



# 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=MjAyMTEyMDIwNDUzNTVfOTk2OA%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:

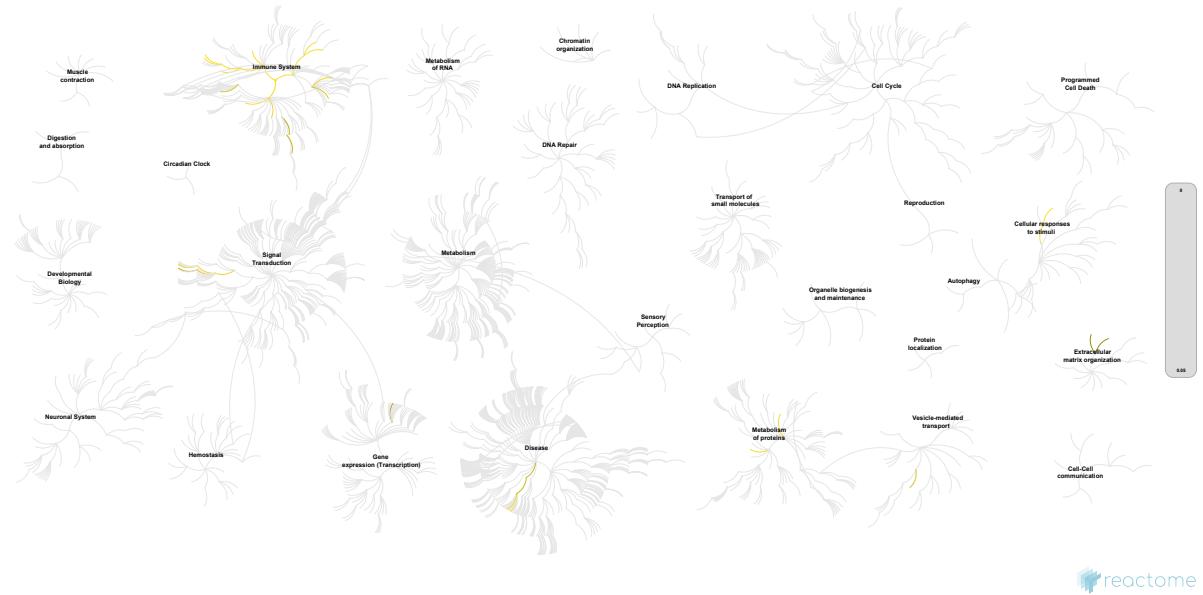
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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. ↗
- 259 out of 417 identifiers in the sample were found in Reactome, where 909 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 MjAyMTEyMDIwNDUzNTVfOTk2OA%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
Endosomal/Vacuolar pathway	72 / 82	0.006	1.11e-16	8.66e-15	4 / 4	2.95e-04
Antigen Presentation: Folding, assembly and peptide loading of class I MHC	71 / 103	0.007	1.11e-16	8.66e-15	13 / 16	0.001
Interferon gamma signaling	82 / 250	0.018	1.11e-16	8.66e-15	13 / 16	0.001
Class I MHC mediated antigen processing & presentation	80 / 474	0.033	1.11e-16	8.66e-15	29 / 48	0.004
ER-Phagosome pathway	77 / 173	0.012	1.11e-16	8.66e-15	5 / 10	7.37e-04
Antigen processing-Cross presentation	79 / 195	0.014	1.11e-16	8.66e-15	11 / 23	0.002
Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell	87 / 316	0.022	1.11e-16	8.66e-15	17 / 44	0.003
Adaptive Immune System	102 / 1,005	0.07	1.11e-16	8.66e-15	66 / 264	0.019
Immune System	186 / 2,684	0.188	1.11e-16	8.66e-15	400 / 1,623	0.12
Interferon Signaling	88 / 394	0.028	1.11e-16	8.66e-15	15 / 69	0.005
Cytokine Signaling in Immune system	115 / 1,092	0.077	1.11e-16	8.66e-15	142 / 708	0.052
Interferon alpha/beta signaling	81 / 186	0.013	1.11e-16	8.66e-15	2 / 22	0.002
Metallothioneins bind metals	9 / 16	0.001	1.43e-08	1.03e-06	20 / 27	0.002
Response to metal ions	9 / 21	0.001	1.40e-07	9.40e-06	20 / 31	0.002
Neutrophil degranulation	40 / 480	0.034	2.77e-06	1.75e-04	10 / 10	7.37e-04
Chemokine receptors bind chemokines	11 / 57	0.004	1.33e-05	7.83e-04	9 / 19	0.001
Post-translational protein phosphorylation	12 / 109	0.008	9.72e-04	0.053	1 / 1	7.37e-05
Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)	13 / 127	0.009	0.001	0.061	2 / 14	0.001
MyD88 deficiency (TLR2/4)	5 / 26	0.002	0.003	0.154	2 / 2	1.47e-04
Innate Immune System	69 / 1,334	0.093	0.004	0.165	195 / 710	0.052
IRAK4 deficiency (TLR2/4)	5 / 27	0.002	0.004	0.165	2 / 2	1.47e-04
Class A/1 (Rhodopsin-like receptors)	27 / 412	0.029	0.004	0.165	24 / 160	0.012
DAP12 interactions	7 / 53	0.004	0.004	0.169	19 / 33	0.002
Peptide ligand-binding receptors	16 / 203	0.014	0.005	0.18	14 / 77	0.006

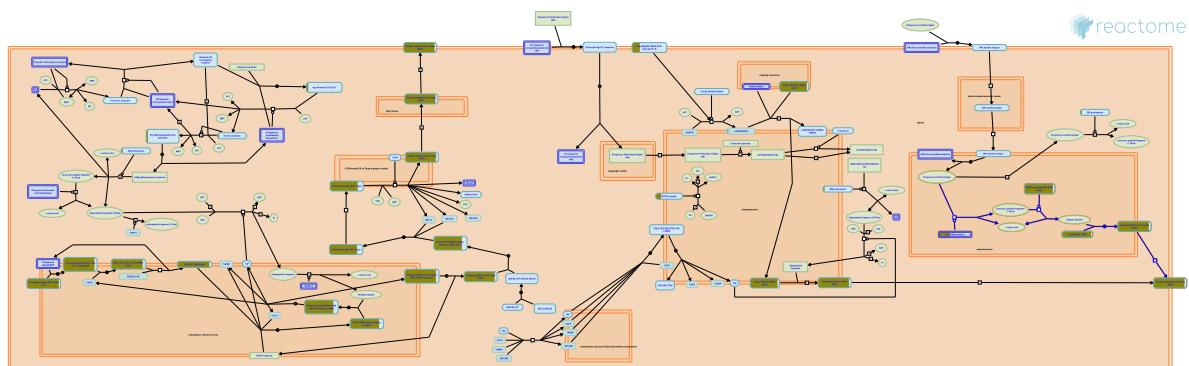
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Interleukin-10 signaling	9 / 86	0.006	0.006	0.205	9 / 15	0.001

\* 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. Endosomal/Vacuolar pathway (R-HSA-1236977)



**Cellular compartments:** early endosome.

Some antigens are cross-presented through a vacuolar mechanism that involves generation of antigenic peptides and their loading onto MHC-I molecules within the endosomal compartment in a proteasome and TAP-independent manner. Antigens within the endosome are processed by cathepsin S and other proteases into antigenic peptides. Loading of these peptides onto MHC-I molecules occurs directly within early and late endosomal compartments. Why certain antigens are cross-presented exclusively by the cytosolic pathway while others use the vacuolar pathway is unknown. It may be because some epitopes cannot be generated by endosomal proteolysis, or are completely destroyed. Alternatively, the physical form of the antigen may influence its accessibility to the endosomal or vacuolar pathways (Shen et al. 2004).

### References

Banchereau J, Montes M, Mellman I, Xue Y, Connolly JE, Clayton S, ... Di Puccio T (2008). Direct proteasome-independent cross-presentation of viral antigen by plasmacytoid dendritic cells on major histocompatibility complex class I. *Nat Immunol*, 9, 551-7. [🔗](#)

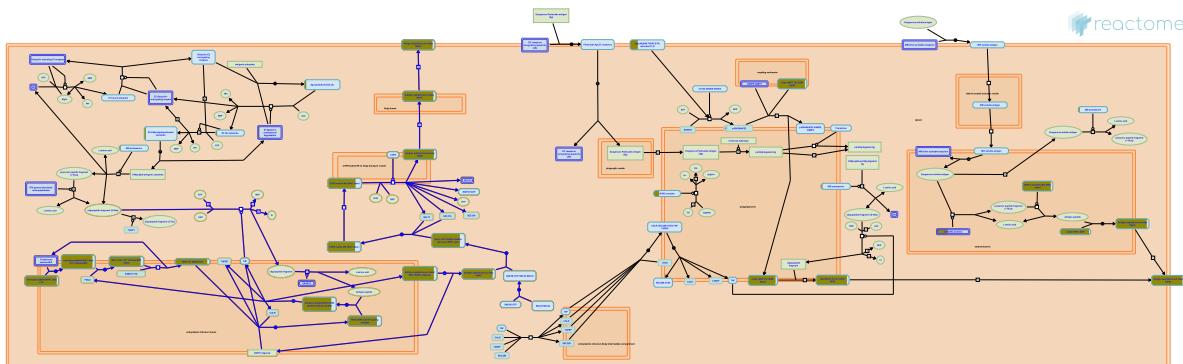
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2011-03-28	Edited	Garapati P V
2011-03-28	Authored	Garapati P V
2011-03-28	Created	Garapati P V
2011-05-13	Reviewed	Desjardins M, English L
2021-09-10	Modified	Weiser JD

5 submitted entities found in this pathway, mapping to 72 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ENSG00000135047	P07711	ENSG00000204525	P04222, P10321, P30499, P30501, P30504, P30505, P30508, P30510, Q07000, Q29865, Q29960, Q29963, Q95604, Q9TNN7	ENSG00000204642	P30511
ENSG00000206503	P01891, P01892, P04439, P05534, P10314, P10316, P13746, P16188, P16189, P16190, P18462, P30443, P30447, P30450, P30453, P30455, P30456, P30457, P30459, P30512, Q09160	ENSG00000234745	P01889, P03989, P10319, P18463, P18464, P18465, P30460, P30461, P30462, P30464, P30466, P30475, P30479, P30480, P30481, P30483, P30484, P30485, P30486, P30487, P30488, P30490, P30491, P30492, P30493, P30495, P30498, P30685, Q04826, Q29718, Q29836, Q29940, Q31610, Q31612, Q95365		

## 2. Antigen Presentation: Folding, assembly and peptide loading of class I MHC (R-HSA-983170)



Unlike other glycoproteins, correct folding of MHC class I molecules is not sufficient to trigger their exit from the ER, they exit only after peptide loading. Described here is the process of antigen presentation which consists of the folding, assembly, and peptide loading of MHC class I molecules. The newly synthesized MHC class I Heavy Chain (HC) is initially folded with the help of several chaperones (calnexin, BiP, ERp57) and then binds with Beta-2-microglobulin (B2M). This MHC:B2M heterodimer enters the peptide loading complex (PLC), a multiprotein complex that includes calreticulin, endoplasmic reticulum resident protein 57 (ERp57), transporter associated with antigen processing (TAP) and tapasin. Peptides generated from Ub-proteolysis are transported into the ER through TAP. These peptides are further trimmed by ER-associated aminopeptidase (ERAP) and loaded on to MHC class I molecules. Stable MHC class I trimers with high-affinity peptide are transported from the ER to the cell surface by the Golgi apparatus.

### References

- Cresswell P & Wearsch PA (2008). The quality control of MHC class I peptide loading. *Curr Opin Cell Biol*, 20, 624-31. [🔗](#)
- Ploegh HL, Van der Veen AG & Vyas JM (2008). The known unknowns of antigen processing and presentation. *Nat Rev Immunol*, 8, 607-18. [🔗](#)
- Jeong E, Kim Y, Ahn K, Lee YJ, Kim I, Kang K, ... Oh C (2009). Molecular mechanisms of MHC class I-antigen processing: redox considerations. *Antioxid Redox Signal*, 11, 907-36. [🔗](#)
- Powis SJ, Elliott T & Antoniou AN (2003). Assembly and export of MHC class I peptide ligands. *Curr Opin Immunol*, 15, 75-81. [🔗](#)
- Rock KL, Goldberg AL & York IA (2004). Post-proteasomal antigen processing for major histocompatibility complex class I presentation. *Nat Immunol*, 5, 670-7. [🔗](#)

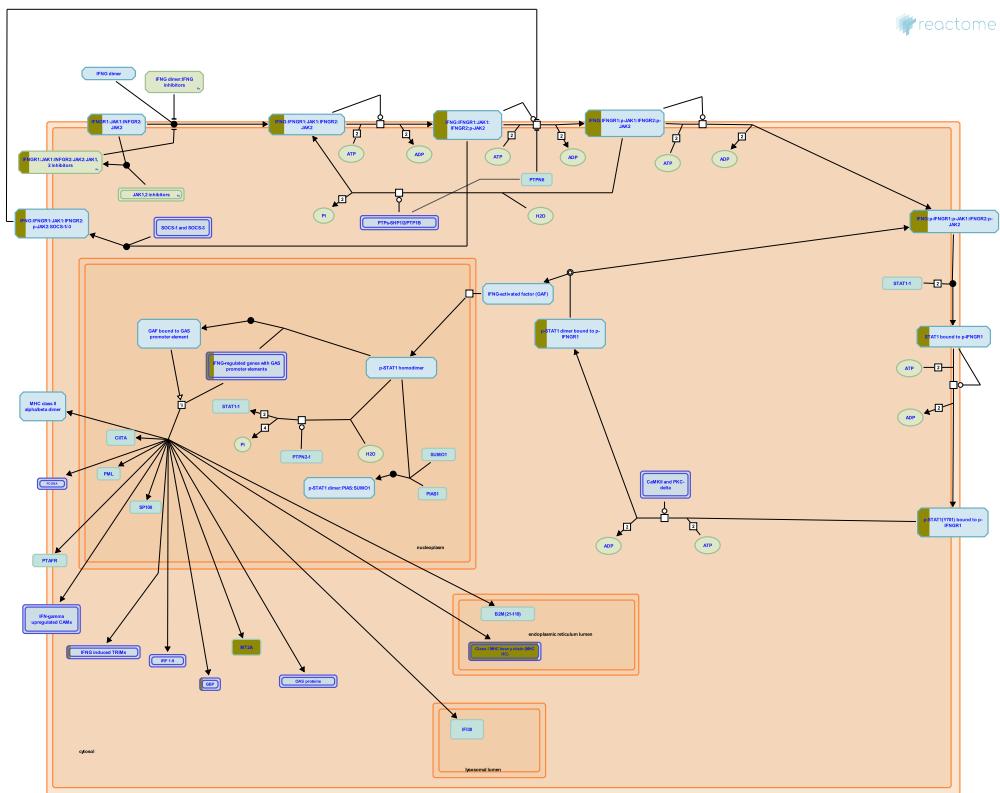
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Date	Action	Author
2010-10-29	Edited	Garapati P V
2010-10-29	Authored	Garapati P V
2010-10-29	Created	Garapati P V
2011-02-11	Reviewed	Elliott T
2021-09-10	Modified	Weiser JD

## 4 submitted entities found in this pathway, mapping to 71 Reactome entities

Input	UniProt Id	Input	UniProt Id
ENSG00000204525	P04222, P10321, P30499, P30501, P30504, P30505, P30508, P30510, Q07000, Q29865, Q29960, Q29963, Q95604, Q9TNN7	ENSG00000204642	P30511
ENSG00000206503	P01891, P01892, P04439, P05534, P10314, P10316, P13746, P16188, P16189, P16190, P18462, P30443, P30447, P30450, P30453, P30455, P30456, P30457, P30459, P30512, Q09160	ENSG00000234745	P01889, P03989, P10319, P18463, P18464, P18465, P30460, P30461, P30462, P30464, P30466, P30475, P30479, P30480, P30481, P30483, P30484, P30485, P30486, P30487, P30488, P30490, P30491, P30492, P30493, P30495, P30498, P30685, Q04826, Q29718, Q29836, Q29940, Q31610, Q31612, Q95365

### 3. 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 (STAT-1) 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

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

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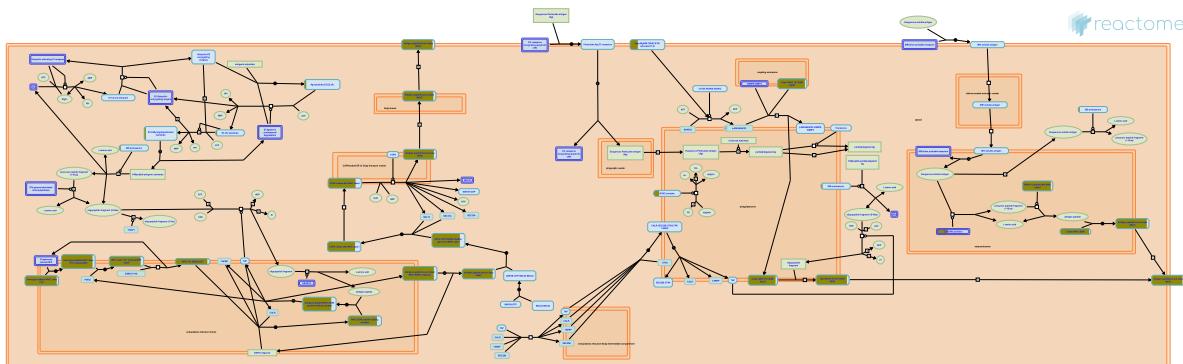
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2010-06-08	Edited	Garapati P V
2010-06-08	Authored	Garapati P V
2010-06-11	Created	Garapati P V
2010-08-17	Reviewed	Abdul-Sater AA, Schindler C
2021-09-20	Modified	Weiser JD

**8 submitted entities found in this pathway, mapping to 82 Reactome entities**

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ENSG0000027697	P15260	ENSG00000112343	O00635	ENSG00000117228	P32455
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ENSG00000206503	P1891, P01892, P04439, P05534, P10314, P10316, P13746, P16188, P16189, P16190, P18462, P30443, P30447, P30450, P30453, P30455, P30456, P30457, P30459, P30512, Q09160	ENSG00000234745	P01889, P03989, P10319, P18463, P18464, P18465, P30460, P30461, P30462, P30464, P30466, P30475, P30479, P30480, P30481, P30483, P30484, P30485, P30486, P30487, P30488, P30490, P30491, P30492, P30493, P30495, P30498, P30685, Q04826, Q29718, Q29836, Q29940, Q31610, Q31612, Q95365		

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
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ENSG00000204525	ENSG00000204525	ENSG00000204642	ENSG00000204642	ENSG00000206503	ENSG00000206503
ENSG00000234745	ENSG00000234745				

#### 4. Class I MHC mediated antigen processing & presentation (R-HSA-983169)



Major histocompatibility complex (MHC) class I molecules play an important role in cell mediated immunity by reporting on intracellular events such as viral infection, the presence of intracellular bacteria or tumor-associated antigens. They bind peptide fragments of these proteins and presenting them to CD8+ T cells at the cell surface. This enables cytotoxic T cells to identify and eliminate cells that are synthesizing abnormal or foreign proteins. MHC class I is a trimeric complex composed of a polymorphic heavy chain (HC or alpha chain) and an invariable light chain, known as beta2-microglobulin (B2M) plus an 8-10 residue peptide ligand. Represented here are the events in the biosynthesis of MHC class I molecules, including generation of antigenic peptides by the ubiquitin/26S-proteasome system, delivery of these peptides to the endoplasmic reticulum (ER), loading of peptides to MHC class I molecules and display of MHC class I complexes on the cell surface.

#### References

- Cresswell P & Wearsch PA (2008). The quality control of MHC class I peptide loading. *Curr Opin Cell Biol*, 20, 624-31. [🔗](#)
- Ploegh HL & Loureiro J (2006). Antigen presentation and the ubiquitin-proteasome system in host-pathogen interactions. *Adv Immunol*, 92, 225-305. [🔗](#)
- Rock KL & York IA (1996). Antigen processing and presentation by the class I major histocompatibility complex. *Annu Rev Immunol*, 14, 369-96. [🔗](#)
- Ploegh HL, Van der Veen AG & Vyas JM (2008). The known unknowns of antigen processing and presentation. *Nat Rev Immunol*, 8, 607-18. [🔗](#)
- Powis SJ, Elliott T & Antoniou AN (2003). Assembly and export of MHC class I peptide ligands. *Curr Opin Immunol*, 15, 75-81. [🔗](#)

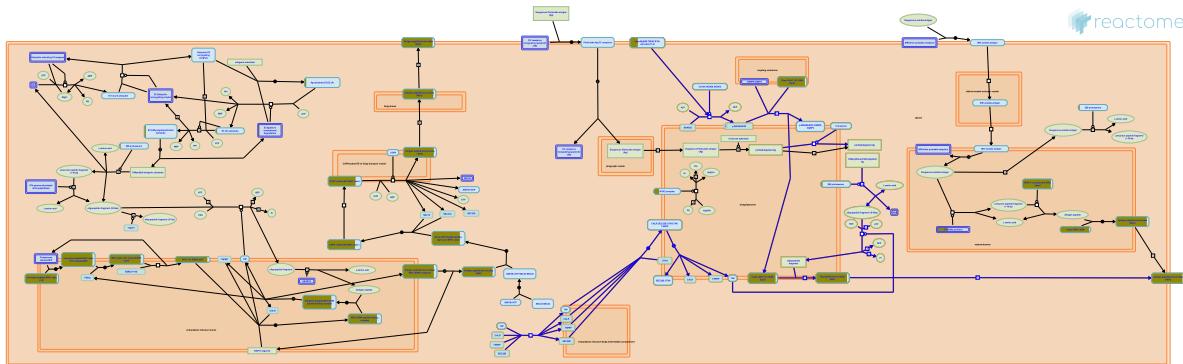
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Date	Action	Author
2010-10-29	Edited	Garapati P V
2010-10-29	Authored	Garapati P V
2010-10-29	Created	Garapati P V
2011-02-11	Reviewed	Elliott T
2021-09-10	Modified	Weiser JD

13 submitted entities found in this pathway, mapping to 80 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ENSG00000100628	Q96Q27	ENSG00000135047	P07711	ENSG00000143546	P05109
ENSG00000158517	P14598	ENSG00000163220	P06702	ENSG00000170458	P08571
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ENSG00000240065	P28065				

## 5. ER-Phagosome pathway (R-HSA-1236974)



The other TAP-dependent cross-presentation mechanism in phagocytes is the endoplasmic reticulum (ER)-phagosome model. Desjardins proposed that ER is recruited to the cell surface, where it fuses with the plasma membrane, underneath phagocytic cups, to supply membrane for the formation of nascent phagosomes (Gagnon et al. 2002). Three independent studies simultaneously showed that ER contributes to the vast majority of phagosome membrane (Guermonprez et al. 2003, Houde et al. 2003, Ackerman et al. 2003). The composition of early phagosome membrane contains ER-resident proteins, the components required for cross-presentation. This model is similar to the phagosome-to-cytosol model in that Ag is translocated to cytosol for proteasomal degradation, but differs in that antigenic peptides are translocated back into the phagosome (instead of ER) for peptide:MHC-I complexes. ER fusion with phagosome introduces molecules that are involved in Ag transport to cytosol (Sec61) and proteasome-generated peptides back into the phagosome (TAP) for loading onto MHC-I.

Although the ER-phagosome pathway is controversial, the concept remains attractive as it explains how peptide-receptive MHC-I molecules could intersect with a relatively high concentration of exogenous antigens, presumably a crucial prerequisite for efficient cross-presentation (Basha et al. 2008).

## References

- Paroutis P, Grinstein S & Touret N (2005). The nature of the phagosomal membrane: endoplasmic reticulum versus plasmalemma. *J Leukoc Biol*, 77, 878-85. [🔗](#)
- Savina A & Amigorena S (2010). Intracellular mechanisms of antigen cross presentation in dendritic cells. *Curr Opin Immunol*, 22, 109-17. [🔗](#)
- Barreiro L, Carruthers NJ, LaBoissière S, Goyette G, Dermine JF, Desjardins M, ... Duclos S (2012). Proteomic characterization of phagosomal membrane microdomains during phagolysosome biogenesis and evolution. *Mol. Cell Proteomics*, 11, 1365-77. [🔗](#)
- Houde M, Brunet S, Laplante A, Goyette G, Bertholet S, Desjardins M, ... Princiotta MF (2003). Phagosomes are competent organelles for antigen cross-presentation. *Nature*, 425, 402-6. [🔗](#)
- Bergeron JJ, Desjardins M & Gagnon E (2005). ER-mediated phagocytosis: myth or reality?. *J Leukoc Biol*, 77, 843-5. [🔗](#)

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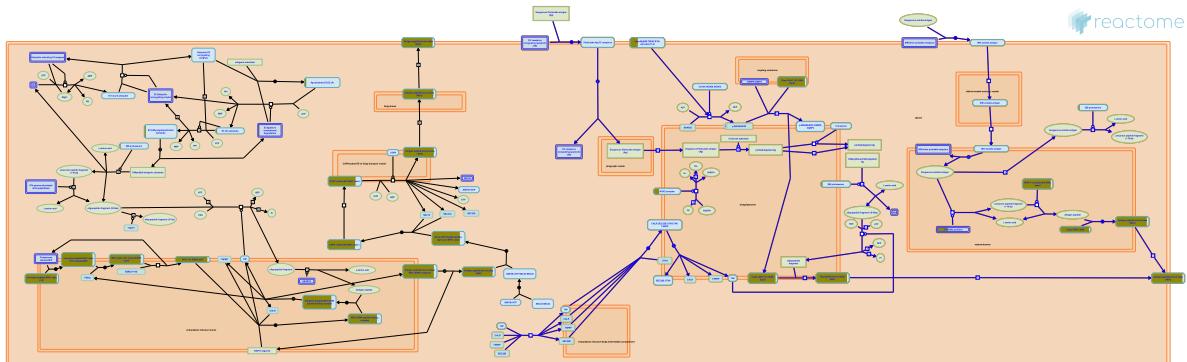
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Date	Action	Author
2011-03-28	Authored	Garapati P V
2011-03-28	Created	Garapati P V
2011-05-13	Reviewed	Desjardins M, English L
2016-05-16	Reviewed	Bergeron JJ
2021-09-10	Modified	Weiser JD

## 10 submitted entities found in this pathway, mapping to 77 Reactome entities

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ENSG00000204642	P30511	ENSG00000206503	P18462, P30443, P30447, P30450, P30453, P30455, P30456, P30457, P30459, P30512, Q09160	ENSG00000234745	P01891, P01892, P04439, P05534, P10314, P10316, P13746, P16188, P16189, P16190, P01889, P03989, P10319, P18463, P18464, P18465, P30460, P30461, P30462, P30464, P30466, P30475, P30479, P30480, P30481, P30483, P30484, P30485, P30486, P30487, P30488, P30490, P30491, P30492, P30493, P30495, P30498, P30685, Q04826, Q29718, Q29836, Q29940, Q31610, Q31612, Q95365
ENSG00000240065	P28065				

## 6. Antigen processing-Cross presentation ([R-HSA-1236975](#))



MHC class I molecules generally present peptide antigens derived from proteins synthesized by the cell itself to CD8+ T cells. However, in some circumstances, antigens from extracellular environment can be presented on MHC class I to stimulate CD8+ T cell immunity, a process termed cross-presentation (Rock & Shen. 2005). Cross-presentation/cross-priming is the ability of antigen presenting cells (APCs) to present exogenous antigens on MHC class I molecules to CD8+ T lymphocytes. Among all the APCs, Dendritic cells (DC) are the dominant antigen cross presenting cell types in vivo, although macrophages and B cells appear to cross present model antigens in vitro with a low degree of efficiency (Amigorena & Savina. 2010, Ackermann & Peter Cresswell. 2004). Compared to macrophages, DCs have low levels of lysosomal proteases and exhibit limited lysosomal degradation (Delamarre et al. 2005). This limited proteolysis of internalized antigens by DCs might contribute to their high efficiency for cross presentation (Monua & Trombetta. 2007). APCs acquire the exogenous antigens through endocytic mechanisms, especially phagosomes for particulate/cell-associated antigens and endosomes for soluble protein antigens. There does not seem to be a unique pathway for cross-presentation but rather different potential mechanisms of cross-presentation have been proposed. These proposed pathways can be classified according to the location where two key events occur: 1) processing of the antigenic protein and 2) loading of the processed peptide on to MHC I molecule (Blanchard & Shastri. 2010). Based on the requirement for TAP and cytosolic proteases two mechanisms have been described, a cytosolic pathway (TAP-dependent and proteasome-dependent) or a vacuolar pathway (TAP- and proteasome-independent) (Blanchard & Shastri. 2010, Amigorena & Savina. 2010). Regarding peptide-loading, MHC I could be loaded in the ER or in the phagosome and recycled to cell surface (Blanchard & Shastri. 2010). Exogenous soluble antigens are cross-presented by dendritic cells, albeit with lower efficiency than for particulate substrates. Soluble antigens destined for cross-presentation are taken up by distinct endocytosis mechanisms which route them into stable early endosomes and then to the cytoplasm for proteasomal degradation and peptide loading. The outcome of the cross presentation can be either tolerance or immunity (Rock & Shen. 2005).

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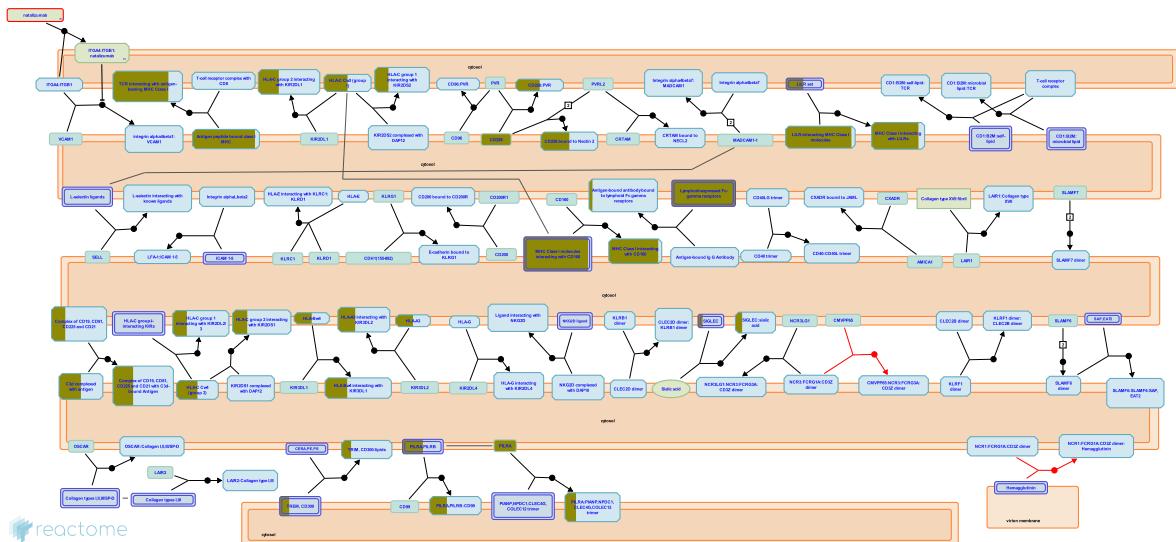
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2011-03-28	Edited	Garapati P V
2011-03-28	Authored	Garapati P V
2011-03-28	Created	Garapati P V
2011-05-13	Reviewed	Desjardins M, English L
2021-09-10	Modified	Weiser JD

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7. Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell ([R-HSA-198933](#))



A number of receptors and cell adhesion molecules play a key role in modifying the response of cells of lymphoid origin (such as B-, T- and NK cells) to self and tumor antigens, as well as to pathogenic organisms.

Molecules such as KIRs and LILRs form part of a crucial surveillance system that looks out for any derangement, usually caused by cancer or viral infection, in MHC Class I presentation. Somatic cells are also able to report internal functional impairment by displaying surface stress markers such as MICA. The presence of these molecules on somatic cells is picked up by C-lectin NK immune receptors.

Lymphoid cells are able to regulate their location and movement in accordance to their state of activation, and home in on tissues expressing the appropriate complementary ligands. For example, lymphoid cells may fine tune the presence and concentration of adhesion molecules belonging to the IgSF, Selectin and Integrin class that interact with a number of vascular markers of inflammation.

Furthermore, there are a number of avenues through which lymphoid cells may interact with antigen. This may be presented directly to a specific T-cell receptor in the context of an MHC molecule. Antigen-antibody complexes may anchor to the cell via a small number of lymphoid-specific Fc receptors that may, in turn, influence cell function further. Activated complement factor C3d binds to both antigen and to cell surface receptor CD21. In such cases, the far-reaching influence of CD19 on B-lymphocyte function is tempered by its interaction with CD21.

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Shaw A & Cemerski S (2006). Immune synapses in T-cell activation. *Curr Opin Immunol*, 18, 298-304. [🔗](#)

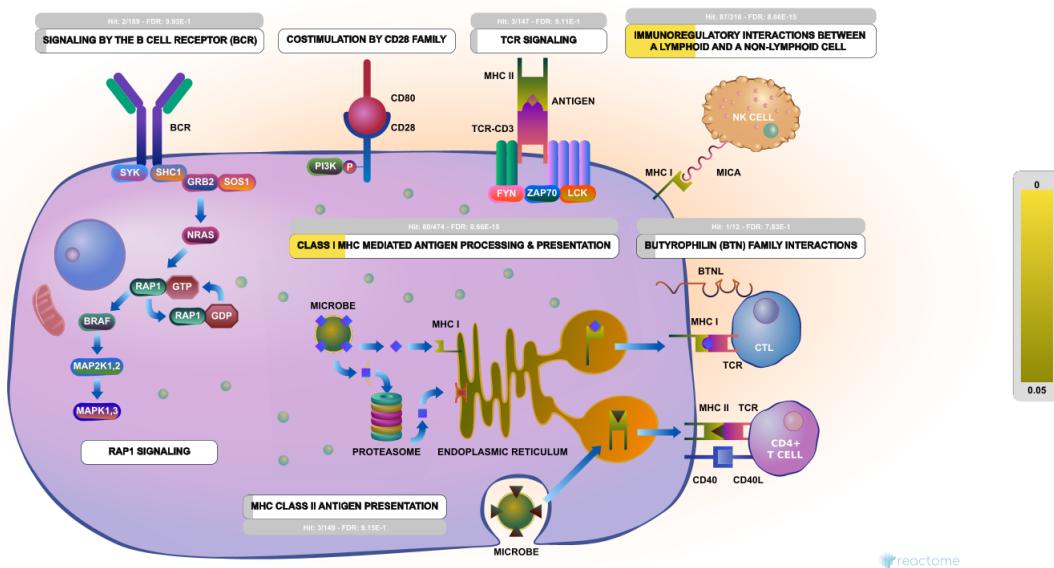
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2007-07-08	Authored	de Bono B
2007-07-08	Created	de Bono B
2007-08-07	Reviewed	Trowsdale J
2015-03-27	Authored	Garapati P V
2015-05-13	Reviewed	Barrow AD
2021-09-10	Modified	Weiser JD

**20 submitted entities found in this pathway, mapping to 87 Reactome entities**

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ENSG00000239961	P59901	ENSG00000239998	Q8N149		

## 8. Adaptive Immune System (R-HSA-1280218)



Adaptive immunity refers to antigen-specific immune response efficiently involved in clearing the pathogens. The adaptive immune system is comprised of B and T lymphocytes that express receptors with remarkable diversity tailored to recognize aspects of particular pathogens or antigens. During infection, dendritic cells (DC) which act as sentinels in the peripheral tissues recognize and pick up the pathogen in the form of antigenic determinants and then process these antigens and present them to T cells. These T cells of appropriate specificity respond to the antigen, and either kill the pathogen directly or secrete cytokines that will stimulate B lymphocyte response. B cells provide humoral immunity by secreting antibodies specific for the pathogen or antigen.

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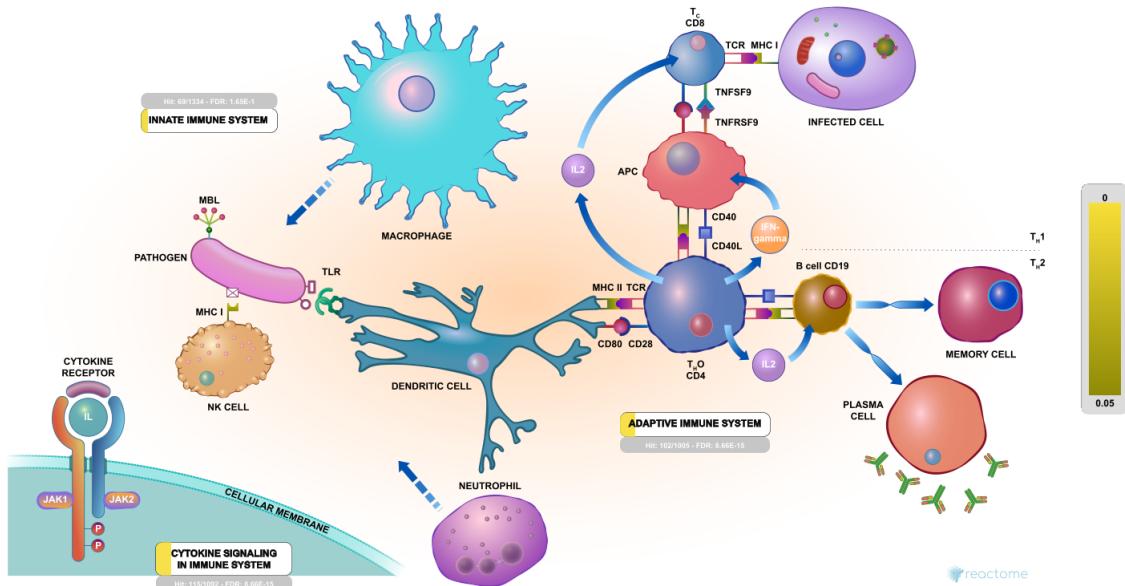
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2011-05-12	Created	Garapati P V
2011-05-22	Edited	May B, Jupe S, Garapati P V, de Bono B
2011-05-22	Authored	May B, Jupe S, Garapati P V, de Bono B
2011-05-29	Reviewed	Heemskerk JW, Bluestone JA, Elliott T, Trowsdale J, Esensten J
2021-09-10	Modified	Weiser JD

35 submitted entities found in this pathway, mapping to 102 Reactome entities

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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

### 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

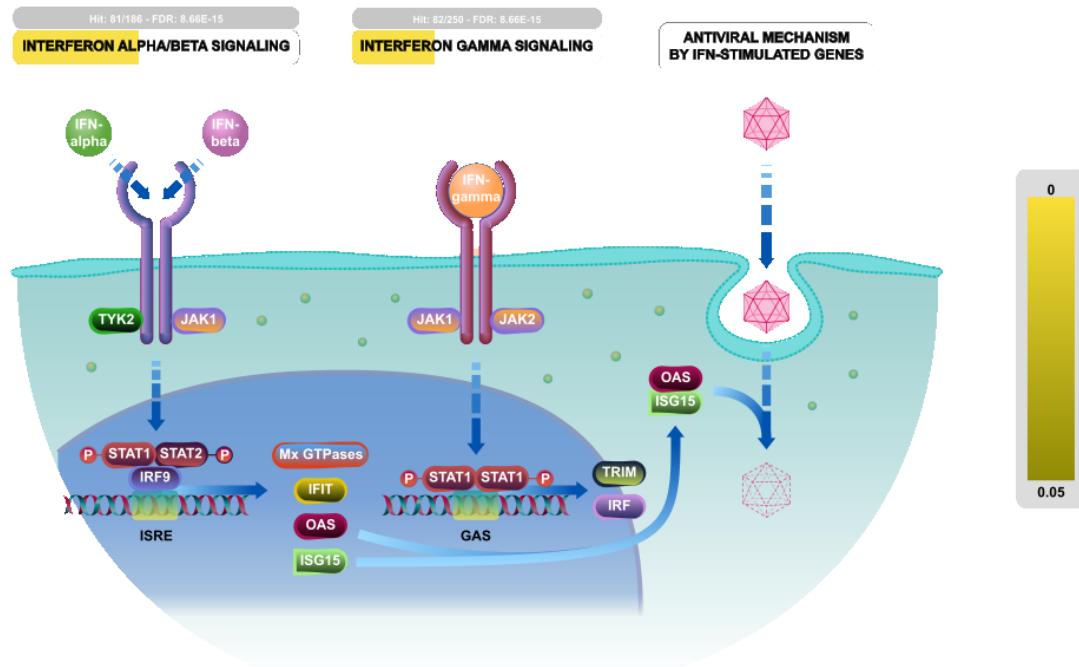
96 submitted entities found in this pathway, mapping to 187 Reactome entities

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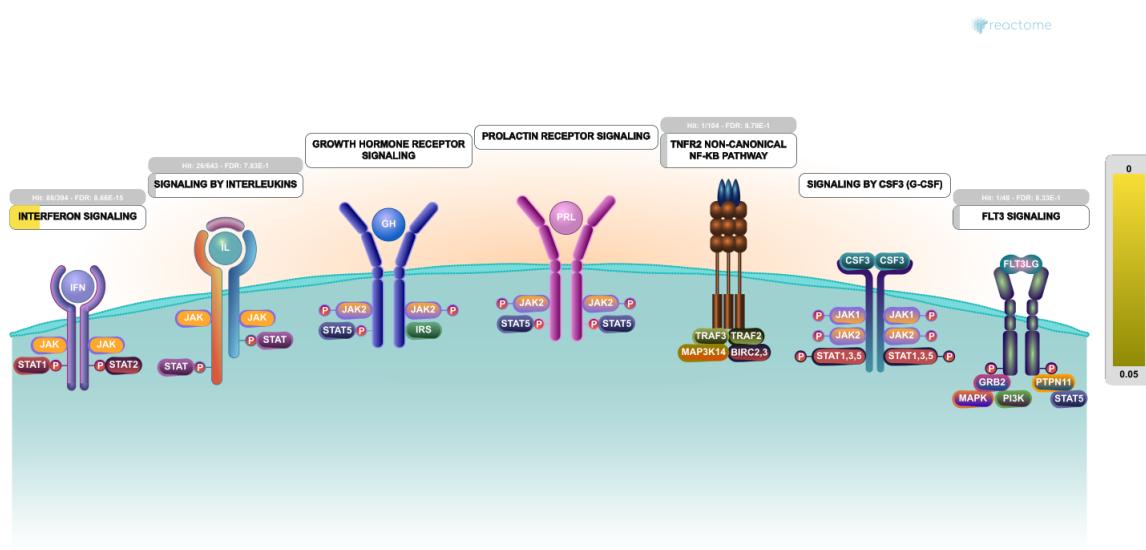
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2010-07-07	Authored	Garapati P V
2010-07-16	Created	Garapati P V
2010-08-17	Reviewed	Abdul-Sater AA, Schindler C
2021-09-10	Modified	Weiser JD

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## 11. 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.

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

### 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
2021-09-10	Modified	Weiser JD

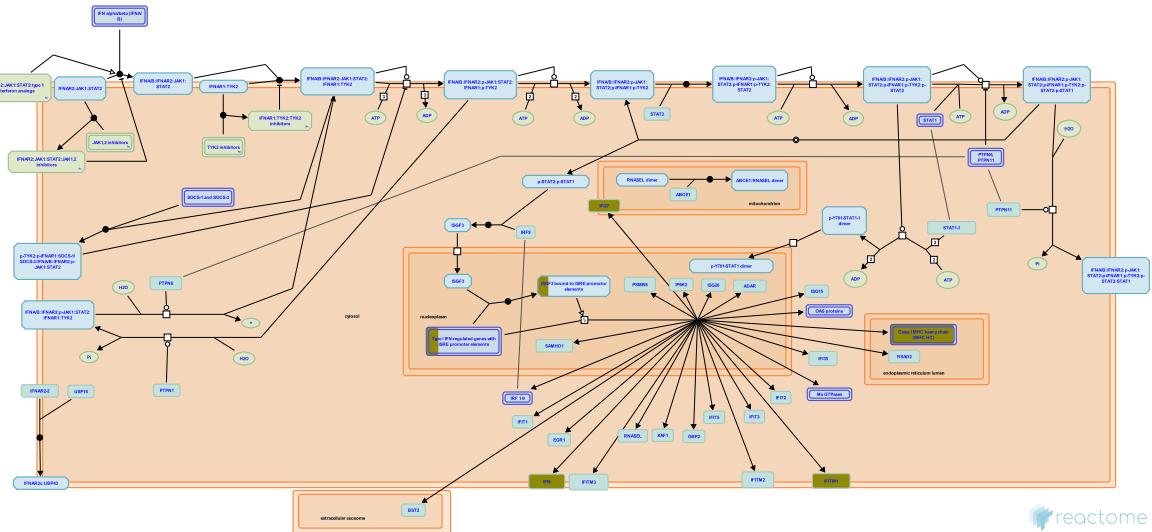
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ENSG00000234745	P01889, P03989, P10319, P18463, P18464, P18465, P30460, P30461, P30462, P30464, P30466, P30475, P30479, P30480, P30481, P30483, P30484, P30485, P30486, P30487, P30488, P30490, P30491, P30492, P30493, P30495, P30498, P30685, Q04826, Q29718, Q29836, Q29940, Q31610, Q31612, Q95365		ENSG00000240065	P28065	ENSG00000243646	Q08334

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ENSG00000234745	ENSG00000234745				

## 12. 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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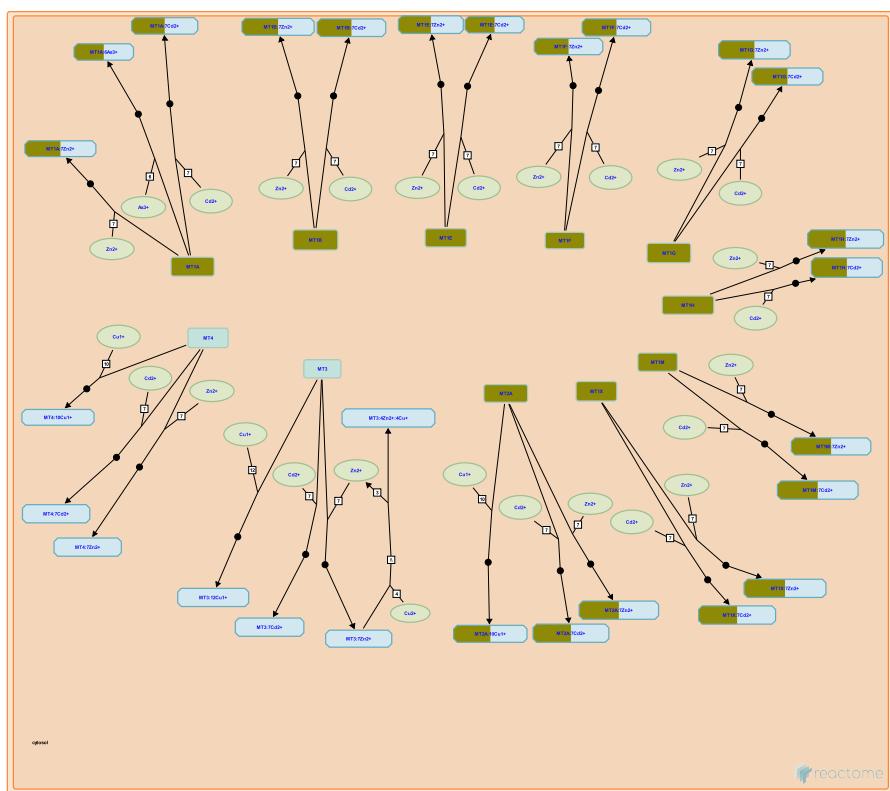
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2010-07-07	Authored	Garapati P V
2010-07-07	Created	Garapati P V
2010-08-17	Reviewed	Abdul-Sater AA, Schindler C

Date	Action	Author
2021-09-10	Modified	Weiser JD

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ENSG00000204525	ENSG00000204525	ENSG00000204642	ENSG00000204642	ENSG00000206503	ENSG00000206503
ENSG00000234745	ENSG00000234745				

### 13. Metallothioneins bind metals (R-HSA-5661231)



Metallothioneins are highly conserved, cysteine-rich proteins that bind metals via thiolate bonds (recent general reviews in Capdevila et al. 2012, Blindauer et al. 2014, reviews of mammalian metallothioneins in Miles et al. 2000, Maret 2011, Vasak and Meloni 2011, Thirumoorthy et al. 2001, Babula et al. 2012). Mammals contain 4 general metallothionein isoforms (MT1,2,3,4). The MT1 isoform has radiated in primates to 8 or 9 functional proteins (depending on classification of MT1L). Each mammalian metallothionein binds a total of 7 divalent metal ions in two clusters, the alpha and beta clusters. Though the functions of metallothioneins have not been fully elucidated, they appear to participate in detoxifying heavy metals (reviewed in Sharma et al. 2013), storing and transporting zinc, and redox biochemistry. Metallothioneins interact with many other cellular proteins, with most interactions involving proteins of the central nervous system (reviewed in Atrian and Capdevila 2013).

### References

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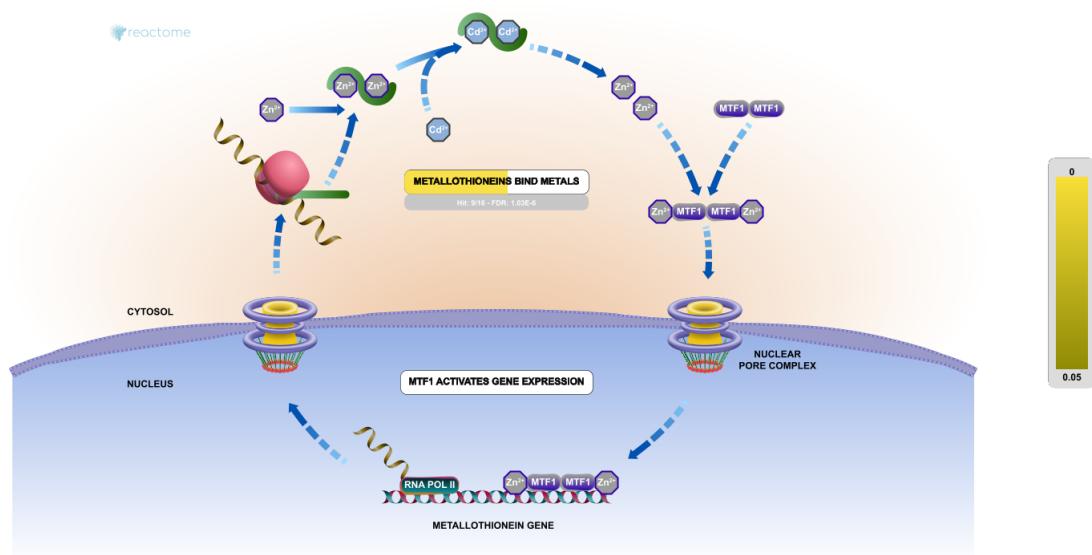
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Date	Action	Author
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2015-01-07	Authored	May B
2015-01-10	Created	May B
2015-09-19	Reviewed	Atrian S
2021-09-10	Modified	Weiser JD

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

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ENSG00000125144	P13640	ENSG00000125148	P02795	ENSG00000169688	P07438
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ENSG00000205358	P80294	ENSG00000205362	P04731	ENSG00000205364	Q8N339

## 14. Response to metal ions (R-HSA-5660526)



Though metals such as zinc, copper, and iron are required as cofactors for cellular enzymes they can also catalyze damaging metal substitution or unspecific redox reactions if they are not sequestered. The transcription factor MTF1 directs the major cellular response to zinc, cadmium, and copper. MTF1 activates gene expression to up-regulate genes encoding proteins, such as metallothioneins and glutamate-cysteine ligase (GCLC), involved in sequestering metals. MTF1 represses gene expression to down-regulate genes encoding transporters that import the metals into the cell (reviewed in Laity and Andrews 2007, Jackson et al. 2008, Günther et al. 2012, Dong et al. 2015). During activation MTF1 in the cytosol binds zinc ions and is translocated into the nucleus, where it binds metal response elements in the promoters of target genes. Activation of MTF1 by cadmium and copper appears to be indirect as these metals displace zinc from metallothioneins and the displaced zinc then binds MTF1.

Metallothioneins bind metals and participate in detoxifying heavy metals, storing and transporting zinc, and redox biochemistry.

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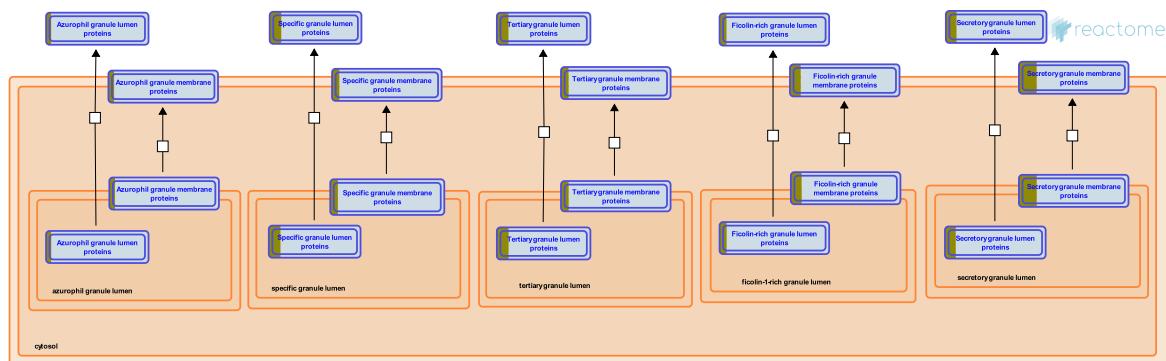
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2015-01-05	Created	May B
2015-09-19	Reviewed	Atrian S
2021-09-10	Modified	Weiser JD

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ENSG00000205358	P80294	ENSG00000205362	P04731	ENSG00000205364	Q8N339

## 15. Neutrophil degranulation (R-HSA-6798695)



Neutrophils are the most abundant leukocytes (white blood cells), indispensable in defending the body against invading microorganisms. In response to infection, neutrophils leave the circulation and migrate towards the inflammatory focus. They contain several subsets of granules that are mobilized to fuse with the cell membrane or phagosomal membrane, resulting in the exocytosis or exposure of membrane proteins. Traditionally, neutrophil granule constituents are described as anti-microbial or proteolytic, but granules also introduce membrane proteins to the cell surface, changing how the neutrophil responds to its environment (Borregaard et al. 2007). Primed neutrophils actively secrete cytokines and other inflammatory mediators and can present antigens via MHC II, stimulating T-cells (Wright et al. 2010).

Granules form during neutrophil differentiation. Granule subtypes can be distinguished by their content but overlap in structure and composition. The differences are believed to be a consequence of changing protein expression and differential timing of granule formation during the terminal processes of neutrophil differentiation, rather than sorting (Le Cabec et al. 1996).

The classical granule subsets are Azurophil or primary granules (AG), secondary granules (SG) and gelatinase granules (GG). Neutrophils also contain exocytosable storage cell organelles, storage vesicles (SV), formed by endocytosis they contain many cell-surface markers and extracellular, plasma proteins (Borregaard et al. 1992). Ficolin-1-rich granules (FG) are like GGs highly exocytosable but gelatinase-poor (Rorvig et al. 2009).

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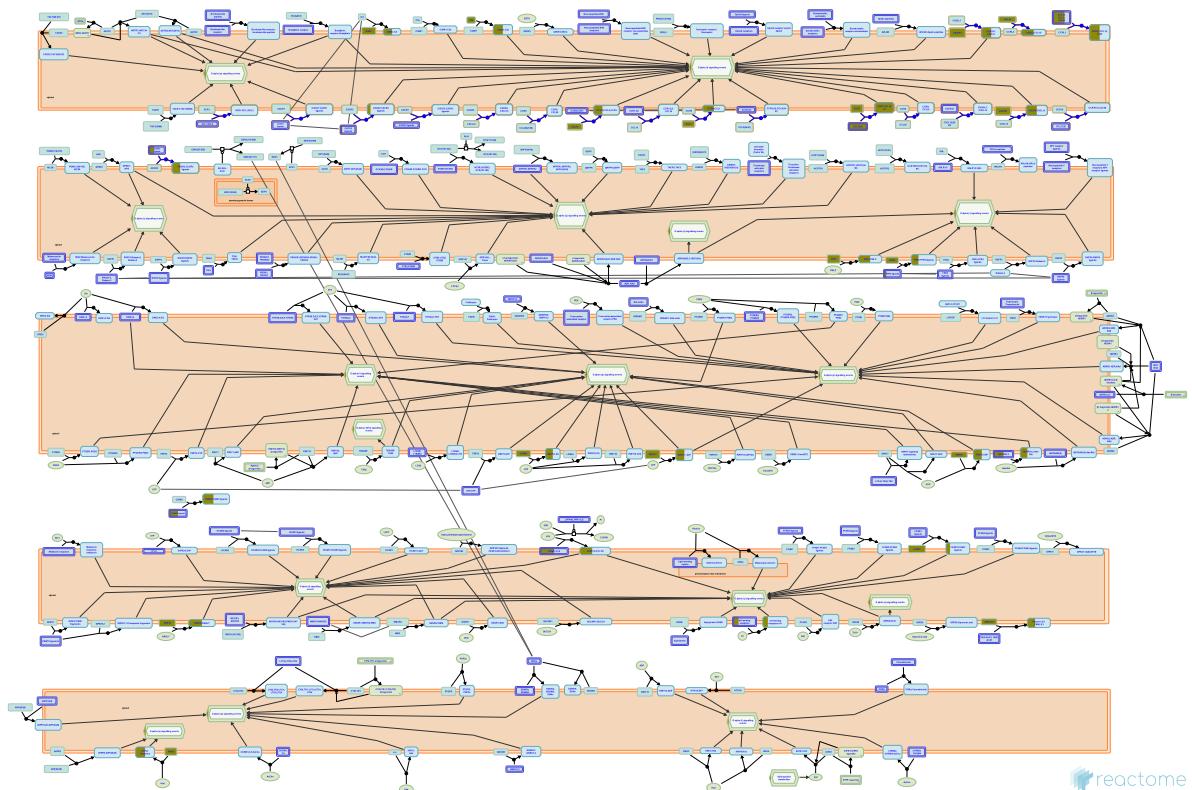
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2015-09-21	Created	Jupe S
2016-06-13	Edited	Jupe S
2016-06-13	Reviewed	Heegaard N
2021-09-10	Modified	Weiser JD

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ENSG00000109107	P09972	ENSG0000115828	Q16769	ENSG0000116260	O00391
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ENSG00000163220	P06702	ENSG0000163221	P80511	ENSG0000163993	P25815
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ENSG00000234745	P01889	ENSG0000257017	P00738	ENSG0000261371	P16284

## 16. 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

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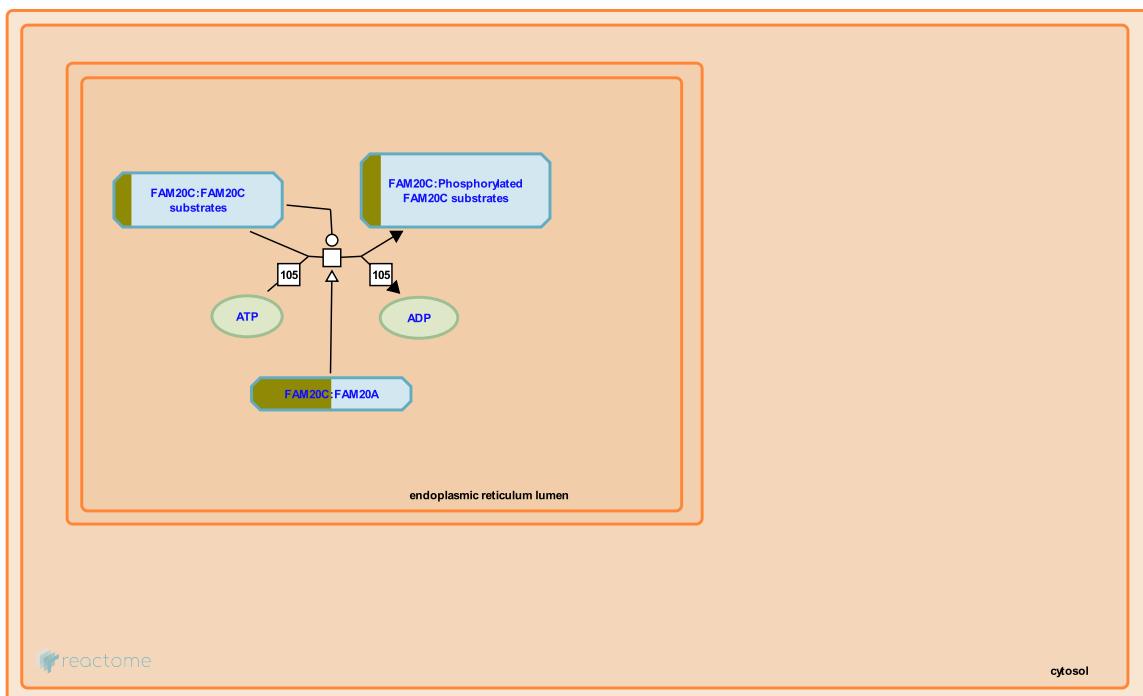
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2021-09-10	Modified	Weiser JD

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ENSG00000181374	Q99616				

## 17. Post-translational protein phosphorylation (R-HSA-8957275)



Secretory pathway kinases phosphorylate a diverse array of substrates involved in many physiological processes.

### References

Kinch LN, Tagliabracci VS & Sreelatha A (2015). The secretory pathway kinases. *Biochim. Biophys. Acta*, 1854, 1687-93. [View](#)

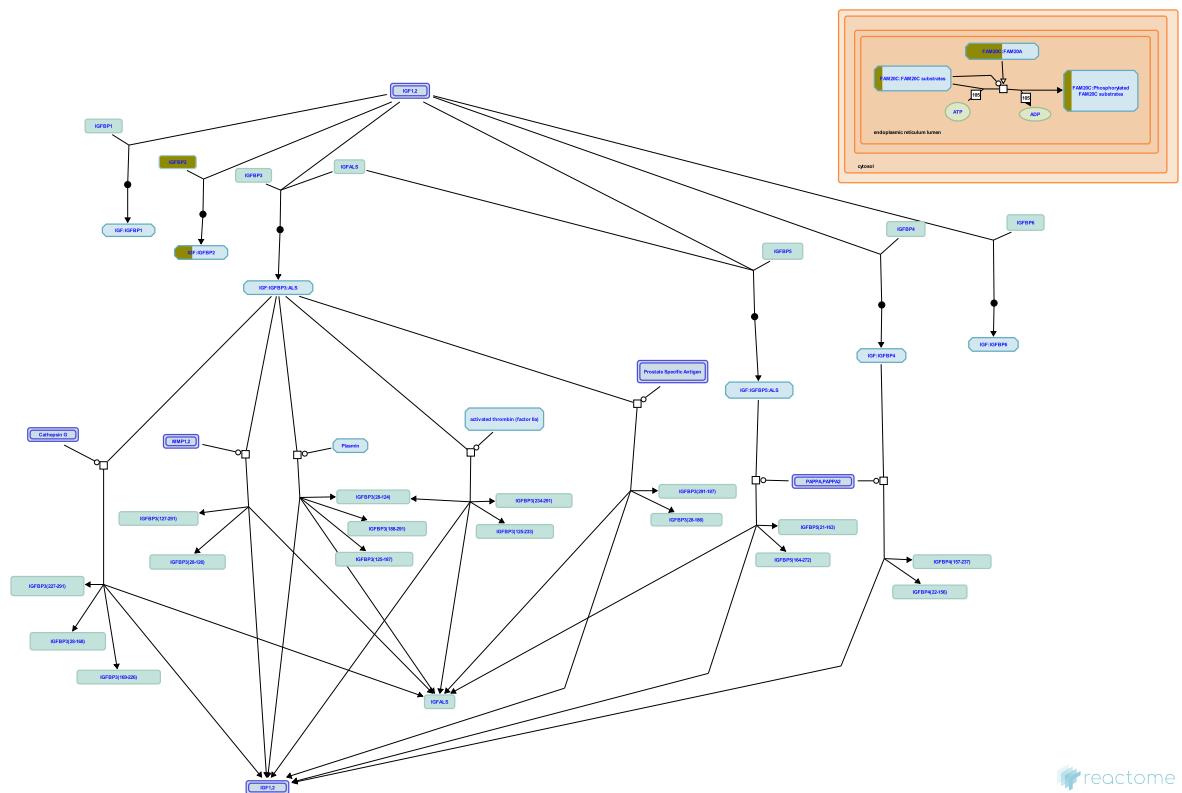
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2017-01-24	Edited	Jupe S
2017-01-24	Created	Jupe S
2021-09-20	Modified	Weiser JD

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ENSG00000136026	Q07065	ENSG00000169439	P34741	ENSG00000197249	P01009

## 18. Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs) ([R-HSA-381426](#))



**Cellular compartments:** extracellular region.

The family of Insulin like Growth Factor Binding Proteins (IGFBPs) share 50% amino acid identity with conserved N terminal and C terminal regions responsible for binding Insulin like Growth Factors I and II (IGF I and IGF II). Most circulating IGFs are in complexes with IGFBPs, which are believed to increase the residence of IGFs in the body, modulate availability of IGFs to target receptors for IGFs, reduce insulin like effects of IGFs, and act as signaling molecules independently of IGFs.

About 75% of circulating IGFs are in 1500-220 KDa complexes with IGFBP3 and ALS. Such complexes are too large to pass the endothelial barrier. The remaining 20-25% of IGFs are bound to other IGFBPs in 40-50 KDa complexes. IGFs are released from IGF:IGFBP complexes by proteolysis of the IGFBP. IGFs become active after release, however IGFs may also have activity when still bound to some IGFBPs.

IGFBP1 is enriched in amniotic fluid and is produced in the liver under control of insulin (insulin suppresses production). IGFBP1 binding stimulates IGF function. It is unknown which if any protease degrades IGFBP1.

IGFBP2 is enriched in cerebrospinal fluid; its binding inhibits IGF function. IGFBP2 is not significantly degraded in circulation.

IGFBP3, which binds most IGF in the body is enriched in follicular fluid and found in many other tissues. IGFBP 3 may be cleaved by plasmin, thrombin, Prostate specific Antigen (PSA, KLK3), Matrix Metalloprotease-1 (MMP1), and Matrix Metalloprotease-2 (MMP2). IGFBP3 also binds extracellular matrix and binding lowers its affinity for IGFs. IGFBP3 binding stimulates the effects of IGFs.

IGFBP4 acts to inhibit IGF function and is cleaved by Pregnancy associated Plasma Protein A (PAPPA) to release IGF.

IGFBP5 is enriched in bone matrix; its binding stimulates IGF function. IGFBP5 is cleaved by Pregnancy Associated Plasma Protein A2 (PAPPA2), ADAM9, complement C1s from smooth muscle, and thrombin. Only the cleavage site for PAPPA2 is known.

IGFBP6 is enriched in cerebrospinal fluid. It is unknown which if any protease degrades IGFBP6.

## References

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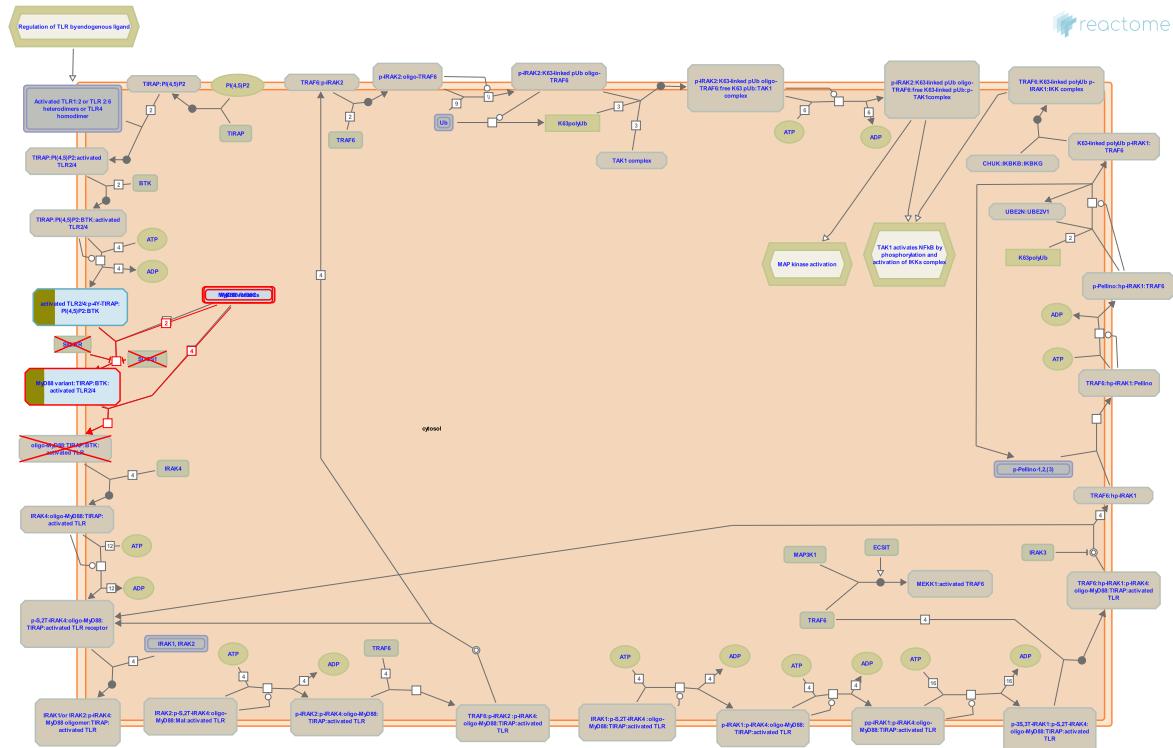
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2008-11-20	Created	May B

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2008-12-02	Reviewed	Matthews L, Gillespie ME, D'Eustachio P
2021-09-10	Modified	Weiser JD

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ENSG0000115457	P18065	ENSG0000116260	O00391	ENSG0000118785	P10451
ENSG0000125730	P01024	ENSG0000136026	Q07065	ENSG0000169439	P34741
ENSG0000197249	P01009				

## 19. MyD88 deficiency (TLR2/4) (R-HSA-5602498)



**Diseases:** primary immunodeficiency disease.

Myeloid differentiation primary response (MyD88) is an adaptor protein that mediates intracellular signaling pathways evoked by all Toll-like receptors (TLRs) except for TLR3 and by several interleukin-1 receptors (IL-1Rs) (Medzhitov R et al. 1998). Upon ligand binding, TLRs hetero- or homodimerize and recruit MyD88 through their respective TIR domains. Then, MyD88 oligomerizes via its death domain (DD) and TIR domain and interacts with the interleukin-1 receptor-associated kinases (IRAKs) to form the Myddosome complex (MyD88:IRAK4:IRAK1/2) (Motshwene PG et al. 2009; Lin SC et al. 2010). The Myddosome complex transmits the signal leading to activation of transcription factors such as nuclear factor-kappaB (NFκB) and activator protein 1 (AP1).

Studies have identified patients with autosomal recessive (AR) form of MyD88 deficiency caused by homozygous or compound heterozygous mutations in MYD88 gene leading to abolished protein production (von Bernuth et al. 2008). AR MyD88 deficiency is a type of a primary immunodeficiency characterized by greater susceptibility to pyogenic bacteria (such as *Streptococcus pneumoniae*, *Staphylococcus aureus* or *Pseudomonas aeruginosa*) manifested in infancy and early childhood. Patients with MyD88 deficiency show delayed or weak signs of inflammation (Picard C et al. 2010; Picard C et al. 2011).

Functional assessment of MyD88 deficiency revealed that cytokine responses were impaired in patient-derived blood cells upon stimulation with the agonists of TLR2 and TLR4 (PAM2CSK4 and LPS respectively), although some were produced in response to LPS. (von Bernuth et al. 2008). NFkB luciferase reporter gene assays using human embryonic kidney 293 (HEK293T) cells showed that MyD88 variants, S34Y, E52del, E53X, L93P, R98C, and R196C, were compromised in their ability to enhance NFkB activation (Yamamoto T et al. 2014). The molecular basis for the observed functional effects (reported for selected mutations) probably faulty Myddosome formation due to impaired MyD88 oligomerization and/or interaction with IRAK4 (George J et al. 2011; Nagpal K et al. 2011; Yamamoto T et al. 2014).

While MyD88-deficiency might be expected to perturb MyD88?IRAK4 dependent TLR7 and TLR8 signaling events associated with the sensing viral infections, patients with MyD88 and IRAK4 deficiencies have so far not been reported to be susceptible to viral infection.

## References

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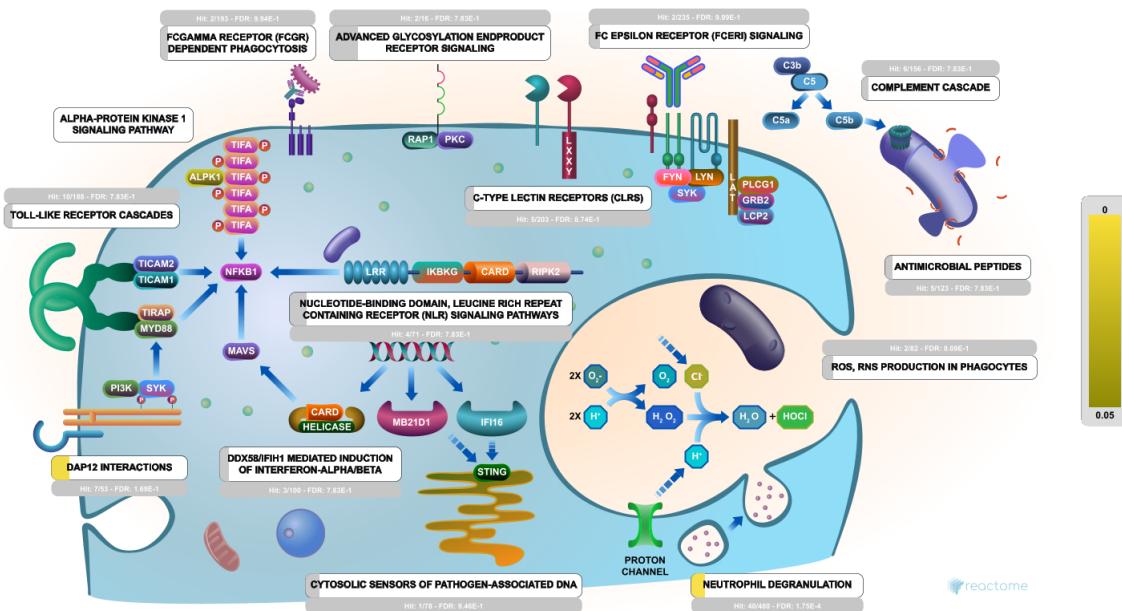
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2014-05-21	Authored	Shamovsky V
2014-06-24	Created	Shamovsky V
2014-09-06	Reviewed	D'Eustachio P
2015-02-10	Edited	Shamovsky V
2015-02-15	Reviewed	McDonald DR
2021-09-20	Modified	Weiser JD

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## 20. Innate Immune System (R-HSA-168249)



Innate immunity encompasses the nonspecific part of immunity that are part of an individual's natural biologic makeup

### References

### Edit history

Date	Action	Author
2005-11-12	Created	Gillespie ME
2021-09-10	Modified	Weiser JD

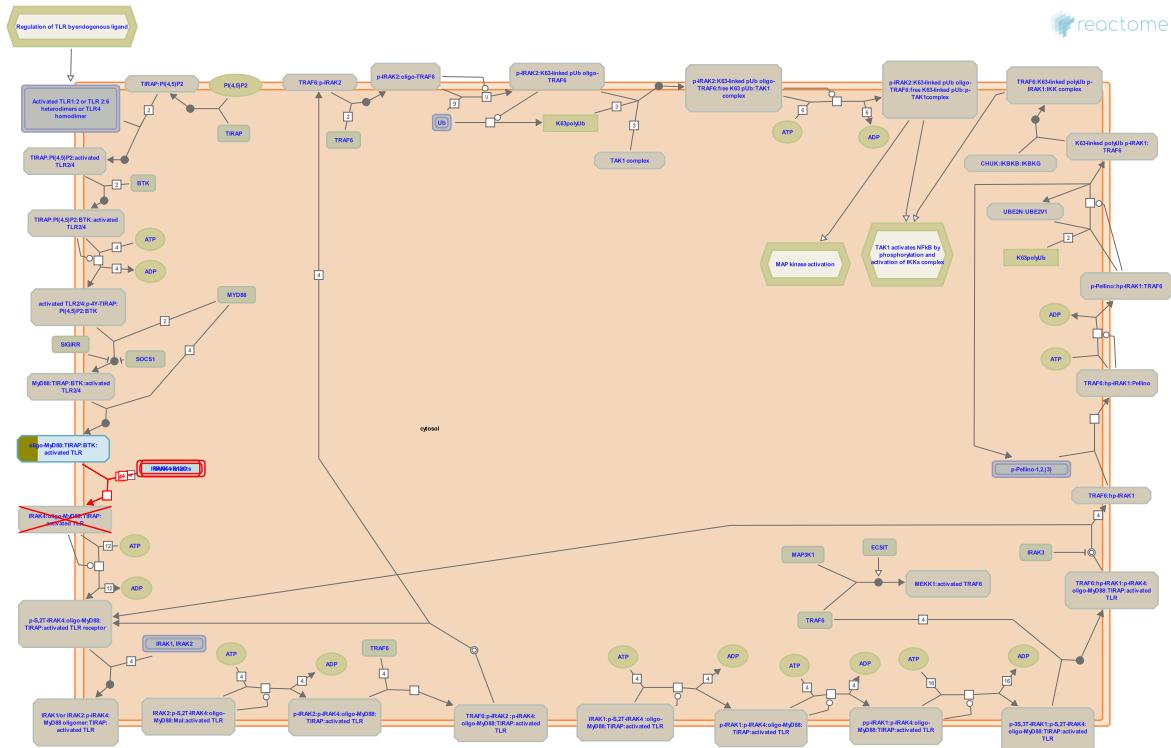
64 submitted entities found in this pathway, mapping to 69 Reactome entities

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Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
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ENSG00000234745	P01889, Q95365	ENSG00000240065	P28065	ENSG00000243649	P00751
ENSG00000257017	P00738	ENSG00000261371	P16284	ENSG00000265972	Q9H3M7

Input	Ensembl Id
ENSG00000102970	ENSG00000102970

## 21. IRAK4 deficiency (TLR2/4) (R-HSA-5603041)



**Diseases:** primary immunodeficiency disease.

Interleukin-1 receptor-associated kinase 4 (IRAK4) is a serine/threonine kinase, that mediates activation of transcriptional factors such as NF $\kappa$ B and AP1 downstream of IL-1 receptors and all toll like receptors (TLR) except for TLR3 (Suzuki N et al. 2002). IRAK4 is recruited to the TLR receptor complex through a homophilic interaction of the death domains of IRAK4 and adaptor myeloid differentiation factor 88 protein (MyD88) (Motshwene PG et al. 2009; Lin SC et al. 2010). Studies have identified patients with an autosomal recessive (AR) form of IRAK4 deficiency, a health condition with clinical manifestation in infancy or early childhood, that predisposes affected patients to recurrent pyogenic bacterial infection (e.g., *Streptococcus pneumoniae* and *Staphylococcus aureus*) (Picard C et al. 2003; Ku CL et al. 2007; Picard C et al. 2010; Picard C et al. 2011). Leukocytes derived from IRAK4-deficient patients display a lack of production of inflammatory cytokines such as TNF alpha, IL-6 and IL-1 beta by whole blood or a lack of CD62 ligand (CD62L) shedding from granulocytes following activation with the most TLR agonists including those of TLR1/2 (Pam3CSK4), TLR2/6 (Pam2CSK4) and TLR4 (LPS) (Picard C et al. 2003; McDonald DR et al. 2006; Ku CL et al. 2007). However, LPS-induced TLR4-mediated production of some cytokines (IL8 and MIP-1 $\beta$ ) was reduced but not abolished (Ku CL et al. 2007). LPS-stimulated induction of type I IFN via MyD88-IRAK4 independent signaling axis was normal or weakly affected suggesting that TLR4 could induce some responses in IRAK4 deficient patients(Yang K et al. 2005).

Patients with AR IRAK4 deficiency were found to bear homozygous or compound heterozygous mutations in the IRAK4 gene (Picard C et al. 2003; Ku CL et al. 2007; McDonald DR et al. 2006). Here we describe selected mutations, that have been functionally characterized. Cell-based assay as well as in vitro protein-interaction analyses with IRAK4 variants showed that the loss-of-function of defective IRAK4 is caused by either loss of protein production (reported for IRAK4 Q293X and E402X) or an impaired interaction with MyD88 as shown for missense mutation IRAK4 R12C (Ku CL et al. 2007; Yamamoto T et al. 2014).

Besides defective TLR2/4 mediated signaling, the Reactome module describes the impact of functional deficiency of IRAK4 on TLR5 pathways. The module does not include defective TLR7, TLR8 and TLR9 signaling events, which are associated mostly with viral infections, although studies using patient-derived blood cells showed abolished cytokine production by peripheral blood mononuclear cells (PBMCs) and lack of CD62 ligand (CD62L) shedding from granulocytes in response to TLR7-9 agonists (McDonald DR et al. 2006; von Bernuth H et al. 2006; Ku CL et al. 2007). In addition to the TLR-NFkB signaling axis, endosomal TLR7-9 activates IFN-alpha/beta and IFN-gamma responses and these are also impaired in IRAK4-deficient PBMC (Yang K et al. 2005). Nevertheless, IFN-alpha/beta and -gamma production in IRAK4-deficient blood cells in response to 9 of 11 viruses was normal or weakly affected, suggesting that IRAK4-deficient patients may control viral infections by TLR7-9-independent production of IFNs such as IRAK4-independent antiviral RIGI and MDA5 pathways (Yang K et al. 2005). So it is not yet possible to annotate a definitive molecular pathway between IRAK4 deficiency and changes in TLR7-9 signaling.

## References

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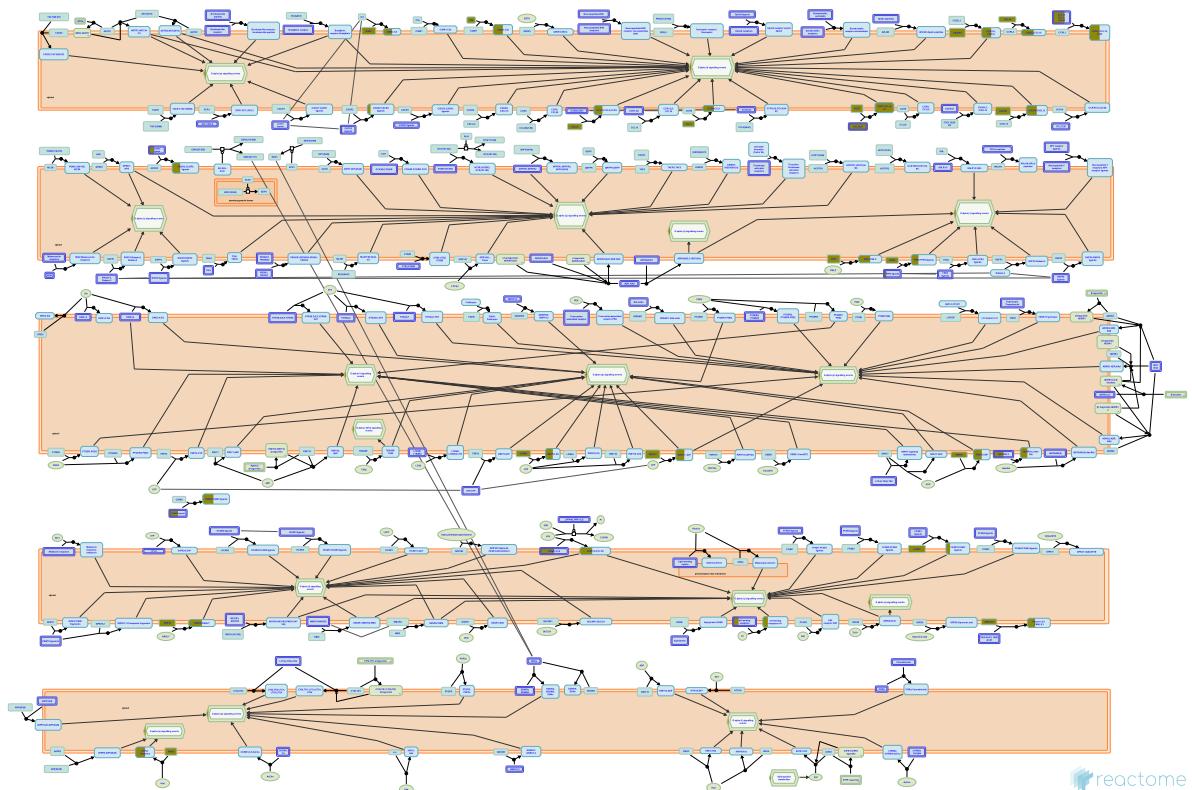
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Date	Action	Author
2014-05-21	Authored	Shamovsky V
2014-06-26	Created	Shamovsky V
2014-09-06	Reviewed	D'Eustachio P
2015-02-10	Edited	Shamovsky V
2015-02-15	Reviewed	McDonald DR
2021-09-20	Modified	Weiser JD

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## 22. Class A/1 (Rhodopsin-like receptors) (R-HSA-373076)



Rhodopsin-like receptors (class A/1) are the largest group of GPCRs and are the best studied group from a functional and structural point of view. They show great diversity at the sequence level and thus, can be subdivided into 19 subfamilies (Subfamily A1-19) based on a phylogenetic analysis (Joost P and Methner A, 2002). They represent members which include hormone, light and neurotransmitter receptors and encompass a wide range of functions including many autocrine, paracrine and endocrine processes.

## References

Bouhelal R, Jacoby E, Gerspacher M & Seuwen K (2006). The 7 TM G-protein-coupled receptor target family. *ChemMedChem*, 1, 761-82. [View](#)

## Edit history

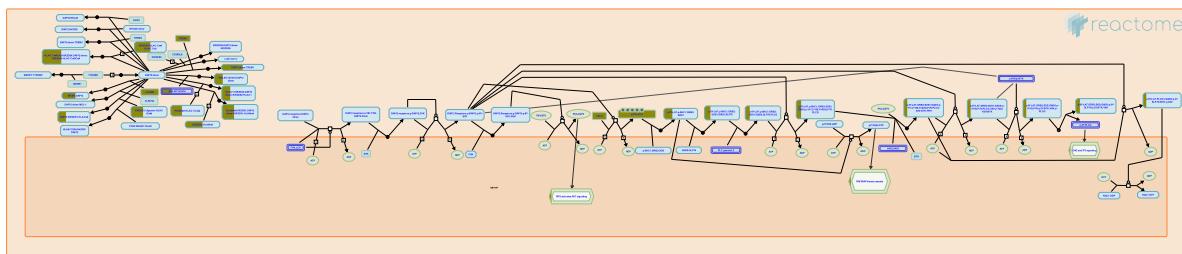
Date	Action	Author
2008-07-03	Authored	Jassal B
2008-07-14	Created	Jassal B
2008-09-01	Edited	D'Eustachio P
2008-09-01	Reviewed	Bockaert J
2016-11-18	Revised	D'Eustachio P
2021-09-10	Modified	Weiser JD

26 submitted entities found in this pathway, mapping to 28 Reactome entities

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## 23. DAP12 interactions (R-HSA-2172127)



DNAX activation protein of 12kDa (DAP12) is an immunoreceptor tyrosine-based activation motif (ITAM)-bearing adapter molecule that transduces activating signals in natural killer (NK) and myeloid cells. It mediates signalling for multiple cell-surface receptors expressed by these cells, associating with receptor chains through complementary charged transmembrane amino acids that form a salt-bridge in the context of the hydrophobic lipid bilayer (Lanier et al. 1998). DAP12 homodimers associate with a variety of receptors expressed by macrophages, monocytes and myeloid cells including TREM2, Siglec H and SIRP-beta, as well as activating KIR, LY49 and the NKG2C proteins expressed by NK cells. DAP12 is expressed at the cell surface, with most of the protein lying on the cytoplasmic side of the membrane (Turnbull & Colonna 2007, Tessarz & Cerwenka 2008).

## References

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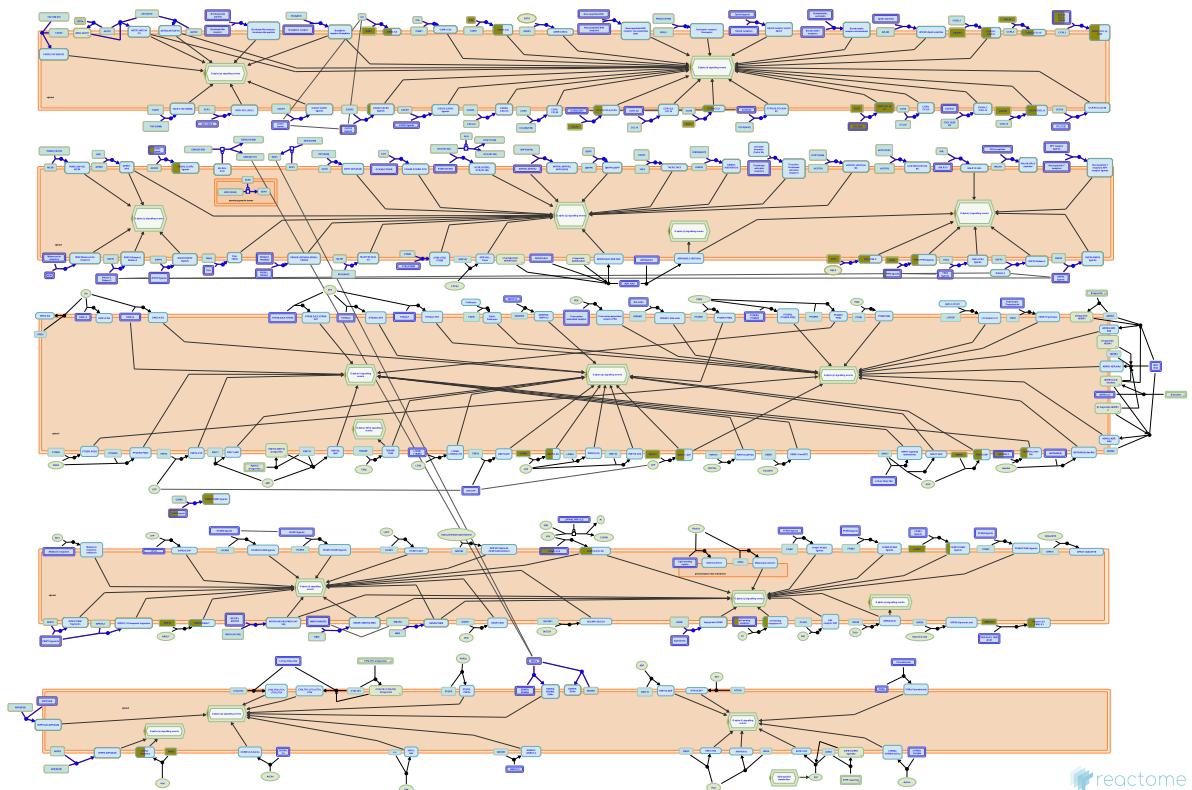
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Date	Action	Author
2012-03-28	Created	Garapati P V
2012-05-25	Edited	Garapati P V
2012-05-25	Authored	Garapati P V
2012-08-09	Reviewed	Lanier LL
2021-09-10	Modified	Weiser JD

## 6 submitted entities found in this pathway, mapping to 7 Reactome entities

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ENSG00000204525	P04222, P30504	ENSG00000213658	O43561-2	ENSG00000234745	Q95365

## 24. 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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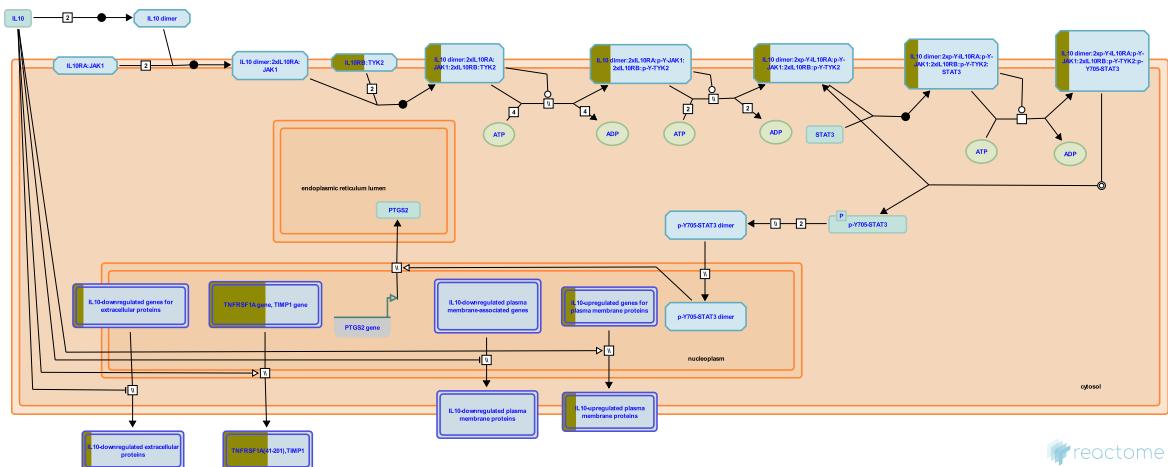
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2008-08-21	Authored	Jassal B
2008-08-21	Created	Jassal B
2008-09-01	Edited	D'Eustachio P
2008-09-01	Reviewed	Bockaert J
2016-11-18	Revised	D'Eustachio P

Date	Action	Author
2021-09-10	Modified	Weiser JD

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

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ENSG00000171049	P25090	ENSG00000171051	P21462	ENSG00000172724	Q99731
ENSG00000173432	P0DJI8	ENSG00000181374	Q99616	ENSG00000213088	Q16570

## 25. 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

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## 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
2021-09-20	Modified	Weiser JD

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## 6. Identifiers found

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ENSG00000239961	P59901	ENSG00000239998	Q8N149	ENSG00000240065	P28065
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## 7. Identifiers not found

These 158 identifiers were not found neither mapped to any entity in Reactome.

ENSG0000002933 ENSG0000016864 ENSG0000039560 ENSG0000049239 ENSG0000054965 ENSG0000054967 ENSG0000059728 ENSG0000065600 ENSG0000077063 ENSG0000085117 ENSG0000086300 ENSG0000088451 ENSG0000095370 ENSG0000099954 ENSG00000101331 ENSG0000102007 ENSG0000102359 ENSG0000102471 ENSG0000104894 ENSG0000105352 ENSG0000105374 ENSG00000105793 ENSG0000106565 ENSG0000106780 ENSG0000106991 ENSG0000107738 ENSG0000108352 ENSG0000109103 ENSG00000113621 ENSG0000116857 ENSG0000117016 ENSG0000119986 ENSG0000120658 ENSG0000122122 ENSG0000124496 ENSG00000125812 ENSG0000126464 ENSG0000126882 ENSG0000127220 ENSG0000128284 ENSG0000128594 ENSG0000130775 ENSG00000133055 ENSG0000133246 ENSG0000133561 ENSG0000133597 ENSG0000133985 ENSG0000134028 ENSG0000134575 ENSG00000135953 ENSG0000136444 ENSG0000136490 ENSG0000137959 ENSG0000138772 ENSG0000139263 ENSG0000139793 ENSG00000142405 ENSG0000143110 ENSG0000145416 ENSG0000145824 ENSG0000151117 ENSG0000151715 ENSG0000152213 ENSG00000153029 ENSG0000156875 ENSG0000157111 ENSG0000157426 ENSG0000157833 ENSG0000158714 ENSG0000159166 ENSG00000160993 ENSG0000161249 ENSG0000161929 ENSG0000162078 ENSG0000162222 ENSG0000163346 ENSG0000163958 ENSG00000165959 ENSG0000167077 ENSG0000167208 ENSG0000167536 ENSG0000168016 ENSG0000168758 ENSG0000169087 ENSG00000170801 ENSG0000170955 ENSG0000171617 ENSG0000172932 ENSG0000174307 ENSG0000174705 ENSG0000175066 ENSG00000175857 ENSG0000177383 ENSG0000177946 ENSG0000178385 ENSG0000182162 ENSG0000183621 ENSG0000183734 ENSG00000184232 ENSG0000185033 ENSG0000185090 ENSG0000185862 ENSG0000186806 ENSG0000186812 ENSG0000187650 ENSG00000188483 ENSG0000196227 ENSG0000196544 ENSG0000197093 ENSG0000197982 ENSG0000198483 ENSG0000198832 ENSG00000198959 ENSG0000204859 ENSG0000205927 ENSG0000213160 ENSG0000213203 ENSG0000213889 ENSG0000214212 ENSG00000226091 ENSG0000230647 ENSG0000232838 ENSG0000233621 ENSG0000235106 ENSG0000235531 ENSG0000239213 ENSG00000248049 ENSG0000249992 ENSG0000251442 ENSG0000253831 ENSG0000255833 ENSG0000260898 ENSG0000260916 ENSG00000266962 ENSG0000267416 ENSG0000274536 ENSG0000275385 ENSG0000283839 ENSG0000285304