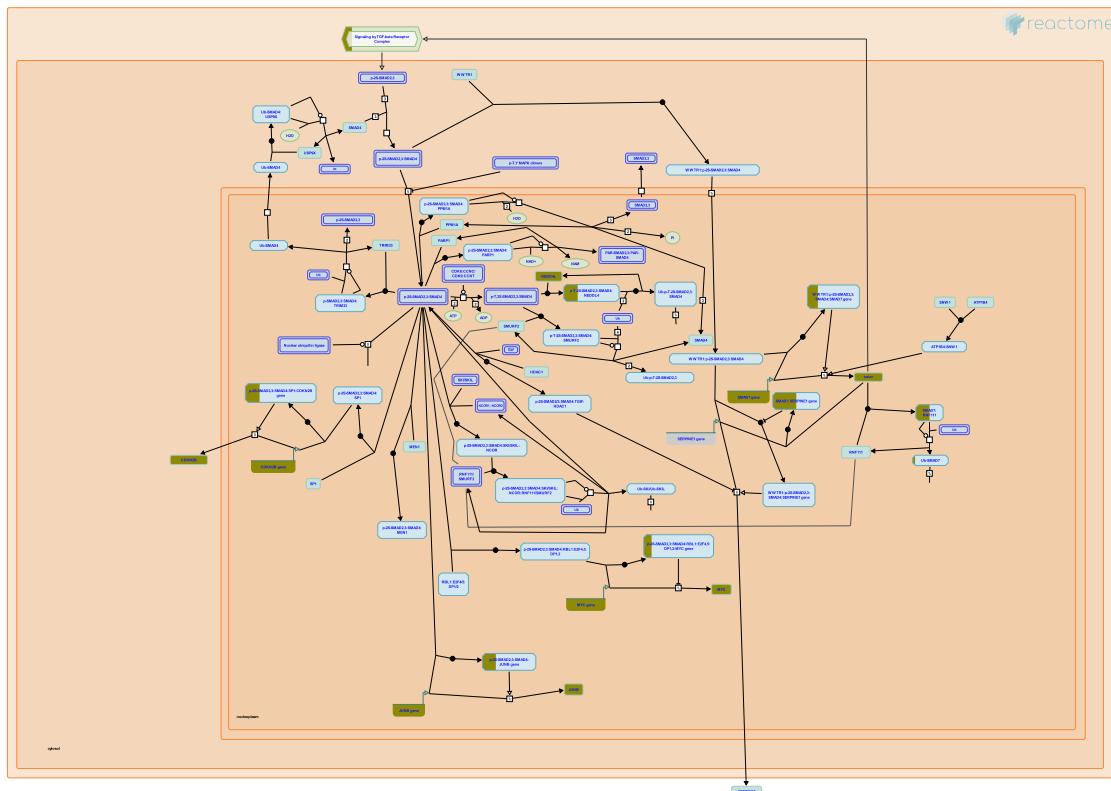
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Date	Action	Author
2017-12-01	Created	Rothfels K
2019-08-16	Authored	Rothfels K
2020-01-17	Reviewed	Aletta J M
2020-02-24	Edited	Rothfels K
2021-09-10	Modified	Weiser JD

7 submitted entities found in this pathway, mapping to 9 Reactome entities

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ENSG00000117525	P13726	ENSG00000118515	O00141	ENSG00000138386	Q13506
ENSG00000166592	P55042	ENSG00000171223	P17275	ENSG00000175592	P15407
ENSG00000179388	Q06889				
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ENSG00000117525	ENSG00000117525	ENSG00000166592	ENSG00000166592		

15. Transcriptional activity of SMAD2/SMAD3:SMAD4 heterotrimer (R-HSA-2173793)



In the nucleus, SMAD2/3:SMAD4 heterotrimer complex acts as a transcriptional regulator. The activity of SMAD2/3 complex is regulated both positively and negatively by association with other transcription factors (Chen et al. 2002, Varelas et al. 2008, Stroschein et al. 1999, Wotton et al. 1999). In addition, the activity of SMAD2/3:SMAD4 complex can be inhibited by nuclear protein phosphatases and ubiquitin ligases (Lin et al. 2006, Dupont et al. 2009).

References

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Date	Action	Author
2012-04-02	Created	Orlic-Milacic M

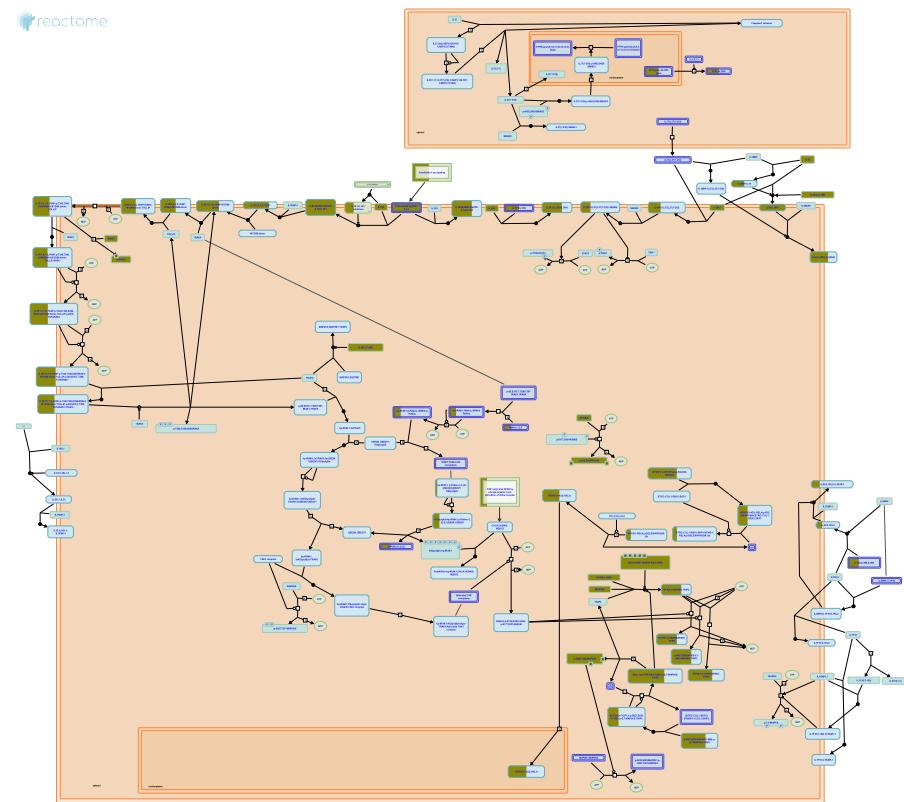
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2012-04-05	Authored	Orlic-Milacic M
2012-04-10	Edited	Jassal B
2012-05-14	Reviewed	Huang T
2012-11-14	Reviewed	Chen YG
2021-09-10	Modified	Weiser JD

5 submitted entities found in this pathway, mapping to 9 Reactome entities

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ENSG00000147883	P42772	ENSG00000171223	P17275		

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ENSG00000147883	ENSG00000147883	ENSG00000171223	ENSG00000171223

16. Interleukin-1 family signaling (R-HSA-446652)



Cellular compartments: plasma membrane.

The Interleukin-1 (IL1) family of cytokines comprises 11 members, namely Interleukin-1 alpha (IL1A), Interleukin-1 beta (IL1B), Interleukin-1 receptor antagonist protein (IL1RN, IL1RA), Interleukin-18 (IL18), Interleukin-33 (IL33), Interleukin-36 receptor antagonist protein (IL36RN, IL36RA), Interleukin-36 alpha (IL36A), Interleukin-36 beta (IL36B), Interleukin-36 gamma (IL36G), Interleukin-37 (IL37) and Interleukin-38 (IL38). The genes encoding all except IL18 and IL33 are on chromosome 2. They share a common C-terminal three-dimensional structure and with apart from IL1RN they are synthesized without a hydrophobic leader sequence and are not secreted via the classical reticulum endoplasmic-Golgi pathway.

IL1B and IL18, are produced as biologically inactive propeptides that are cleaved to produce the mature, active interleukin peptide.

The IL1 receptor (IL1R) family comprises 10 members: Interleukin-1 receptor type 1 (IL1R1, IL1RA), Interleukin-1 receptor type 2 (IL1R2, IL1RB), Interleukin-1 receptor accessory protein (IL1RAP, IL1RAcP, IL1R3), Interleukin-18 receptor 1 (IL18R1, IL18RA), Interleukin-18 receptor accessory protein (IL18RAP, IL18RB), Interleukin-1 receptor-like 1 (IL1RL1, ST2, IL33R), Interleukin-1 receptor-like 2 (IL1RL2, IL36R), Single Ig IL-1-related receptor (SIGIRR, TIR8), Interleukin-1 receptor accessory protein-like 1 (IL1RAPL1, TIGGIR2) and X-linked interleukin-1 receptor accessory protein-like 2 (IL1RAPL2, TIGGIR1). Most of the genes encoding these receptors are on chromosome 2.

IL1 family receptors heterodimerize upon cytokine binding. IL1, IL33 and IL36 bind specific receptors, IL1R1, IL1RL1, and IL1RL2 respectively. All use IL1RAP as a co-receptor. IL18 binds IL18R1 and uses IL18RAP as co-receptor.

The complexes formed by IL1 family cytokines and their heterodimeric receptors recruit intracellular signaling molecules, including Myeloid differentiation primary response protein MyD88 (MYD88), members of the IL1R-associated kinase (IRAK) family, and TNF receptor-associated factor 6 (TRAF6), activating Nuclear factor NF-kappa-B (NFB), as well as Mitogen-activated protein kinase 14 (MAPK14, p38), c-Jun N-terminal kinases (JNKs), extracellular signal-regulated kinases (ERKs) and other Mitogen-activated protein kinases (MAPKs).

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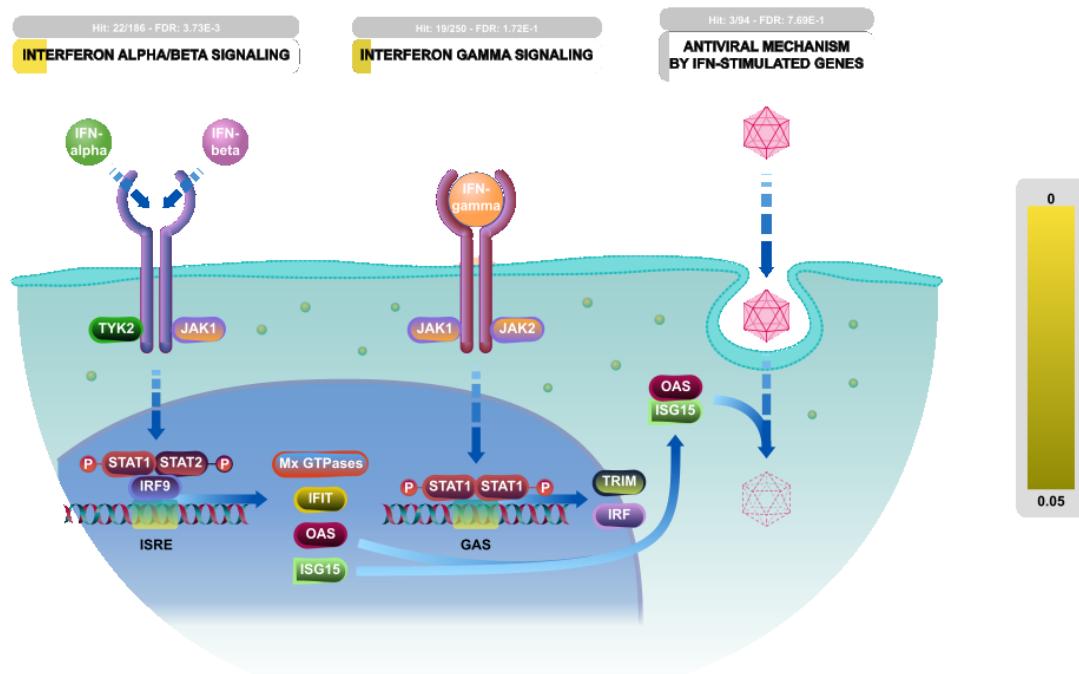
Date	Action	Author
2009-11-16	Created	Jupe S
2010-05-17	Edited	Jupe S
2010-05-17	Reviewed	Pinteaux E

Date	Action	Author
2010-05-17	Authored	Ray KP
2021-09-10	Modified	Weiser JD

15 submitted entities found in this pathway, mapping to 17 Reactome entities

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ENSG0000077150	Q00653	ENSG0000100906	P25963	ENSG0000104312	O43353
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ENSG0000136689	P18510	ENSG0000150782	Q14116, Q14116-2	ENSG0000197329	Q96FA3
Input	Ensembl Id				
ENSG0000150782	ENSG0000150782				

17. 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.

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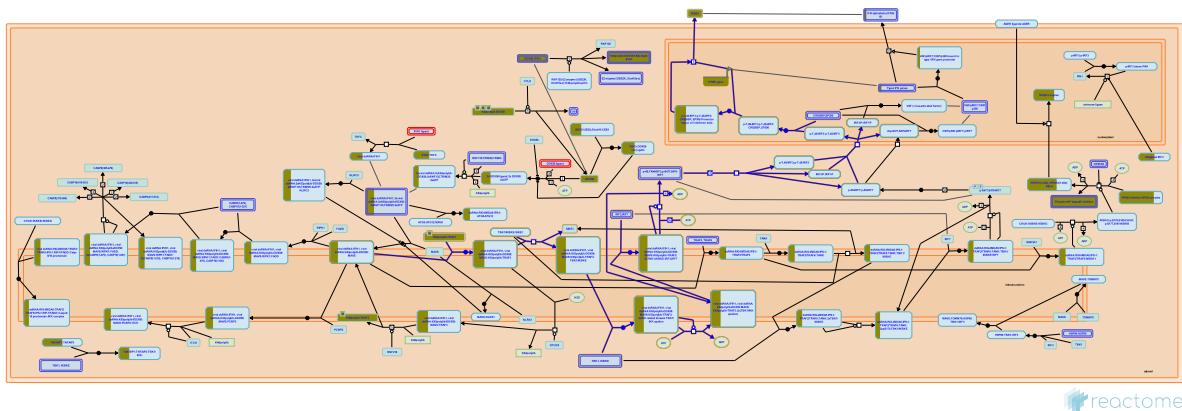
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2010-07-07	Authored	Garapati P V
2010-07-16	Created	Garapati P V
2010-08-17	Reviewed	Abdul-Sater AA, Schindler C
2021-09-10	Modified	Weiser JD

18 submitted entities found in this pathway, mapping to 31 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
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ENSG0000125148	P02795	ENSG0000125347	P10914	ENSG0000135114	Q15646
ENSG0000152778	Q13325	ENSG0000162645	P32456	ENSG0000171855	P01574
ENSG0000172183	Q96AZ6	ENSG0000184557	O14543	ENSG0000185338	O15524
ENSG0000187608	P05161	ENSG0000196396	P18031	ENSG0000204642	P30511

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ENSG0000119917	ENSG0000119917	ENSG0000119922	ENSG0000119922	ENSG0000125148	ENSG0000125148
ENSG0000125347	ENSG0000125347	ENSG0000135114	ENSG0000135114	ENSG0000152778	ENSG0000152778
ENSG0000162645	ENSG0000162645	ENSG0000172183	ENSG0000172183	ENSG0000187608	ENSG0000187608
ENSG0000204642	ENSG0000204642				

18. TRAF3-dependent IRF activation pathway (R-HSA-918233)



Cellular compartments: mitochondrial outer membrane.

MAVS via its TRAF-interaction motif (TIM) directly interacts with TRAF3 and recruits TRAF3 to the signaling complex. TRAF3 acts as a scaffold for the assembly of a signaling complex composed of IKK epsilon/TBK1, leading to the activation of transcription factors IRF3/IRF7.

References

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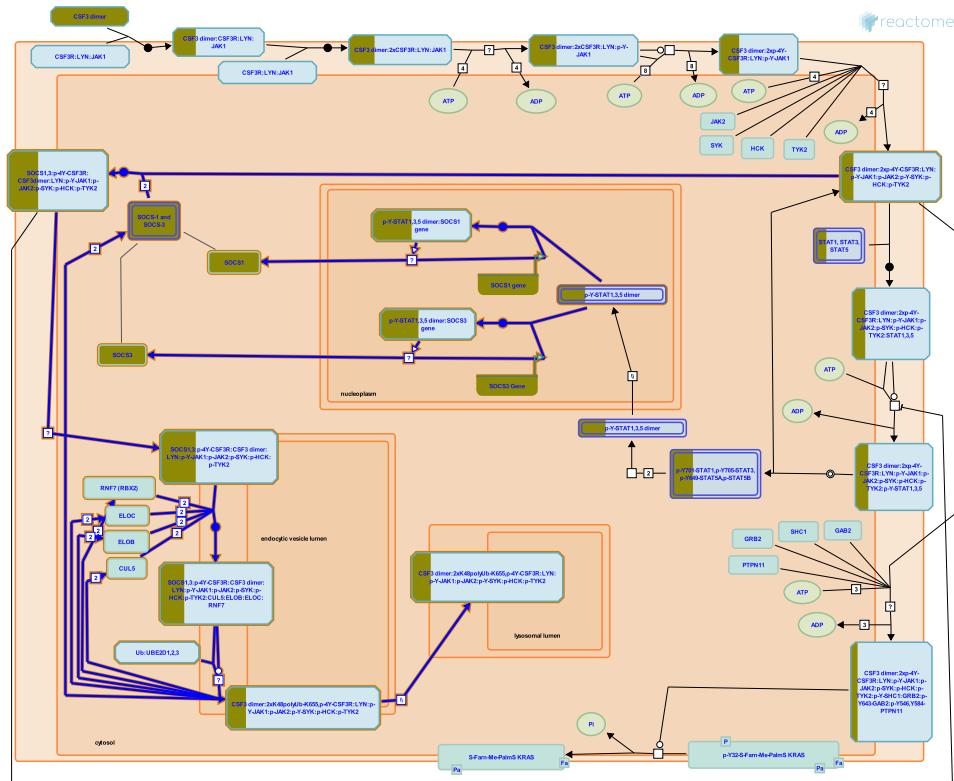
Date	Action	Author
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2010-08-02	Authored	Garapati P V
2010-08-02	Created	Garapati P V
2010-10-30	Reviewed	Akira S, Kawai T
2021-09-10	Modified	Weiser JD

4 submitted entities found in this pathway, mapping to 5 Reactome entities

Input	UniProt Id	Input	UniProt Id
ENSG00000107201	O95786	ENSG00000115267	Q9BYX4
ENSG00000131323	Q13114	ENSG00000171855	P01574

Input	Ensembl Id
ENSG00000171855	ENSG00000171855

19. Inactivation of CSF3 (G-CSF) signaling (R-HSA-9705462)



Signaling by CSF3 causes its own inactivation, thereby preventing overproliferation of neutrophils (reviewed in Beekman and Touw 2010, Palande et al. 2013). Activated CSF3R recruits and activates JAK2, which phosphorylates STAT1, STAT3, and STAT5. The phosphorylated STATs transit to the nucleus and enhance the expression of SOCS1 and SOCS3, inhibitors of CSF3R signaling (inferred from mouse homologs). SOCS3, the principle negative regulator, binds the phosphorylated C-terminal region of CSF3R (Hörtner et al. 2002, van de Geijn et al. 2004, and inferred from mouse homologs) and acts in two ways: direct inhibition of the phosphorylation activity of JAK2 (van de Geijn et al. 2004) and promotion of endocytosis (Ward et al. 1999, Aarts et al. 2004, Irandoost et al. 2007) and ubiquitination (Irandoost et al. 2007, Wölfler et al. 2009) of CSF3R.

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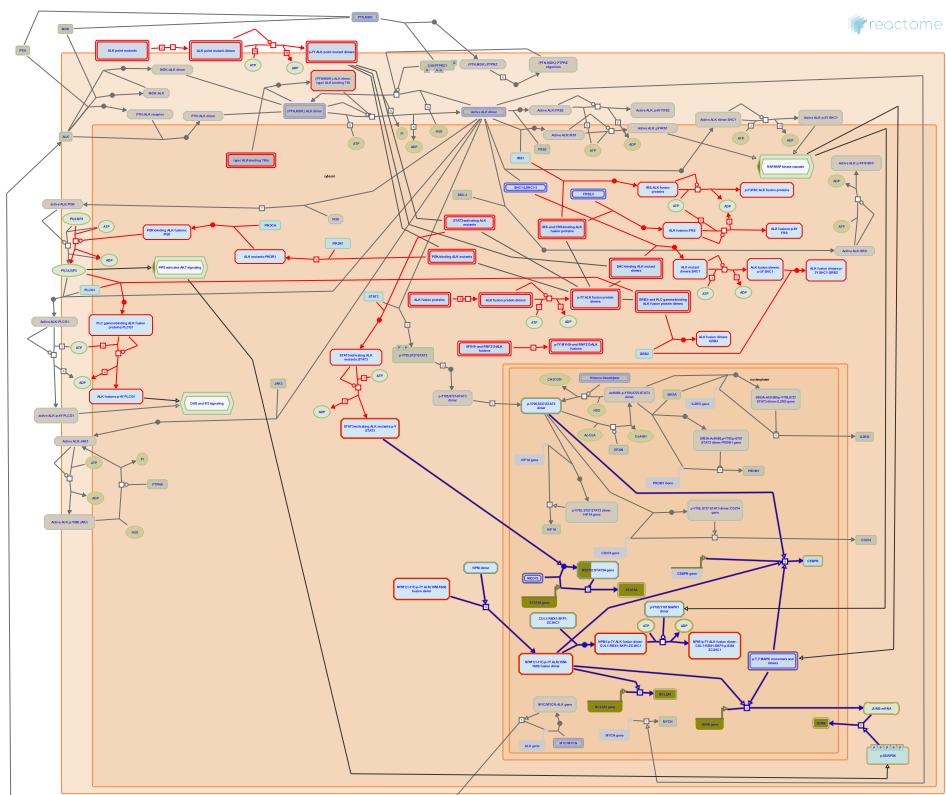
Edit history

Date	Action	Author
2020-10-18	Edited	May B
2020-10-18	Authored	May B
2020-10-24	Created	May B
2020-12-12	Reviewed	Touw IP
2021-09-20	Modified	Weiser JD

4 submitted entities found in this pathway, mapping to 6 Reactome entities

Input	UniProt Id	Input	UniProt Id
ENSG00000108342	P09919	ENSG00000126561	P42229
ENSG00000184557	O14543	ENSG00000185338	O15524
Input	Ensembl Id	Input	Ensembl Id
ENSG00000184557	ENSG00000184557	ENSG00000185338	ENSG00000185338

20. Nuclear events stimulated by ALK signaling in cancer (R-HSA-9725371)



Diseases: cancer.

Signaling through oncogenic forms of ALK activate nuclear events that drive cellular survival, escape from apoptosis and transformation (reviewed in Della Corte et al, 2018; Roskoski, 2013; Chiarle et al, 2008). Changes to gene expression are effected both by epigenetic mechanisms and by inducing expression of key transcription factors and cell cycle regulators, among other critical targets. Many of these gene expression events are dependent on activation of STAT3 and to a lesser extent, MAP kinase signaling downstream of ALK (reviewed in Hallberg and Palmer, 2013; Hallberg and Palmer, 2016; Ducray et al, 2019). Unique among fusion proteins identified to date, the well-studied NPM-ALK fusion appears to be partially localized to the nucleus by virtue of oligomerization with endogenous full-length NPM.

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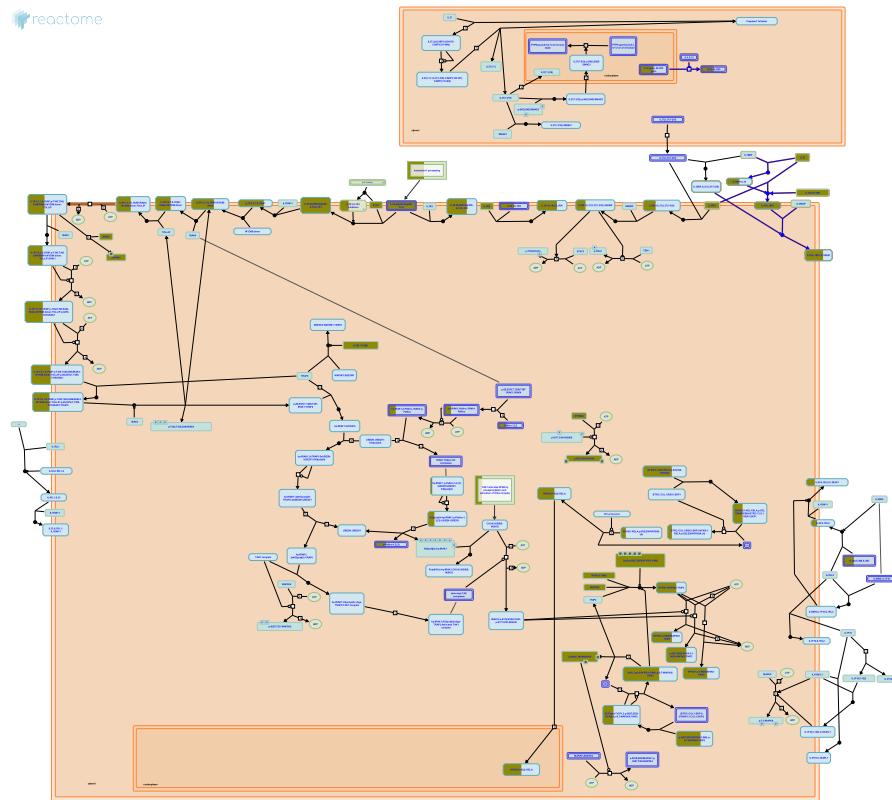
Edit history

Date	Action	Author
2021-03-29	Created	Rothfels K
2021-03-30	Edited	Rothfels K
2021-03-30	Authored	Rothfels K
2021-05-04	Modified	Rothfels K
2021-05-04	Reviewed	Inghirami G

3 submitted entities found in this pathway, mapping to 6 Reactome entities

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ENSG00000126561	P42229	ENSG00000140379	Q16548	ENSG00000171223	P17275
Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
ENSG00000126561	ENSG00000126561	ENSG00000140379	ENSG00000140379	ENSG00000171223	ENSG00000171223

21. Interleukin-18 signaling (R-HSA-9012546)



Interleukin-18 (IL18, pro-IL18) is a pleiotropic and pro inflammatory cytokine. It belongs to the Interleukin-1 (IL1 superfamily (Alboni et al. 2010, Krumm et al. 2017, Dinarello 1999). IL18 is synthesized as an inactive 24-kDa precursor protein that is cleaved by extracellular proteases such as caspase-1, protease 3, serine protease, elastase or cathepsin G (Fantuzzi & Dinarello 1999, Gracie et al. 2004, Sugawara et al. 2001), forming an 18-kDa mature protein (Arend et al. 2008, Akita et al. 1997, Fantuzzi et al. 1998, Ghayur et al. 1997, Gu et al. 1997, Ushio et al. 1996).

IL18 also occurs as a short isoform, the result of an alternative splicing event that removes 57 bp/19 aa (IL18alpha) (Conti et al. 1997, Yang et al. 2005). This short isoform has a modest synergistic action with the IL18 canonical active form.

The IL18 receptor (IL18R) belongs to the Interleukin-1 receptor/Toll like receptor superfamily. It consists of two subunits, Interleukin-18 receptor 1 (IL18R1, IL-18R, IL1Rrp1, IL18R1, IL-1R5) and Interleukin-18 receptor accessory protein (IL18RAP, IL18RB, IL-18R, IL-18RacP, IL-18RII or IL-1R7). Both subunits have three extracellular immunoglobulin-like domains and one intracellular Toll/IL-1 receptor (TIR) domain (O'Neill & Dinarello 2000, Sims 2002). It is believed that IL18 binds first to IL18R1 and later recruits IL18RAP to form a high-affinity heterotrimeric complex (Sims 2002, Sergi & Pentilla 2004, Alboni et al. 2009). A short isoform of IL18R1 lacks the TIR domain (IL18R1 type II) (Alboni et al. 2009), which is required for signaling, leading to the suggestion that IL18R1 type II is a decoy receptor (Colotta et al. 1994). A truncated form of IL18RAP containing only one of the three immunoglobulin domains stabilizes IL18 binding to IL18R1 but prevents signaling.

IL-18 binding protein (IL18BP), a 38-kDa soluble protein, is another negative regulator of IL18 signaling. It has some sequence homology with IL18R1 (Im et al. 2002 , Kim et al. 2002, Novick et al. 1999). IL18BP binds with high affinity to mature IL18, preventing its interaction with IL18R1. Several isoforms IL18BP have been described (Kim et al. 2000). Interleukin-37 (IL37, IL-1F7), another negative regulator of IL18 signaling, is able to bind IL18BP and IL18RAP preventing signaling (Bifulker et al. 2002, Pan et al. 2001, Kumar et al. 2002).

IL18 stimulates Interferon gamma (IFNG, IFN-) production from T-helper lymphocytes cells (Th1) and macrophages and enhances the cytotoxicity of natural killer (NK) cells. IL18 stimulated IFNG production is synergistically amplified by other Th1-related cytokines such as IL2, IL15, IL12 and IL23 (Boraschi & Dinarello 2006, Park et al. 2007, Dinarello 2007, Dinarello & Fantuzzi 2003).

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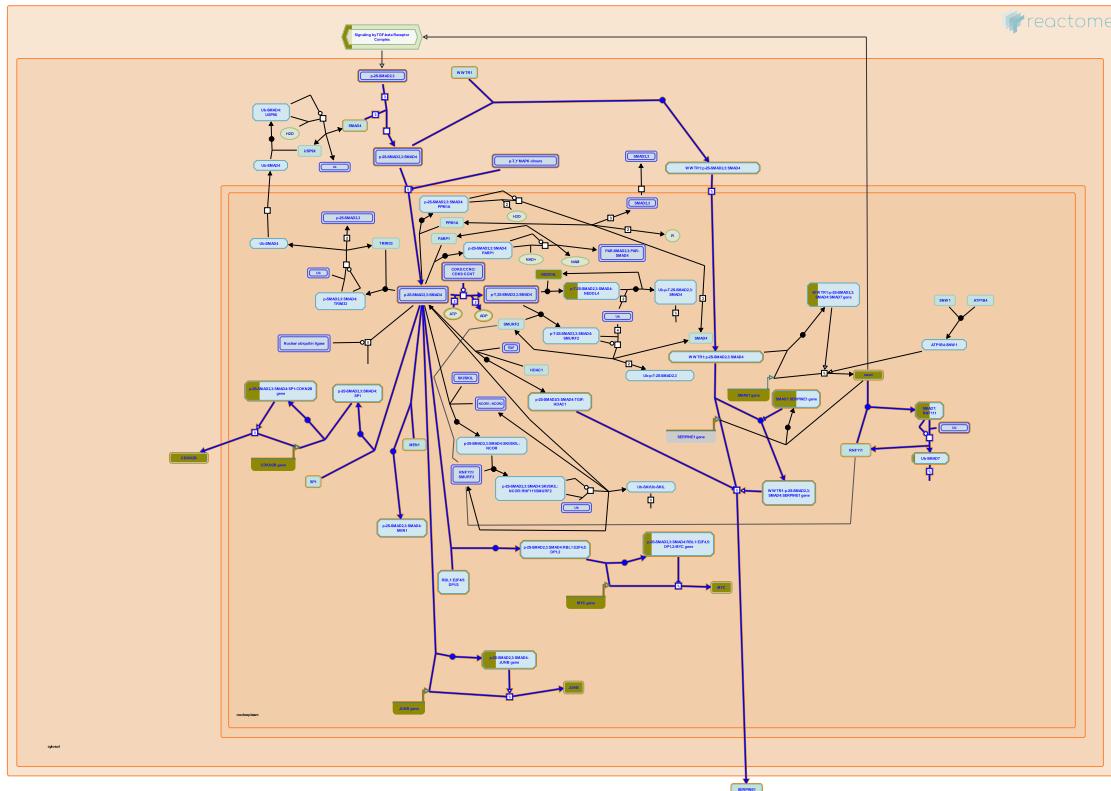
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Date	Action	Author
2016-01-28	Reviewed	Meldal BH
2017-07-17	Created	Duenas C
2017-08-08	Edited	Duenas C
2017-08-08	Authored	Duenas C
2017-11-01	Modified	Jupe S

2 submitted entities found in this pathway, mapping to 4 Reactome entities

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ENSG00000115604	Q13478	ENSG00000150782	Q14116, Q14116-2
Input		Ensembl Id	
ENSG00000150782		ENSG00000150782	

22. SMAD2/SMAD3:SMAD4 heterotrimer regulates transcription (R-HSA-2173796)



After phosphorylated SMAD2 and/or SMAD3 form a heterotrimer with SMAD4, SMAD2/3:SMAD4 complex translocates to the nucleus (Xu et al. 2000, Kurisaki et al. 2001, Xiao et al. 2003). In the nucleus, linker regions of SMAD2 and SMAD3 within SMAD2/3:SMAD4 complex can be phosphorylated by CDK8 associated with cyclin C (CDK8:CCNC) or CDK9 associated with cyclin T (CDK9:CCNT). CDK8/CDK9-mediated phosphorylation of SMAD2/3 enhances transcriptional activity of SMAD2/3:SMAD4 complex, but also primes it for ubiquitination and consequent degradation (Alarcon et al. 2009).

The transfer of SMAD2/3:SMAD4 complex to the nucleus can be assisted by other proteins, such as WWTR1. In human embryonic cells, WWTR1 (TAZ) binds SMAD2/3:SMAD4 heterotrimer and mediates TGF-beta-dependent nuclear accumulation of SMAD2/3:SMAD4. The complex of WWTR1 and SMAD2/3:SMAD4 binds promoters of SMAD7 and SERPINE1 (PAI-1 i.e. plasminogen activator inhibitor 1) genes and stimulates their transcription (Varelas et al. 2008). Stimulation of SMAD7 transcription by SMAD2/3:SMAD4 represents a negative feedback loop in TGF-beta receptor signaling. SMAD7 can be downregulated by RNF111 ubiquitin ligase (Arkadia), which binds and ubiquitinates SMAD7, targeting it for degradation (Koinuma et al. 2003).

SMAD2/3:SMAD4 heterotrimer also binds the complex of RBL1 (p107), E2F4/5 and TFDPI/2 (DP1/2). The resulting complex binds MYC promoter and inhibits MYC transcription. Inhibition of MYC transcription contributes to anti-proliferative effect of TGF-beta (Chen et al. 2002). SMAD2/3:SMAD4 heterotrimer also associates with transcription factor SP1. SMAD2/3:SMAD4:SP1 complex stimulates transcription of a CDK inhibitor CDKN2B (p15-INK4B), also contributing to the anti-proliferative effect of TGF-beta (Feng et al. 2000).

MEN1 (menin), a transcription factor tumor suppressor mutated in a familial cancer syndrome multiple endocrine neoplasia type 1, forms a complex with SMAD2/3:SMAD4 heterotrimer, but transcriptional targets of SMAD2/3:SMAD4:MEN1 have not been elucidated (Kaji et al. 2001, Sowa et al. 2004, Canaff et al. 2012).

JUNB is also an established transcriptional target of SMAD2/3:SMAD4 complex (Wong et al. 1999).

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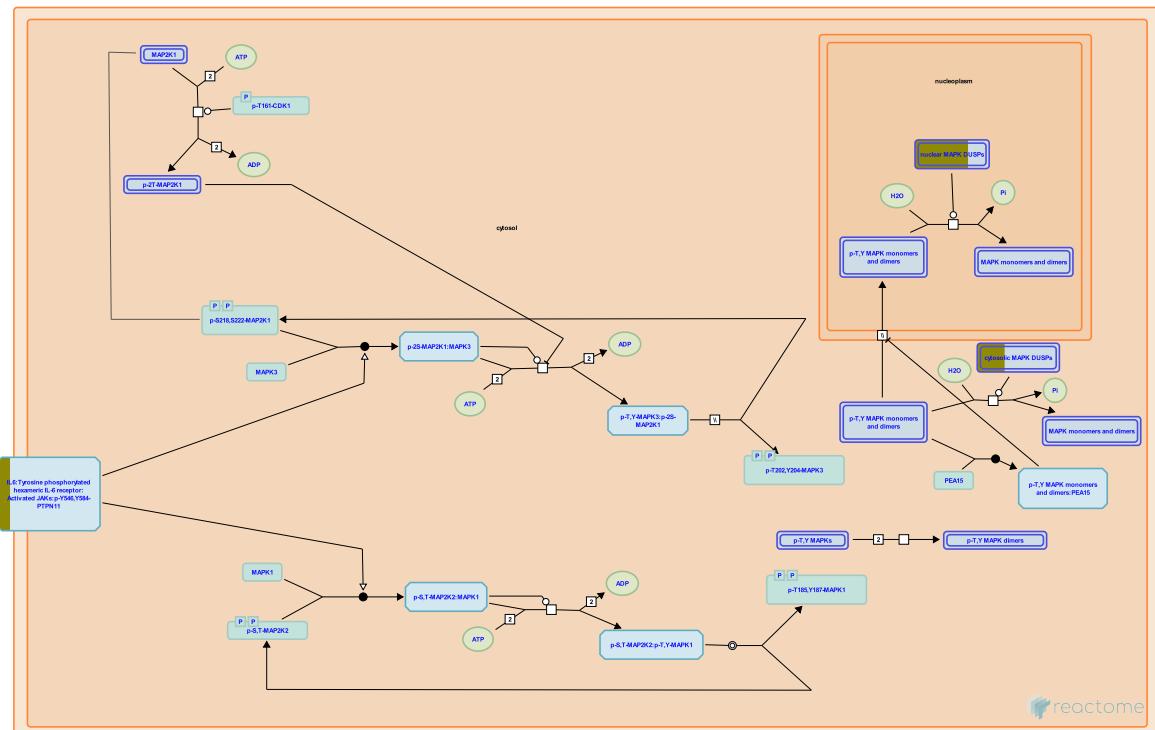
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Date	Action	Author
2012-04-02	Created	Orlic-Milacic M
2012-04-05	Authored	Orlic-Milacic M
2012-04-10	Edited	Jassal B
2012-05-14	Reviewed	Huang T
2021-09-20	Modified	Weiser JD

4 submitted entities found in this pathway, mapping to 7 Reactome entities

Input	UniProt Id	Input	UniProt Id		
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ENSG00000147883	P42772	ENSG00000171223	P17275		
ENSG00000136997	ENSG00000136997	ENSG00000147883	ENSG00000147883	ENSG00000171223	ENSG00000171223

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



Cellular compartments: nucleoplasm, cytosol.

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

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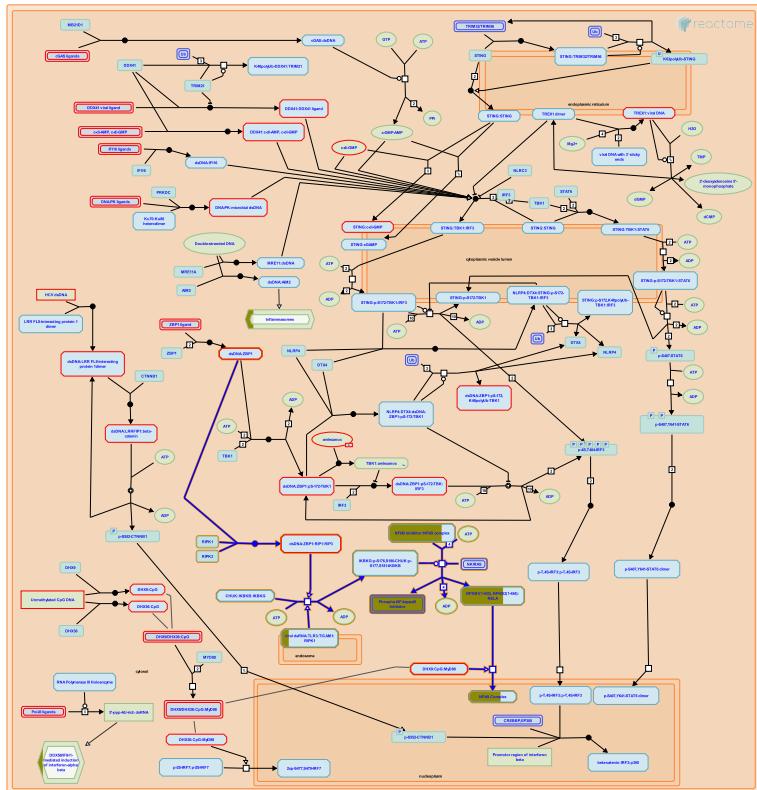
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Date	Action	Author
2004-04-29	Created	Charalambous M
2007-11-08	Reviewed	Greene LA
2021-09-20	Modified	Weiser JD

6 submitted entities found in this pathway, mapping to 6 Reactome entities

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

24. RIP-mediated NF κ 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- κ B-dependent promoter in a dose-dependent manner. Two RHIM-containing kinases RIP1 and RIP3 are implicated in ZBP1-induced NF κ B activation (Rebsamen M et al 2009; Kaiser WJ et al 2008).

References

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

Benedict CA, Rebsamen M, Vazquez J, Hofmann K, Michallet MC, Schroder K, ... Heinz LX (2009). DAI/ZBP1 recruits RIP1 and RIP3 through RIP homotypic interaction motifs to activate NF- κ B. *EMBO Rep*, 10, 916-22. [\[link\]](#)

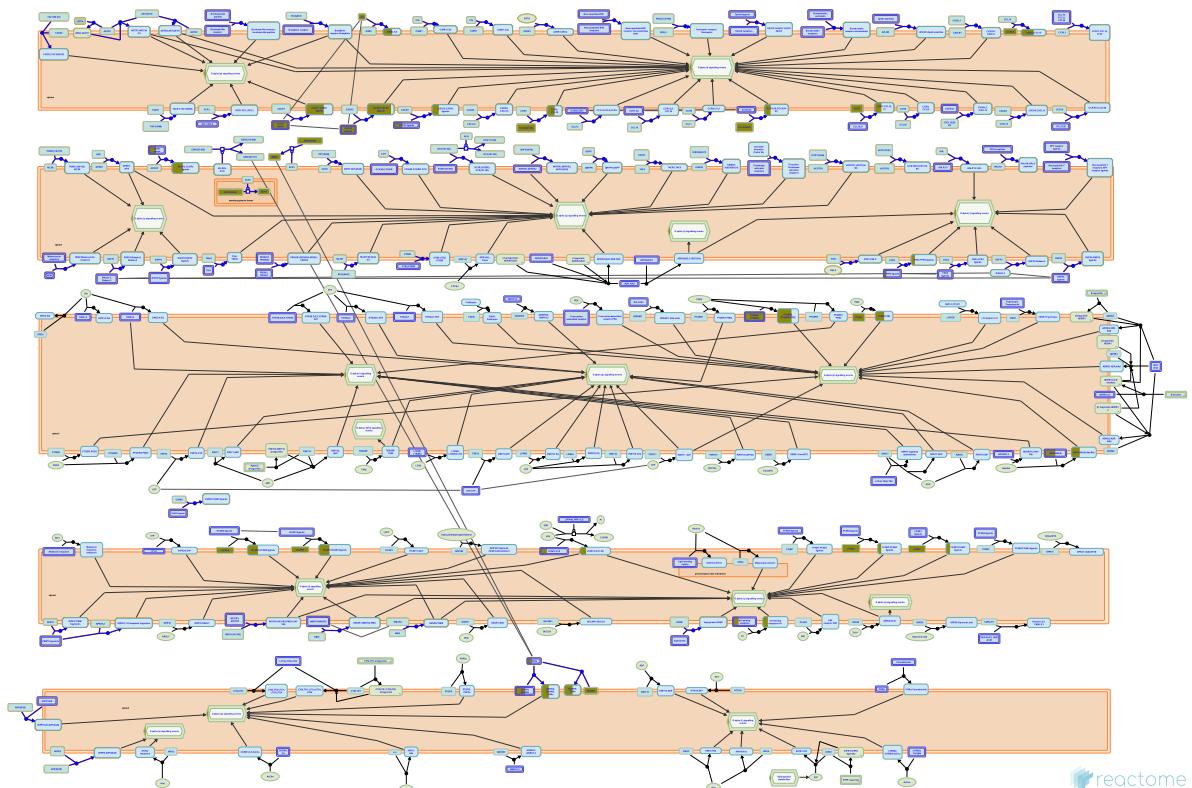
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Date	Action	Author
2011-09-21	Authored	Shamovsky V
2011-10-25	Created	Shamovsky V
2011-12-08	Reviewed	D'Eustachio P
2012-02-19	Reviewed	Mocarski ES, Upton JW
2012-02-24	Edited	Shamovsky V
2021-09-20	Modified	Weiser JD

5 submitted entities found in this pathway, mapping to 5 Reactome entities

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ENSG00000077150	Q00653	ENSG00000100906	P25963	ENSG00000104825	Q15653
ENSG00000109320	P19838	ENSG00000127666	Q8IUC6		

25. Peptide ligand-binding receptors (R-HSA-375276)



These receptors, a subset of the Class A/1 (Rhodopsin-like) family, all bind peptide ligands which include the chemokines, opioids and somatostatins.

References

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Edit history

Date	Action	Author
2008-08-21	Authored	Jassal B
2008-08-21	Created	Jassal B
2008-09-01	Edited	D'Eustachio P
2008-09-01	Reviewed	Bockaert J
2016-11-18	Revised	D'Eustachio P

Date	Action	Author
2021-09-10	Modified	Weiser JD

18 submitted entities found in this pathway, mapping to 21 Reactome entities

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ENSG0000151617	P25101	ENSG0000163734	P19876	ENSG0000163735	P42830
ENSG0000163736	P02775, P02776	ENSG0000163739	P09341	ENSG0000169245	P02778
ENSG0000169429	P02775, P10145	ENSG0000271503	P13501	ENSG0000274736	P55773-2
ENSG0000275302	P10147, P13236	ENSG0000276085	P16619	ENSG0000277632	P10147

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.

333 of the submitted entities were found, mapping to 441 Reactome entities

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ENSG00000008517	P24001	ENSG00000010810	P06241	ENSG00000011422	Q03405
ENSG00000013619	Q13495	ENSG00000023445	Q13489, Q13490	ENSG00000023608	Q16533
ENSG00000026508	P16070	ENSG00000026652	Q9NRZ5	ENSG00000026751	Q9NQ25
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ENSG00000125347	P10914	ENSG00000125384	P43116	ENSG00000125430	Q9Y662, Q9Y663
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ENSG00000131979	P30793	ENSG00000132510	O15054	ENSG00000133639	P62324
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7. Identifiers not found

These 173 identifiers were not found neither mapped to any entity in Reactome.

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