



# Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 79 on 26/02/2022. The web link to these results is:

<https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMjAyMjYxNzM5NDhfMTc0MTg%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:

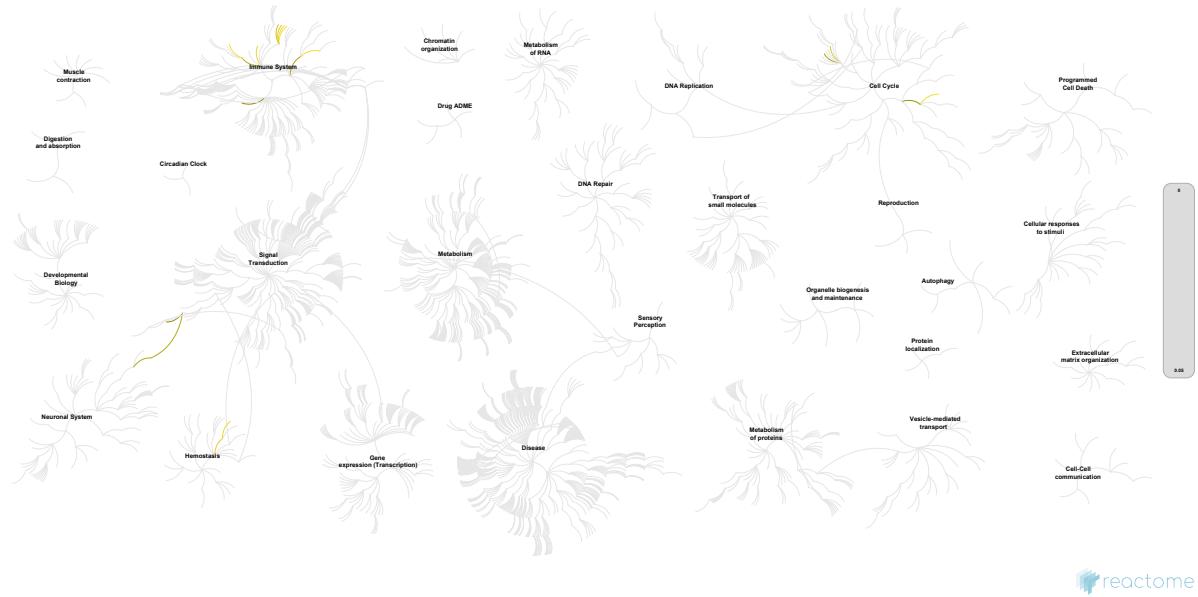
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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. ↗
- 12 out of 27 identifiers in the sample were found in Reactome, where 175 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent. ↗
- IntAct interactors were included to increase the analysis background. This greatly increases the size of Reactome pathways, which maximises the chances of matching your submitted identifiers to the expanded pathway, but will include interactors that have not undergone manual curation by Reactome and may include interactors that have no biological significance, or unexplained relevance.
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAyMjAyMjYxNzM5NDhfMTc0MTg%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.

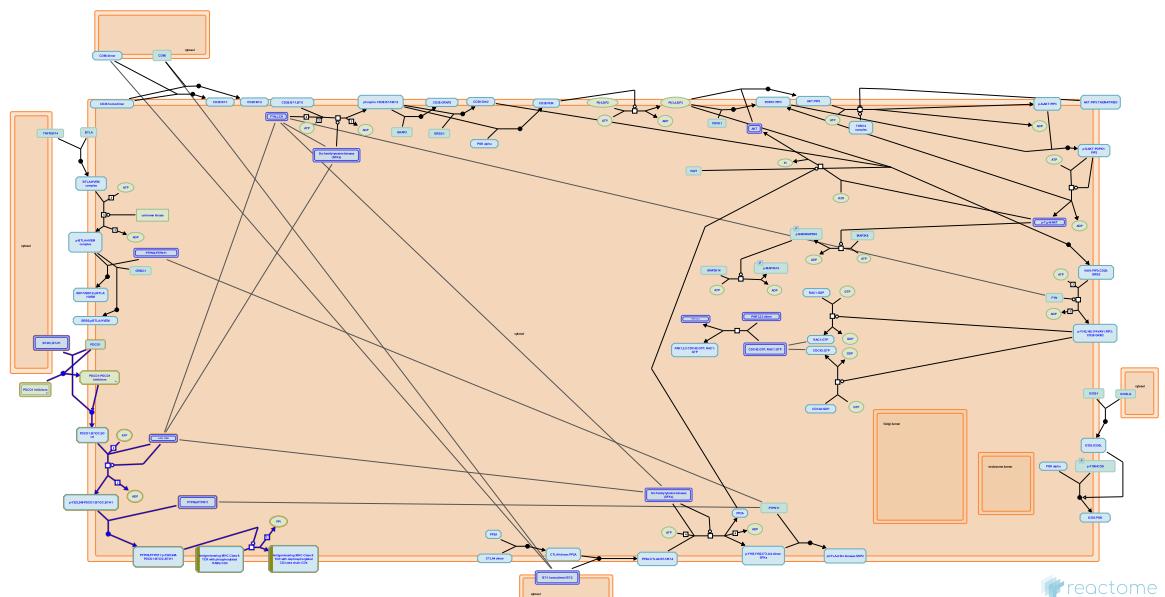
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
PD-1 signaling	3 / 46	0.002	7.03e-05	0.009	1 / 5	3.66e-04
Translocation of ZAP-70 to Immunological synapse	3 / 52	0.002	1.01e-04	0.009	4 / 4	2.93e-04
Phosphorylation of CD3 and TCR zeta chains	3 / 71	0.003	2.51e-04	0.012	5 / 7	5.13e-04
G2/M DNA replication checkpoint	2 / 14	6.28e-04	2.73e-04	0.012	2 / 2	1.47e-04
Interferon gamma signaling	5 / 468	0.021	0.001	0.041	2 / 16	0.001
Platelet degranulation	3 / 185	0.008	0.004	0.117	1 / 11	8.06e-04
MHC class II antigen presentation	3 / 204	0.009	0.005	0.133	24 / 26	0.002
Response to elevated platelet cytosolic Ca2+	3 / 250	0.011	0.009	0.196	1 / 14	0.001
Generation of second messenger molecules	3 / 273	0.012	0.011	0.225	3 / 17	0.001
Cyclin A/B1/B2 associated events during G2/M transition	2 / 100	0.004	0.013	0.229	4 / 25	0.002
Downstream TCR signaling	3 / 331	0.015	0.019	0.301	1 / 24	0.002
Costimulation by the CD28 family	3 / 397	0.018	0.03	0.378	1 / 35	0.003
Adenylate cyclase inhibitory pathway	1 / 19	8.53e-04	0.032	0.378	5 / 5	3.66e-04
Polo-like kinase mediated events	2 / 170	0.008	0.034	0.378	2 / 15	0.001
Interferon Signaling	5 / 1,071	0.048	0.034	0.378	2 / 71	0.005
G2/M Checkpoints	2 / 194	0.009	0.043	0.397	3 / 24	0.002
Neutrophil degranulation	3 / 480	0.022	0.048	0.397	5 / 10	7.33e-04
Adenylate cyclase activating pathway	1 / 29	0.001	0.048	0.397	4 / 4	2.93e-04
TCR signaling	3 / 507	0.023	0.055	0.397	13 / 52	0.004
PKA activation in glucagon signalling	1 / 35	0.002	0.058	0.397	1 / 2	1.47e-04
Platelet activation, signaling and aggregation	4 / 890	0.04	0.064	0.397	2 / 116	0.009
Collagen chain trimerization	1 / 44	0.002	0.072	0.397	1 / 28	0.002
PKA activation	1 / 45	0.002	0.074	0.397	1 / 4	2.93e-04
Chk1/Chk2(Cds1) mediated inactivation of Cyclin B:Cdk1 complex	1 / 49	0.002	0.08	0.397	2 / 5	3.66e-04
Activation of GABAB receptors	1 / 50	0.002	0.082	0.397	5 / 8	5.86e-04

\* False Discovery Rate

## 5. Pathways details

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

### 1. PD-1 signaling (R-HSA-389948)



**Cellular compartments:** plasma membrane.

The Programmed cell death protein 1 (PD-1) is one of the negative regulators of TCR signaling. PD-1 may exert its effects on cell differentiation and survival directly by inhibiting early activation events that are positively regulated by CD28 or indirectly through IL-2. PD-1 ligation inhibits the induction of the cell survival factor Bcl-xL and the expression of transcription factors associated with effector cell function, including GATA-3, Tbet, and Eomes. PD-1 exerts its inhibitory effects by bringing phosphatases SHP-1 and SHP-2 into the immune synapse, leading to dephosphorylation of CD3-zeta chain, PI3K and AKT.

### References

Fife BT & Bluestone JA (2008). Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. *Immunol Rev*, 224, 166-82. [\[CrossRef\]](#)

Keir ME, Sharpe AH, Freeman GJ & Butte MJ (2008). PD-1 and its ligands in tolerance and immunity . *Annu Rev Immunol*, 26, 677-704. [\[CrossRef\]](#)

### Edit history

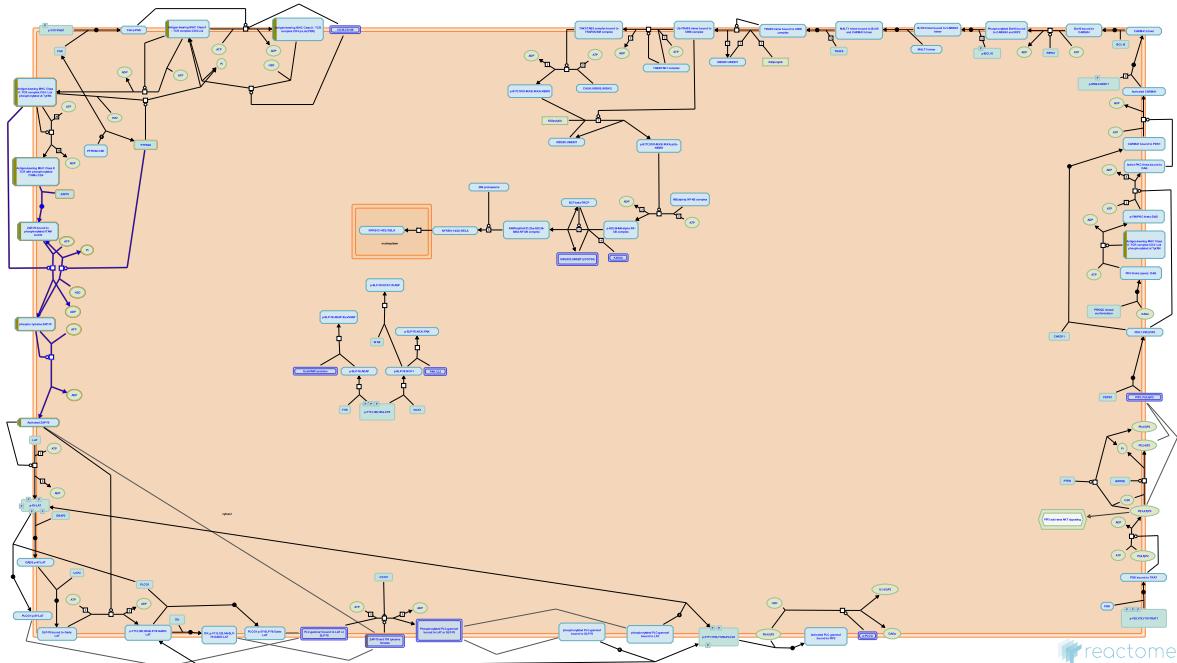
Date	Action	Author
2008-12-16	Edited	Garapati P V
2008-12-16	Authored	Garapati P V
2009-01-21	Created	Garapati P V
2009-06-01	Reviewed	Bluestone JA, Esensten J

Date	Action	Author
2021-11-26	Modified	Weiser JD

**2 submitted entities found in this pathway, mapping to 3 Reactome entities**

Input	UniProt Id	Input	UniProt Id
HLA-DQA1	P01909, P20036	HLA-DRB5	Q30154

## 2. Translocation of ZAP-70 to Immunological synapse (R-HSA-202430)



**Cellular compartments:** plasma membrane.

The dual phosphorylated ITAMs recruit SYK kinase ZAP70 via their tandem SH2 domains (step 8). ZAP70 subsequently undergoes phosphorylation on multiple tyrosine residues for further activation. ZAP70 includes both positive and negative regulatory sites. Tyrosine 493 is a conserved regulatory site found within the activation loop of the kinase domain. This site has shown to be a positive regulatory site required for ZAP70 kinase activity and is phosphorylated by LCK (step 9). This phosphorylation contributes to the active conformation of the catalytic domain. Later ZAP70 undergoes trans-autophosphorylation at Y315 and Y319 (step 10). These sites appear to be positive regulatory sites. ZAP70 achieves its full activation after the trans-autophosphorylation. Activated ZAP70 along with LCK phosphorylates the multiple tyrosine residues in the adaptor protein LAT (step 11). PTPN22 can dephosphorylate and inhibit ZAP70 activity to downregulate TCR signaling (step 12).

## References

van Leeuwen JE & Samelson LE (1999). T cell antigen-receptor signal transduction. Curr Opin Immunol, 11, 242-8. [View](#)

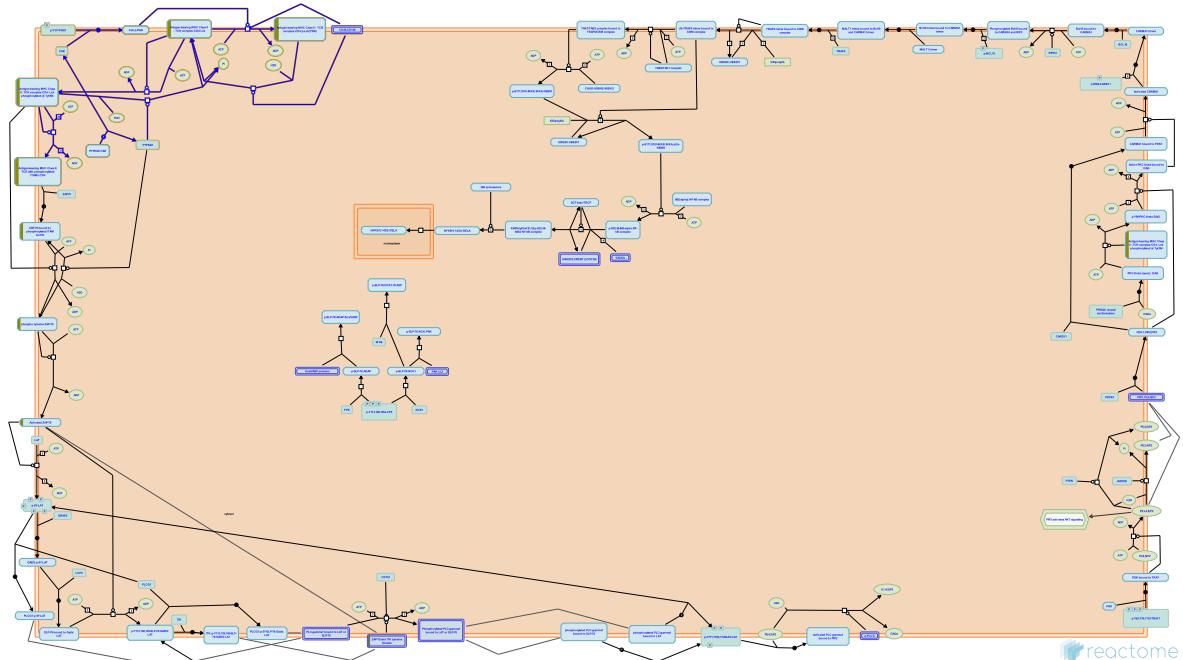
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Date	Action	Author
2007-10-29	Created	Garapati P V
2008-01-24	Authored	Rudd C.E., Garapati P V, de Bono B
2008-02-26	Reviewed	Trowsdale J
2016-05-10	Revised	Stanford S, Bottini N
2021-11-26	Modified	Weiser JD

**2 submitted entities found in this pathway, mapping to 3 Reactome entities**

Input	UniProt Id	Input	UniProt Id
HLA-DQA1	P01909, P20036	HLA-DRB5	Q30154

### 3. Phosphorylation of CD3 and TCR zeta chains (R-HSA-202427)



**Cellular compartments:** plasma membrane.

Prior to T cell receptor (TCR) stimulation, CD4/CD8 associated LCK remains separated from the TCR and is maintained in an inactive state by the action of CSK. PAG bound CSK phosphorylates the negative regulatory tyrosine of LCK and inactivates the LCK kinase domain (step 1). CSK also inhibits PTPN22 by sequestering it via binding (step 2).

Upon TCR stimulation, CSK dissociates from PAG1 (step 3) and PTPN22 (step 4) and is unable to inhibit LCK. Furthermore, LCK becomes activated via PTPRC-mediated dephosphorylation of negative regulatory tyrosine residues (step 5). CD4/CD8 binds MHCII receptor in APC and the associated LCK co-localizes with the TCR.

LCK is further activated by trans-autophosphorylation on the tyrosine residue on its activation loop (step 6). Active LCK further phosphorylates the tyrosine residues on CD3 chains. The signal-transducing CD3 delta/epsilon/gamma and TCR zeta chains contain a critical signaling motif known as the immunoreceptor tyrosine-based activation motif (ITAM). The two critical tyrosines of each ITAM motif are phosphorylated by LCK (step 7).

## References

van Leeuwen JE & Samelson LE (1999). T cell antigen-receptor signal transduction. Curr Opin Immunol, 11, 242-8. [View](#)

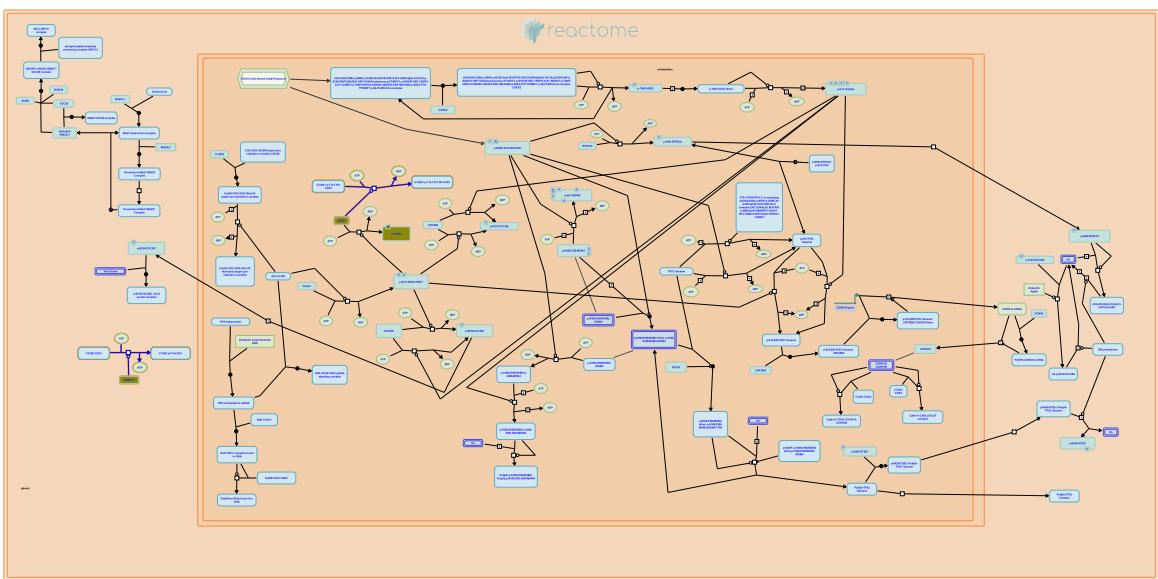
## Edit history

Date	Action	Author
2007-10-29	Created	Garapati P V
2008-01-24	Authored	Rudd C.E., Garapati P V, de Bono B
2008-02-26	Reviewed	Trowsdale J
2016-05-10	Revised	Stanford S, Bottini N
2021-11-26	Modified	Weiser JD

**2 submitted entities found in this pathway, mapping to 3 Reactome entities**

Input	UniProt Id	Input	UniProt Id
HLA-DQA1	P01909, P20036	HLA-DRB5	Q30154

#### 4. G2/M DNA replication checkpoint (R-HSA-69478)



The G2/M DNA replication checkpoint ensures that mitosis is not initiated until DNA replication is complete. If replication is blocked, the DNA replication checkpoint signals to maintain Cyclin B - Cdc2 complexes in their T14Y15 phosphorylated and inactive state. This prevents the phosphorylation of proteins involved in G2/M transition, and prevents mitotic entry.

Failure of these checkpoints results in changes of ploidy: in the case of mitosis without completion of DNA replication, aneuploidy of <2C will result, and the opposite is true if DNA replication is completed more than once in a single cell cycle with an overall increase in ploidy. The mechanism by which unreplicated DNA is first detected by the cell is unknown.

#### References

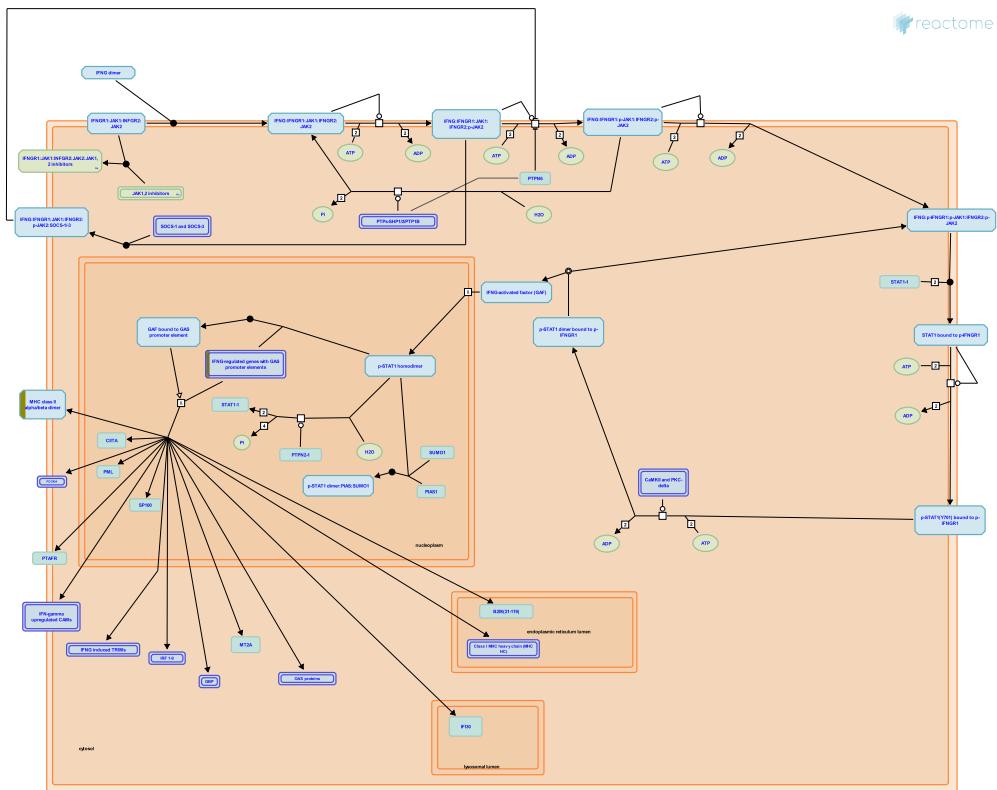
#### Edit history

Date	Action	Author
2003-06-05	Created	Walworth N, O'Donnell M
2021-11-27	Modified	Weiser JD

**1 submitted entities found in this pathway, mapping to 2 Reactome entities**

Input	UniProt Id
WEE1	P30291, Q99640

## 5. 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 IFNGR1 (also known as the IFNGR alpha chain) and IFNGR2 (also known as the IFNGR beta chain). IFNGR1 is the ligand binding receptor and is required but not sufficient for signal transduction, whereas IFNGR2 do not bind IFNG independently but mainly plays a role in IFNG signaling and is generally the limiting factor in IFNG responsiveness. Both IFNGR 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. IFNGR 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. [🔗](#)

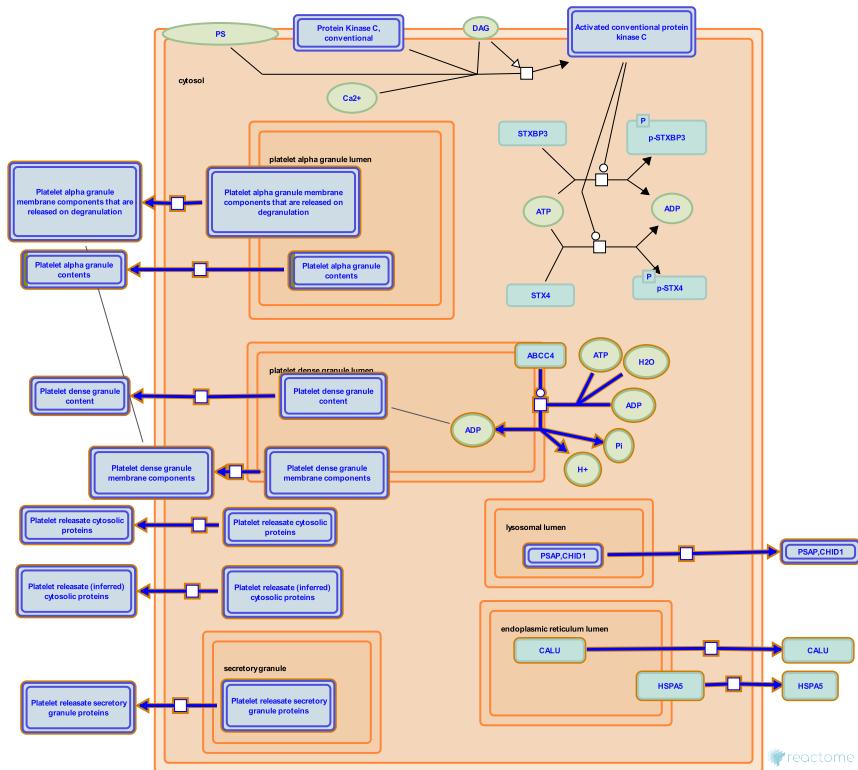
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Date	Action	Author
2010-06-08	Edited	Garapati P V
2010-06-08	Authored	Garapati P V
2010-06-11	Created	Garapati P V
2010-08-17	Reviewed	Abdul-Sater AA, Schindler C
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
HLA-DQA1	P01909, P20036	HLA-DRB5	Q30154
Input	Ensembl Id	Input	Ensembl Id
HLA-DQA1	ENSG00000196735	HLA-DRB5	ENSG00000198502

## 6. Platelet degranulation (R-HSA-114608)



Platelets function as exocytotic cells, secreting a plethora of effector molecules at sites of vascular injury. Platelets contain a number of distinguishable storage granules including alpha granules, dense granules and lysosomes. On activation platelets release a variety of proteins, largely from storage granules but also as the result of apparent cell lysis. These act in an autocrine or paracrine fashion to modulate cell signaling.

Alpha granules contain mainly polypeptides such as fibrinogen, von Willebrand factor, growth factors and protease inhibitors that supplement thrombin generation at the site of injury. Dense granules contain small molecules, particularly adenosine diphosphate (ADP), adenosine triphosphate (ATP), serotonin and calcium, all recruit platelets to the site of injury.

The molecular mechanism which facilitates granule release involves soluble NSF attachment protein receptors (SNAREs), which assemble into complexes to form a universal membrane fusion apparatus. Although all cells use SNAREs for membrane fusion, different cells possess different SNARE isoforms. Platelets and chromaffin cells use many of the same chaperone proteins to regulate SNARE-mediated secretion (Fitch-Tewfik & Flaumenhaft 2013).

## References

Page CP, Vermylen J, Gresele P & Fuster V (2002). *Platelets in thrombotic and non-thrombotic disorders.*, 435-437.

McRedmond JP, Toomey S, Fitzgerald DJ, Cahill DJ, Belton O, Maguire PB, ... Cagney G (2004). Characterization of the proteins released from activated platelets leads to localization of novel platelet proteins in human atherosclerotic lesions. *Blood*, 103, 2096-104. [\[link\]](#)

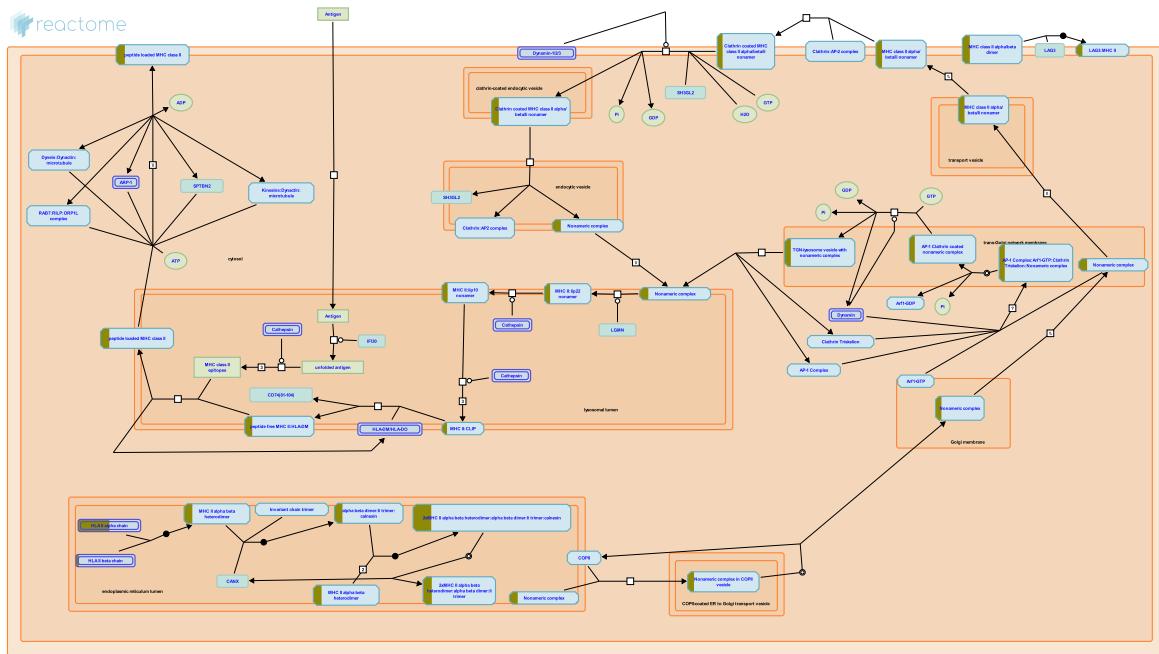
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Date	Action	Author
2004-09-25	Created	Farndale R, Pace NP, de Bono B
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
F13A1	P00488	ORM1	P02763	ORM2	P19652

## 7. MHC class II antigen presentation (R-HSA-2132295)



Antigen presenting cells (APCs) such as B cells, dendritic cells (DCs) and monocytes/macrophages express major histocompatibility complex class II molecules (MHC II) at their surface and present exogenous antigenic peptides to CD4+ T helper cells. CD4+ T cells play a central role in immune protection. On their activation they stimulate differentiation of B cells into antibody-producing B-cell blasts and initiate adaptive immune responses. MHC class II molecules are transmembrane glycoprotein heterodimers of alpha and beta subunits. Newly synthesized MHC II molecules present in the endoplasmic reticulum bind to a chaperone protein called invariant (Ii) chain. The binding of Ii prevents the premature binding of self antigens to the nascent MHC molecules in the ER and also guides MHC molecules to endocytic compartments. In the acidic endosomal environment, Ii is degraded in a stepwise manner, ultimately to free the class II peptide-binding groove for loading of antigenic peptides. Exogenous antigens are internalized by the APC by receptor mediated endocytosis, phagocytosis or pinocytosis into endocytic compartments of MHC class II positive cells, where engulfed antigens are degraded in a low pH environment by multiple acidic proteases, generating MHC class II epitopes. Antigenic peptides are then loaded into the class II ligand-binding groove. The resulting class II peptide complexes then move to the cell surface, where they are scanned by CD4+ T cells for specific recognition (Berger & Roche 2009, Zhou & Blum 2004, Watts 2004, Landsverk et al. 2009).

## References

- Ploegh HL & Wolf PR (1995). How MHC class II molecules acquire peptide cargo: biosynthesis and trafficking through the endocytic pathway. *Annu Rev Cell Dev Biol*, 11, 267-306. ↗
- Jensen PE (1997). Peptide binding and antigen presentation by class II histocompatibility glycoproteins. *Biopolymers*, 43, 303-22. ↗
- Villadangos JA (2001). Presentation of antigens by MHC class II molecules: getting the most out of them. *Mol Immunol*, 38, 329-46. ↗

Landsverk OJ, Gregers TF & Bakke O (2009). MHC II and the endocytic pathway: regulation by invariant chain. *Scand J Immunol*, 70, 184-93. [\[C\]](#)

Simmons D, Harding CV & Ramachandra L (2009). MHC molecules and microbial antigen processing in phagosomes. *Curr Opin Immunol*, 21, 98-104. [\[C\]](#)

## Edit history

Date	Action	Author
2012-02-21	Edited	Garapati P V
2012-02-21	Authored	Garapati P V
2012-02-21	Created	Garapati P V
2012-05-14	Reviewed	Neefjes J
2021-11-28	Modified	Weiser JD

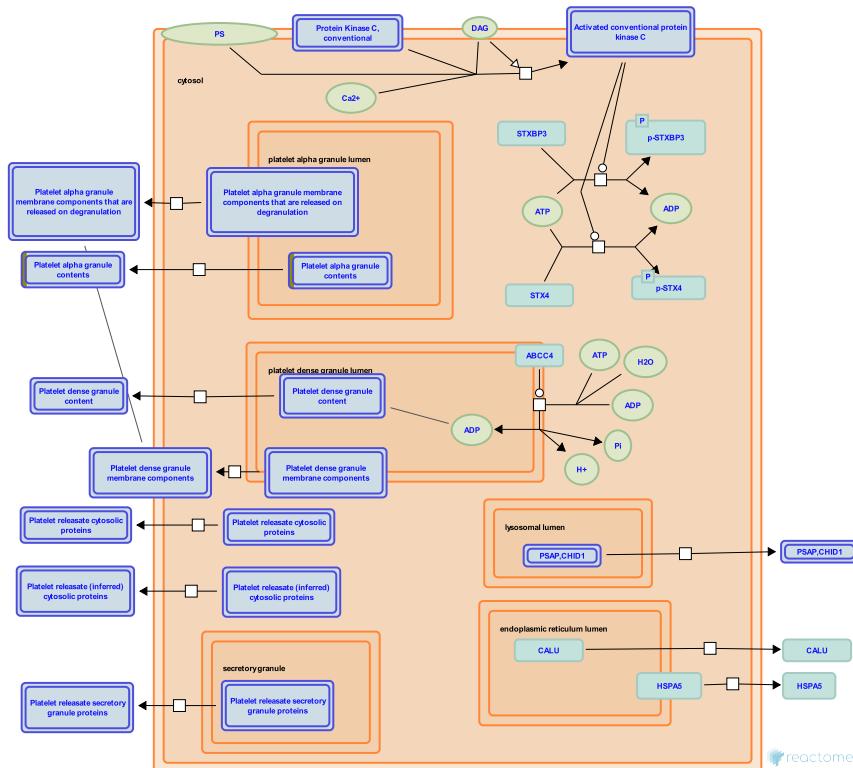
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HLA-DQA1	P01909, P20036	HLA-DRB5	Q30154

## Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
HLA-DQA1	P01909	P04233			

## 8. Response to elevated platelet cytosolic Ca<sup>2+</sup> (R-HSA-76005)



Activation of phospholipase C enzymes results in the generation of second messengers of the phosphatidylinositol pathway. The events resulting from this pathway are a rise in intracellular calcium and activation of Protein Kinase C (PKC). Phospholipase C cleaves the phosphodiester bond in PIP<sub>2</sub> to form 1,2 Diacylglycerol (DAG) and 1,4,5-inositol trisphosphate (IP<sub>3</sub>). IP<sub>3</sub> opens Ca<sup>2+</sup> channels in the platelet dense tubular system, raising intracellular Ca<sup>2+</sup> levels. DAG is a second messenger that regulates a family of Ser/Thr kinases consisting of PKC isozymes (Nishizuka 1995). DAG achieves activation of PKC isozymes by increasing their affinity for phospholipid. Most PKC enzymes are also calcium-dependent, so their activation is in synergy with the rise in intracellular Ca<sup>2+</sup>. Platelets contain several PKC isoforms that can be activated by DAG and/or Ca<sup>2+</sup> (Chang 1997).

## References

Watson SP & Walker TR (1993). Synergy between Ca<sup>2+</sup> and protein kinase C is the major factor in determining the level of secretion from human platelets. *Biochem J*, 289, 277-82. ↗

## Edit history

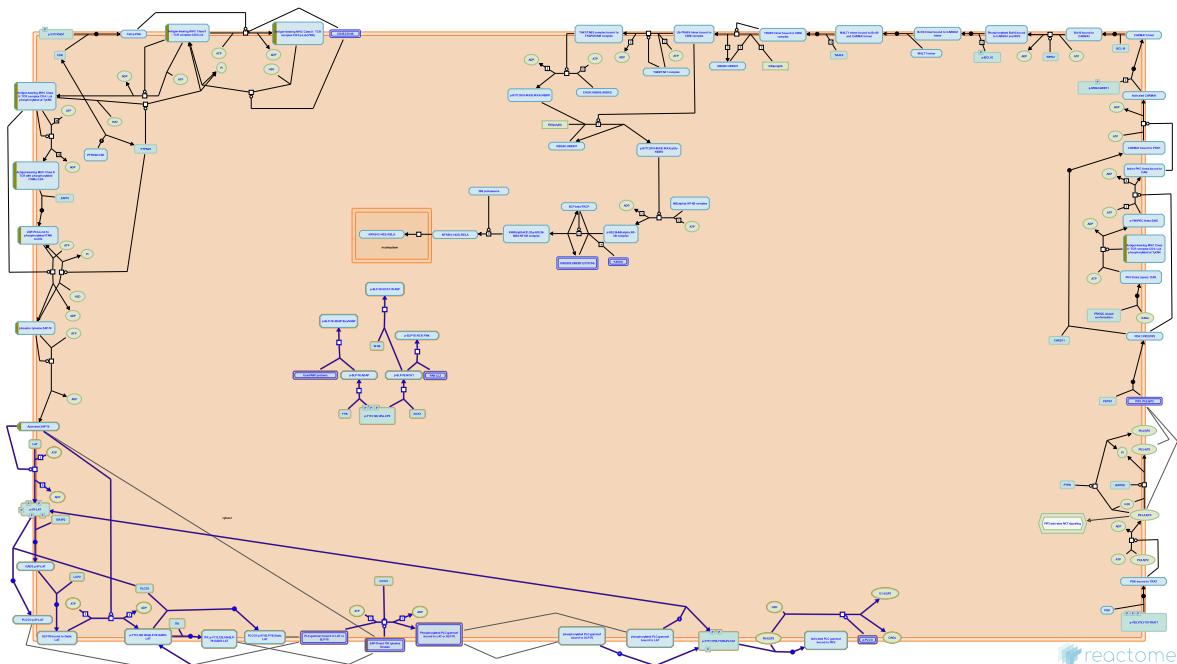
Date	Action	Author
2004-08-13	Authored	de Bono B
2004-09-25	Created	Farndale R, Pace NP, de Bono B
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
F13A1	P00488	ORM1	P02763	ORM2	P19652



## 9. Generation of second messenger molecules (R-HSA-202433)



**Cellular compartments:** plasma membrane.

In addition to serving as a scaffold via auto-phosphorylation, ZAP70 also phosphorylates a restricted set of substrates following TCR stimulation - including LAT (step 13) and LCP2. These substrates have been recognized to play pivotal role in TCR signaling by releasing second messengers. When phosphorylated, LAT and SLP-76 act as adaptor proteins which serve as nucleation points for the construction of a higher order signalosome: PLC-gamma1 (step 14) and GRAP2 (step 15) bind to the LAT on the phosphorylated tyrosine residues. LCP2 is then moved to the signalosome by interacting with the SH3 domains of GRAP2 using their proline rich sequences (step 16). Once LCP2 binds to GRAP2, three LCP2 acidic domain N-term tyrosine residues are phosphorylated by ZAP70 (step 17). These phospho-tyrosine residues act as binding sites to the SH2 domains of ITK (steps 18) and PLC-gamma1 (step 19).

PLC-gamma1 is activated by dual phosphorylation on the tyrosine residues at positions 771, 783 and 1254 by ITK (step 20) and ZAP70 (step 21). Phosphorylated PLC-gamma1 subsequently detaches from LAT and LCP2 and translocates to the plasma membrane by binding to phosphatidylinositol-4,5-bisphosphate (PIP2) via its PH domain (step 22). PLC-gamma1 goes on to hydrolyse PIP2 to second messengers DAG and IP3 (step 23). These second messengers are involved in PKC and NF-kB activation and calcium mobilization.

## References

Huang Y & Wang RL (2004). T cell receptor signaling: beyond complex complexes. *J Biol Chem*, 279, 28827-30. [🔗](#)

## Edit history

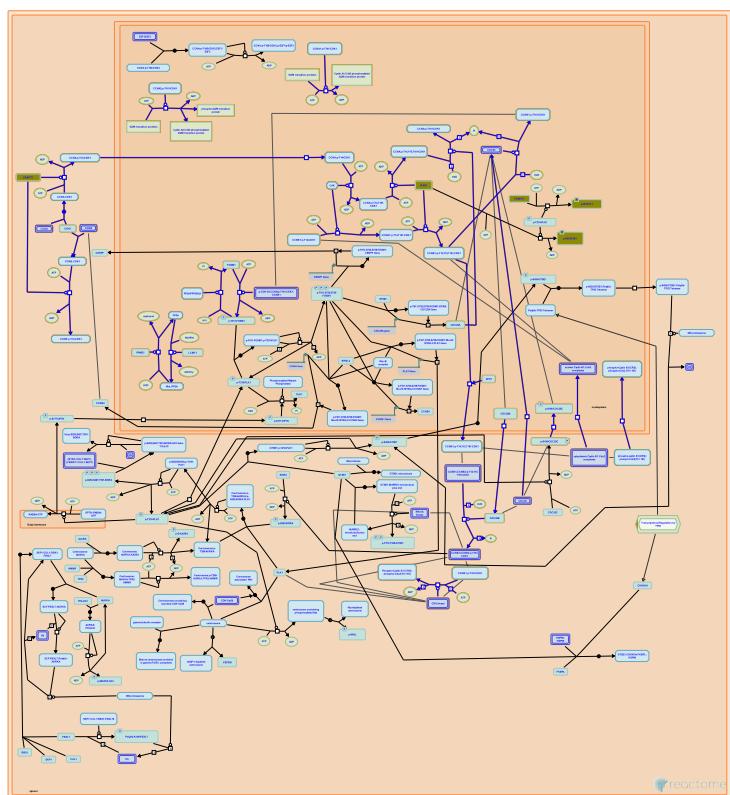
Date	Action	Author
2007-10-29	Created	Garapati P V
2008-01-24	Authored	Rudd C.E., Garapati P V, de Bono B
2008-02-26	Reviewed	Trowsdale J

Date	Action	Author
2021-11-27	Modified	Weiser JD

**2 submitted entities found in this pathway, mapping to 3 Reactome entities**

Input	UniProt Id	Input	UniProt Id
HLA-DQA1	P01909, P20036	HLA-DRB5	Q30154

## 10. Cyclin A/B1/B2 associated events during G2/M transition (R-HSA-69273)



Cell cycle progression is regulated by cyclin-dependent protein kinases at both the G1/S and the G2/M transitions. The G2/M transition is regulated through the phosphorylation of nuclear lamins and histones (reviewed in Sefton, 2001).

The two B-type cyclins localize to different regions within the cell and are thought to have specific roles as CDK1-activating subunits (see Bellanger et al., 2007). Cyclin B1 is primarily cytoplasmic during interphase and translocates into the nucleus at the onset of mitosis (Jackman et al., 1995; Hagting et al., 1999). Cyclin B2 colocalizes with the Golgi apparatus and contributes to its fragmentation during mitosis (Jackman et al., 1995; Draviam et al., 2001).

## References

- Pines J, Hagting A, Simpson K & Jackman M (1999). Translocation of cyclin B1 to the nucleus at prophase requires a phosphorylation-dependent nuclear import signal. *Curr Biol*, 9, 680-9. [🔗](#)
- Firth M, Jackman M & Pines J (1995). Human cyclins B1 and B2 are localized to strikingly different structures: B1 to microtubules, B2 primarily to the Golgi apparatus. *EMBO J*, 14, 1646-54. [🔗](#)
- Sefton BM (2001). Overview of protein phosphorylation. *Curr Protoc Cell Biol*, 14, Unit 14.1. [🔗](#)
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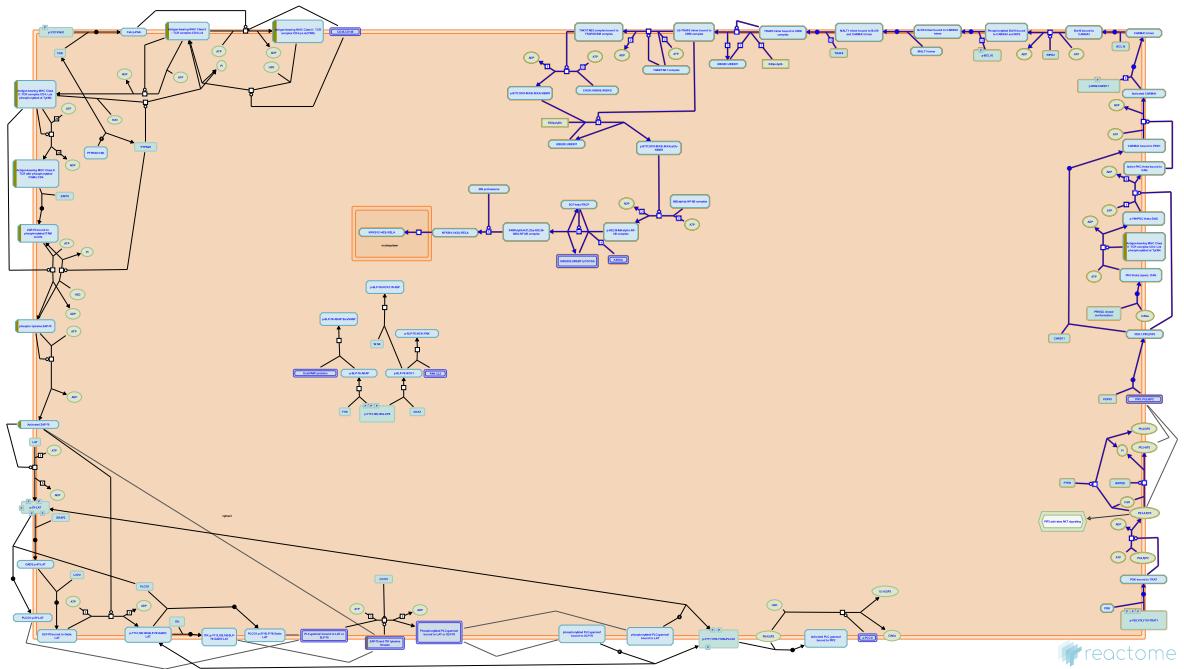
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Date	Action	Author
2003-06-05	Created	Walworth N, O'Donnell M
2021-11-28	Modified	Weiser JD

**1 submitted entities found in this pathway, mapping to 2 Reactome entities**

Input	UniProt Id
WEE1	P30291, Q99640

## 11. Downstream TCR signaling (R-HSA-202424)



Changes in gene expression are required for the T cell to gain full proliferative competence and to produce effector cytokines. Three transcription factors in particular have been found to play a key role in TCR-stimulated changes in gene expression, namely NFkappaB, NFAT and AP-1.

A key step in NFkappaB activation is the stimulation and translocation of PRKCQ. The critical element that effects PRKCQ activation is PI3K. PI3K translocates to the plasma membrane by interacting with phospho-tyrosines on CD28 via its two SH2 domains located in p85 subunit (step 24). The p110 subunit of PI3K phosphorylates the inositol ring of PIP2 to generate PIP3 (steps 25). The reverse dephosphorylation process from PIP3 to PIP2 is catalysed by PTEN (step 27).

PIP3 may also be dephosphorylated by the phosphatase SHIP to generate PI-3,4-P2 (step 26). PIP3 and PI-3,4-P2 acts as binding sites to the PH domain of PDK1 (step 28) and AKT (step 29). PKB is activated in response to PI3K stimulation by PDK1 (step 30). PDK1 has an essential role in regulating the activation of PRKCQ and recruitment of CBM complex to the immune synapse. PRKCQ is a member of novel class (DAG dependent, Ca++ independent) of PKC and the only member known to translocate to this synapse. Prior to TCR stimulation PRKCQ exists in an inactive closed conformation. TCR signals stimulate PRKCQ (step 31) and release DAG molecules. Subsequently, DAG binds to PRKCQ via the C1 domain and undergoes phosphorylation on tyrosine 90 by LCK to attain an open conformation (step 32). PRKCQ is further phosphorylated by PDK1 on threonine 538 (step 33). This step is critical for PKC activity.

CARMA1 translocates to the plasma membrane following the interaction of its SH3 domain with the 'PxxP' motif on PDK1 (step 34). CARMA1 is phosphorylated by PKC-theta on residue S552 (step 35), leading to the oligomerization of CARMA1. This complex acts as a scaffold, recruiting BCL10 to the synapse by interacting with their CARD domains (step 36).

BCL10 undergoes phosphorylation mediated by the enzyme RIP2 (step 37). Activated BCL10 then mediates the ubiquitination of IKBKG by recruiting MALT1 and TRAF6. MALT1 binds to BCL10 with its Ig-like domains and undergoes oligomerization (step 38). TRAF6 binds to the oligomerized MALT1 and also undergoes oligomerization (step 39).

Oligomerized TRAF6 acts as a ubiquitin-protein ligase, catalyzing auto-K63-linked polyubiquitination (step 40). This K-63 ubiquitinated TRAF6 activates MAP3K7 kinase bound to TAB2 (step 41) and also ubiquitinates IKBKG in the IKK complex (step 44). MAP3K7 undergoes autophosphorylation on residues T184 and T187 and gets activated (step 42). Activated MAP3K7 kinase phosphorylates IKBKB on residues S177 and S181 in the activation loop and activates the IKK kinase activity (step 43). IKBKB phosphorylates the NFKBIA bound to the NFkappaB heterodimer, on residues S19 and S23 (step 45) and directs NFKBIA to 26S proteasome degradation (step 47).

The NFkappaB heterodimer with a free NTS sequence finally migrates to the nucleus to regulate gene transcription (step 46).

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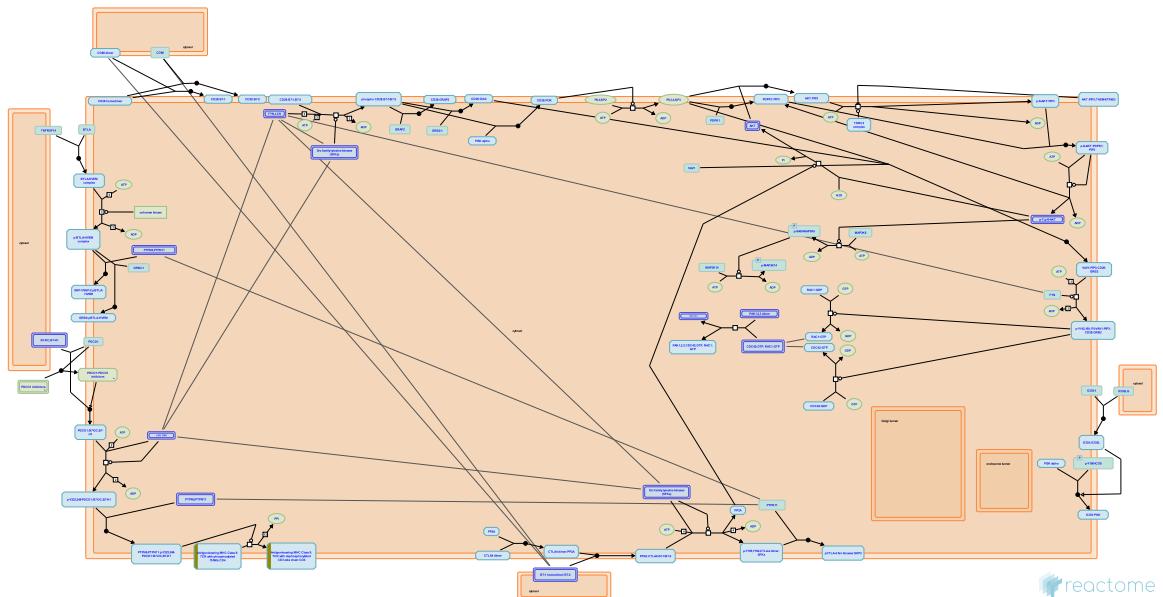
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Date	Action	Author
2007-10-29	Created	Garapati P V
2008-01-24	Authored	Rudd C.E., Garapati P V, de Bono B
2008-02-26	Reviewed	Trowsdale J
2022-01-09	Modified	Weiser JD

**2 submitted entities found in this pathway, mapping to 3 Reactome entities**

Input	UniProt Id	Input	UniProt Id
HLA-DQA1	P01909, P20036	HLA-DRB5	Q30154

## 12. Costimulation by the CD28 family ([R-HSA-388841](#))



**Cellular compartments:** plasma membrane.

Optimal activation of T-lymphocytes requires at least two signals. A primary one is delivered by the T-cell receptor (TCR) complex after antigen recognition and additional costimulatory signals are delivered by the engagement of costimulatory receptors such as CD28. The best-characterized costimulatory pathways are mediated by a set of cosignaling molecules belonging to the CD28 superfamily, including CD28, CTLA4, ICOS, PD1 and BTLA receptors. These proteins deliver both positive and negative second signals to T-cells by interacting with B7 family ligands expressed on antigen presenting cells. Different subsets of T-cells have very different requirements for costimulation. CD28 family mediated costimulation is not required for all T-cell responses *in vivo*, and alternative costimulatory pathways also exist. Different receptors of the CD28 family and their ligands have different regulation of expression. CD28 is constitutively expressed on naive T cells whereas CTLA4 expression is dependent on CD28/B7 engagement and the other receptor members ICOS, PD1 and BTLA are induced after initial T-cell stimulation.

The positive signals induced by CD28 and ICOS molecules are counterbalanced by other members of the CD28 family, including cytotoxic T-lymphocyte associated antigen (CTLA)4, programmed cell death (PD)1, and B and T lymphocyte attenuator (BTLA), which dampen immune responses. The balance of stimulatory and inhibitory signals is crucial to maximize protective immune responses while maintaining immunological tolerance and preventing autoimmunity.

The costimulatory receptors CD28, CTLA4, ICOS and PD1 are composed of single extracellular IgV-like domains, whereas BTLA has one IgC-like domain. Receptors CTLA4, CD28 and ICOS are covalent homodimers, due to an interchain disulphide linkage. The costimulatory ligands B71, B72, B7H2, B7H1 and B7DC, have a membrane proximal IgC-like domain and a membrane distal IgV-like domain that is responsible for receptor binding and dimerization. CD28 and CTLA4 have no known intrinsic enzymatic activity. Instead, engagement by their physiologic ligands B71 and B72 leads to the physical recruitment and activation of downstream T-cell effector molecules.

## References

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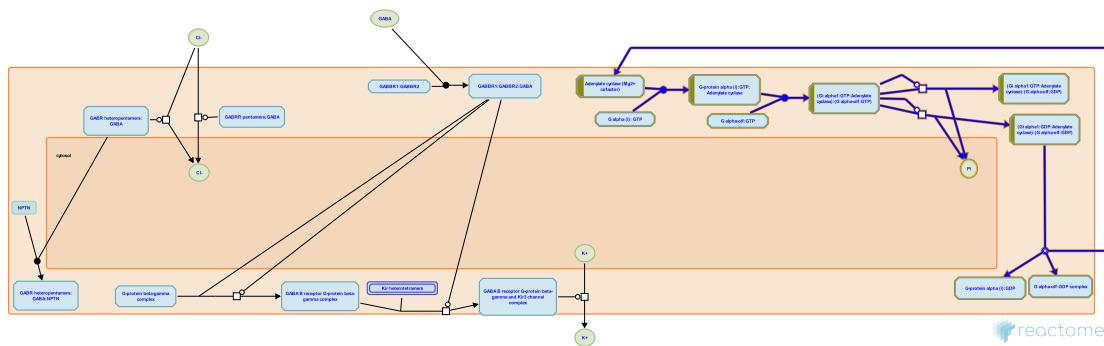
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Date	Action	Author
2008-12-16	Edited	Garapati P V
2008-12-16	Authored	Garapati P V
2008-12-16	Created	Garapati P V
2009-06-01	Reviewed	Bluestone JA, Esensten J
2021-11-28	Modified	Weiser JD

## 2 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id
HLA-DQA1	P01909, P20036	HLA-DRB5	Q30154

### 13. Adenylate cyclase inhibitory pathway (R-HSA-170670)



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

Guanine nucleotide-binding protein G(i) alpha (Gi-alpha) inhibits adenylate cyclase, thus inhibiting the production of cAMP from ATP and ultimately decreasing the activity of cAMP-dependent protein kinase.

### References

Iñiguez-Lluhi JA, Gilman AG & Taussig R (1993). Inhibition of adenylyl cyclase by Gi alpha. *Science*, 261, 218-21. [View](#)

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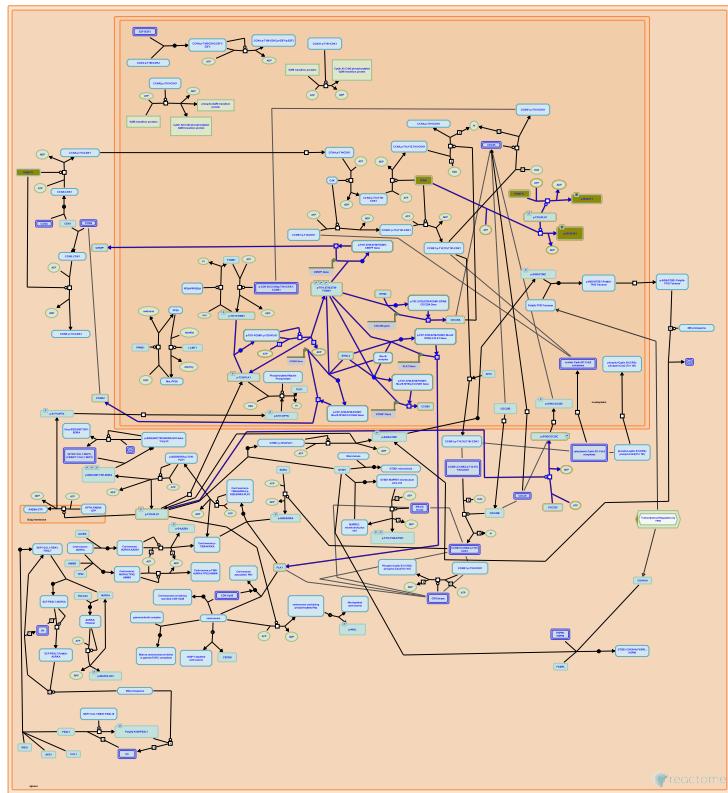
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Date	Action	Author
2004-03-31	Authored	Jassal B, Le Novere N
2006-01-10	Created	Jassal B
2008-11-06	Edited	Jassal B
2008-11-06	Reviewed	Castagnoli L
2021-11-27	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
ADCY4	Q8NFM4

## 14. Polo-like kinase mediated events (R-HSA-156711)



**Cellular compartments:** nucleoplasm.

At mitotic entry, Plk1 phosphorylates and activates Cdc25C phosphatase, whereas it phosphorylates and down-regulates Wee1A (Watanabe et al. 2004). Plk1 also phosphorylates and inhibits Myt1 activity (Sagata 2005). Cyclin B1-bound Cdc2, which is the target of Cdc25C, Wee1A, and Myt1, functions in a feedback loop and phosphorylates the latter components (Cdc25C, Wee1A, Myt1). The Cdc2-dependent phosphorylation provides docking sites for the polo-box domain of Plk1, thus promoting the Plk1-dependent regulation of these components and, as a result, activation of Cdc2-Cyclin B1.

PLK1 phosphorylates and activates the transcription factor FOXM1 which stimulates the expression of a number of genes needed for G2/M transition, including PLK1, thereby creating a positive feedback loop (Laoukili et al. 2005, Fu et al. 2008, Sadasivam et al. 2012, Chen et al. 2013).

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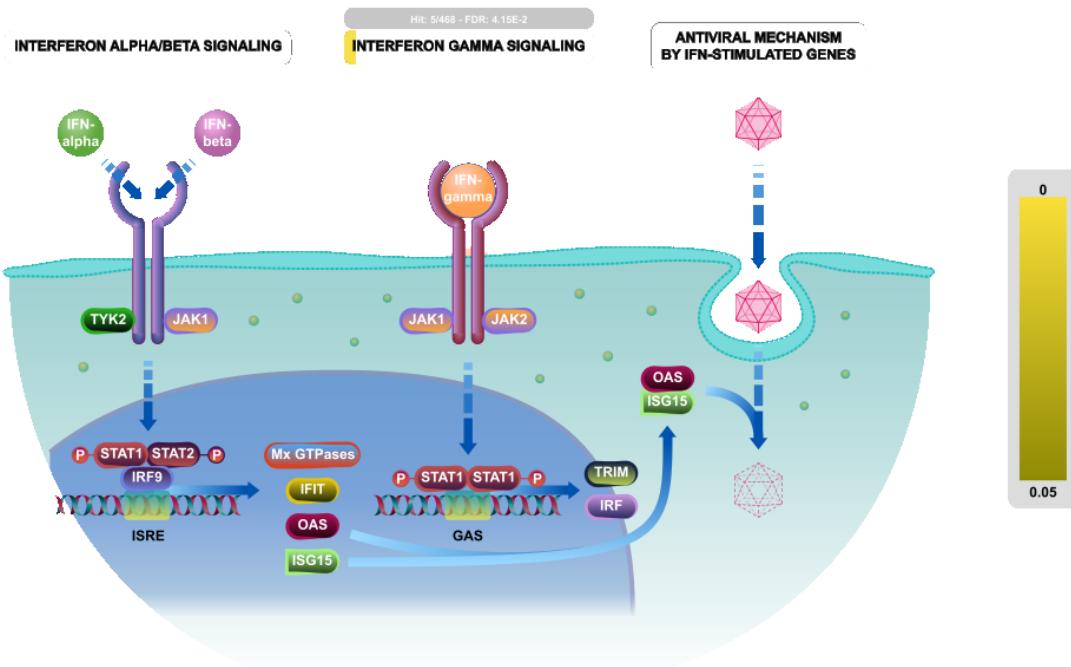
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Date	Action	Author
2004-12-09	Authored	Lee KS
2004-12-09	Created	Gillespie ME
2013-08-21	Reviewed	Bruinsma W
2021-11-23	Edited	Gillespie ME
2021-11-28	Modified	Weiser JD

**1 submitted entities found in this pathway, mapping to 2 Reactome entities**

Input	UniProt Id
WEE1	P30291, Q99640

## 15. 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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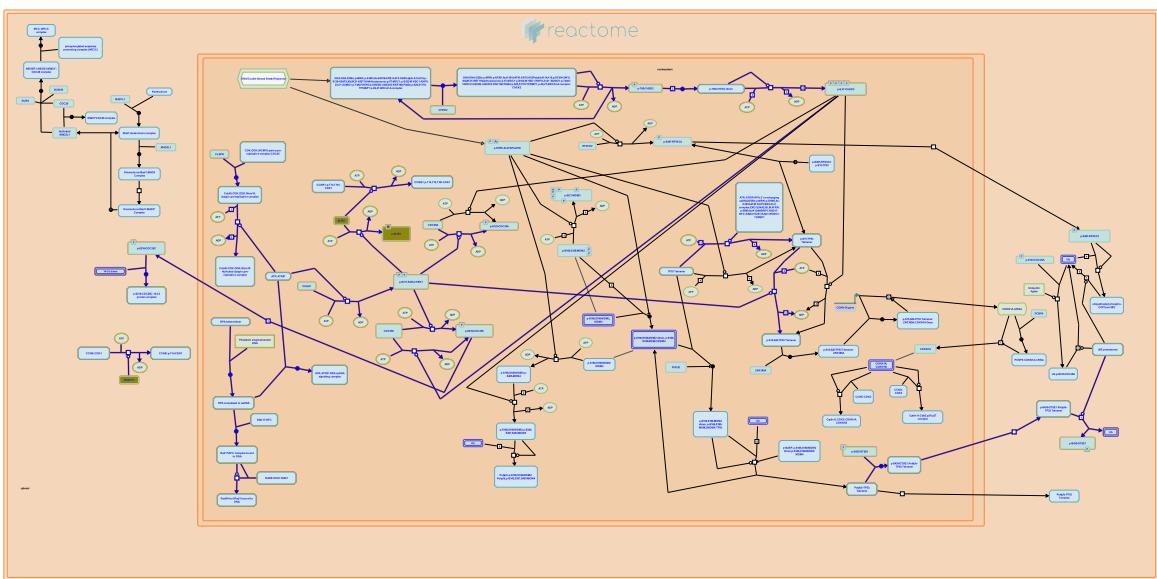
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Date	Action	Author
2010-07-07	Edited	Garapati P V
2010-07-07	Authored	Garapati P V
2010-07-16	Created	Garapati P V
2010-08-17	Reviewed	Abdul-Sater AA, Schindler C
2021-11-27	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
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Input	Ensembl Id	Input	Ensembl Id
HLA-DQA1	ENSG00000196735	HLA-DRB5	ENSG00000198502

## 16. G2/M Checkpoints (R-HSA-69481)



G2/M checkpoints include the checks for damaged DNA, unreplicated DNA, and checks that ensure that the genome is replicated once and only once per cell cycle. If cells pass these checkpoints, they follow normal transition to the M phase. However, if any of these checkpoints fail, mitotic entry is prevented by specific G2/M checkpoint events.

The G2/M checkpoints can fail due to the presence of unreplicated DNA or damaged DNA. In such instances, the cyclin-dependent kinase, Cdc2(Cdk1), is maintained in its inactive, phosphorylated state, and mitotic entry is prevented. Events that ensure that origins of DNA replication fire once and only once per cell cycle are also an example of a G2/M checkpoint.

In the event of high levels of DNA damage, the cells may also be directed to undergo apoptosis (not covered).

## References

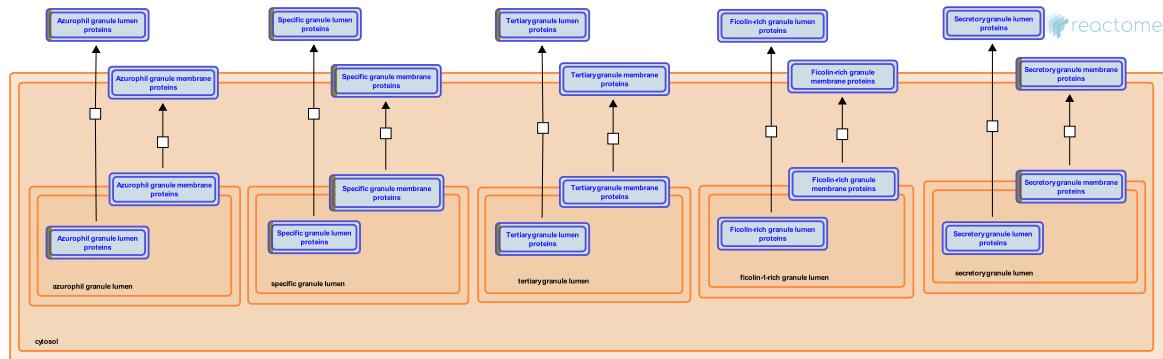
### Edit history

Date	Action	Author
2003-06-05	Created	Walworth N, O'Donnell M
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id
WEE1	P30291, Q99640

## 17. 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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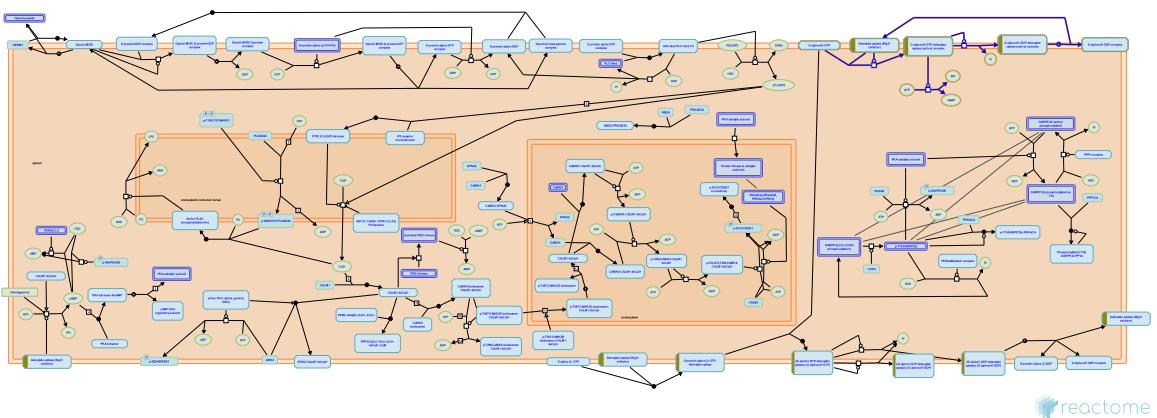
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Date	Action	Author
2015-09-21	Authored	Jupe S
2015-09-21	Created	Jupe S
2016-06-13	Edited	Jupe S
2016-06-13	Reviewed	Heegaard N
2021-11-28	Modified	Weiser JD

**2 submitted entities found in this pathway, mapping to 3 Reactome entities**

Input	UniProt Id	Input	UniProt Id
ORM1	P02763, Q8N138	ORM2	P19652

## 18. Adenylate cyclase activating pathway (R-HSA-170660)



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

Stimulatory G proteins activate adenylate cyclase, which drives the conversion of cAMP from ATP and in turn activates cAMP-dependent protein kinase and subsequent kinase pathways.

### References

Sunahara RK & Taussig R (2002). Isoforms of mammalian adenylyl cyclase: multiplicities of signaling. *Mol Interv*, 2, 168-84. [View](#)

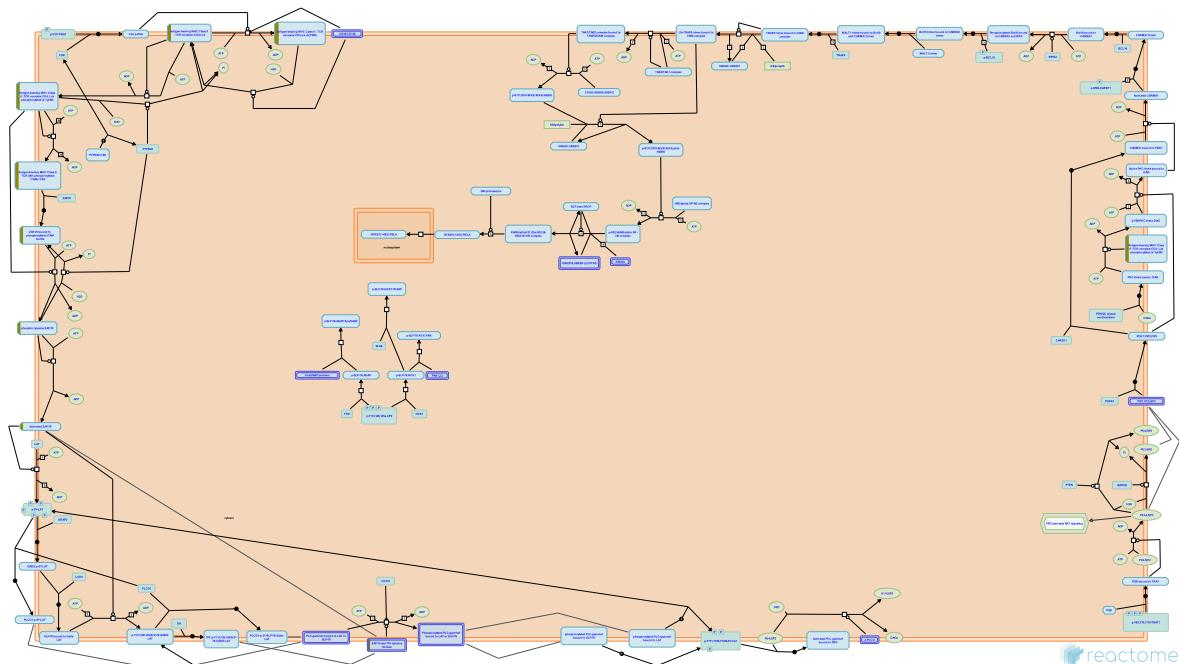
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2006-01-10	Created	Jassal B
2008-11-06	Edited	Jassal B
2008-11-06	Reviewed	Castagnoli L
2021-11-27	Modified	Weiser JD

**1 submitted entities found in this pathway, mapping to 1 Reactome entities**

Input	UniProt Id
ADCY4	Q8NFM4

## 19. TCR signaling (R-HSA-202403)



The TCR is a multisubunit complex that consists of clonotypic alpha/beta chains noncovalently associated with the invariant CD3 delta/epsilon/gamma and TCR zeta chains. T cell activation by antigen presenting cells (APCs) results in the activation of protein tyrosine kinases (PTKs) that associate with CD3 and TCR zeta subunits and the co-receptor CD4. Members of the Src kinases (Lck), Syk kinases (ZAP-70), Tec (Itk) and Csk families of nonreceptor PTKs play a crucial role in T cell activation. Activation of PTKs following TCR engagement results in the recruitment and tyrosine phosphorylation of enzymes such as phospholipase C gamma1 and Vav as well as critical adaptor proteins such as LAT, SLP-76 and Gads. These proximal activation leads to reorganization of the cytoskeleton as well as transcription activation of multiple genes leading to T lymphocyte proliferation, differentiation and/or effector function.

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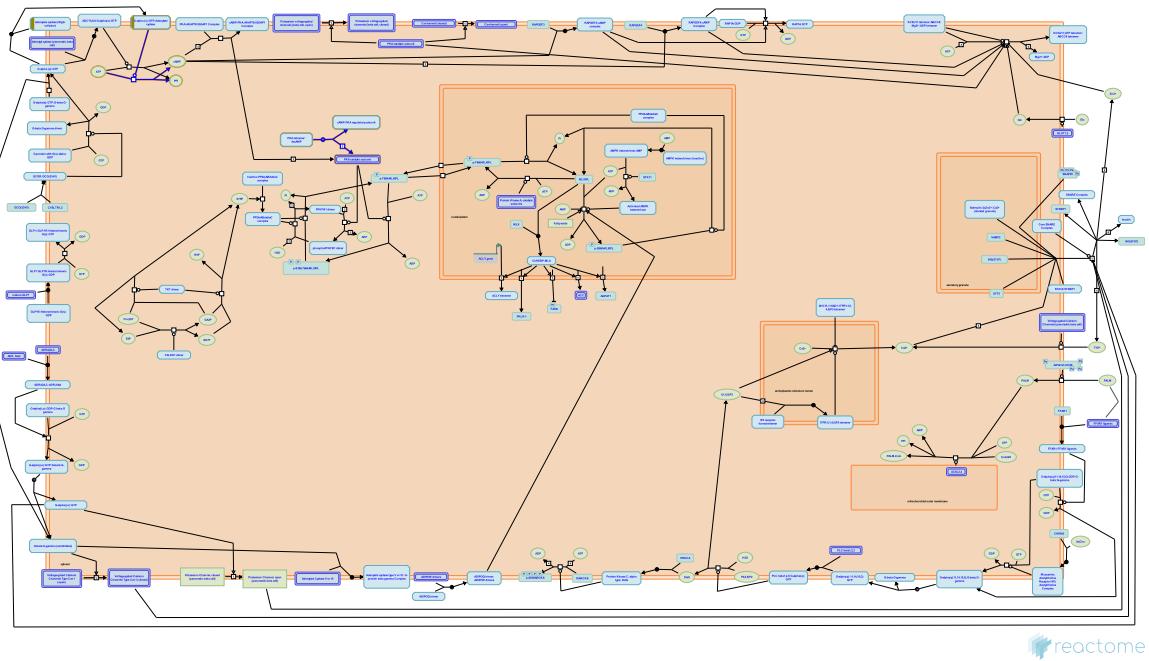
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Date	Action	Author
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2008-01-24	Authored	Rudd C.E., Garapati P V, de Bono B
2008-02-26	Reviewed	Trowsdale J
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
HLA-DQA1	P01909, P20036	HLA-DRB5	Q30154

## 20. PKA activation in glucagon signalling (R-HSA-164378)



**Cellular compartments:** plasma membrane.

Adenylate cyclase catalyses the synthesis of cyclic AMP (cAMP) from ATP. In the absence of cAMP, protein kinase A (PKA) exists as inactive tetramers of two catalytic subunits and two regulatory subunits. cAMP binding to PKA tetramers causes them to dissociate and release their catalytic subunits as active monomers. Four isoforms of the regulatory subunit are known, that differ in their tissue specificity and functional characteristics, but the specific isoform activated in response to glucagon signaling has not yet been identified.

## References

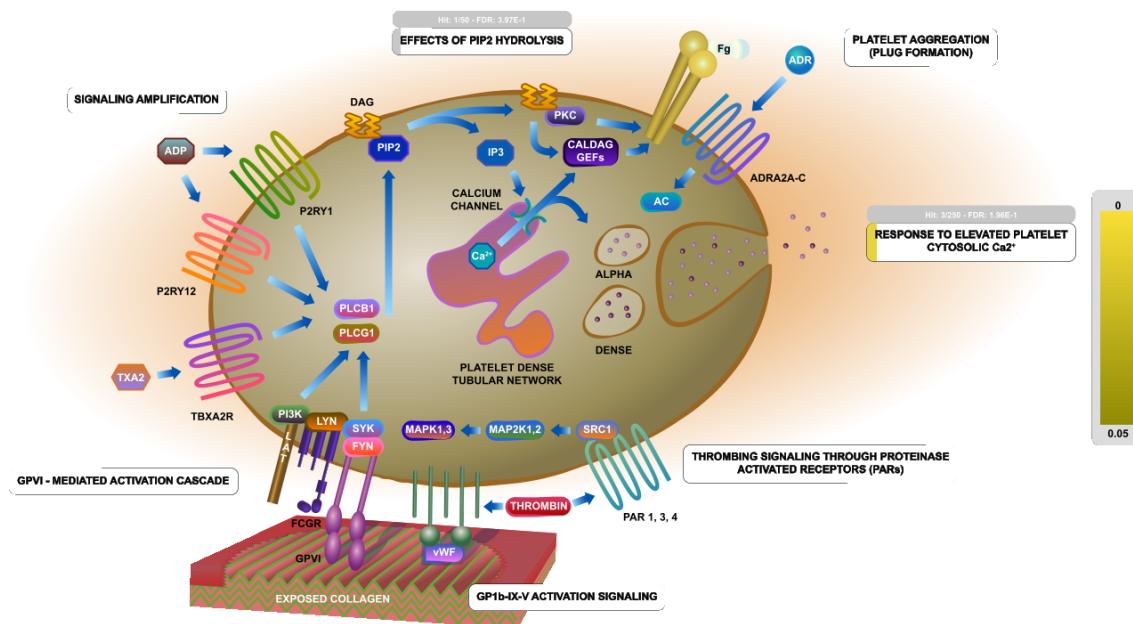
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Date	Action	Author
2005-05-19	Authored	Gopinathrao G, D'Eustachio P
2005-05-19	Created	Gopinathrao G
2021-11-28	Modified	Weiser JD

**1 submitted entities found in this pathway, mapping to 1 Reactome entities**

Input	UniProt Id
ADCY4	Q8NFM4

## 21. Platelet activation, signaling and aggregation (R-HSA-76002)



Platelet activation begins with the initial binding of adhesive ligands and of the excitatory platelet agonists (released or generated at the sites of vascular trauma) to cognate receptors on the platelet membrane (Ruggeri 2002). Intracellular signaling reactions then enhance the adhesive and procoagulant properties of tethered platelets or of platelets circulating in the proximity. Once platelets have adhered they degranulate, releasing stored secondary agents such as ADP, ATP, and synthesize thromboxane A2. These amplify the response, activating and recruiting further platelets to the area and promoting platelet aggregation. These amplify the response, activating and recruiting further platelets to the area and promoting platelet aggregation. Adenosine nucleotides signal through P2 purinergic receptors on the platelet membrane. ADP activates P2Y1 and P2Y12, which signal via both the alpha and gamma:beta components of the heterotrimeric G-protein (Hirsch et al. 2001, 2006), while ATP activates the ionotropic P2X1 receptor (Kunapuli et al. 2003). Activation of these receptors initiates a complex signaling cascade that ultimately results in platelet activation, aggregation and thrombus formation (Kahner et al. 2006).

Integrin AlphaIIbBeta3 is the most abundant platelet receptor, with 40 000 to 80 000 copies per resting platelet, acting as a major receptor for fibrinogen and other adhesive molecules (Wagner et al. 1996). Activation of AlphaIIbBeta3 enhances adhesion and leads to platelet-platelet interactions, and thus aggregation (Philips et al. 1991). GP VI is the most potent collagen receptor initiating signal generation, an ability derived from its interaction with the FcRI gamma chain. This results in the phosphorylation of the gamma-chain by non-receptor tyrosine kinases of the Src family (1). The phosphotyrosine motif is recognized by the SH2 domains of Syk, a tyrosine kinase. This association activates the Syk enzyme, leading to activation (by tyrosine phosphorylation) of PLC gamma2 (2). Thrombin is an important platelet agonist generated on the membrane of stimulated platelets. Thrombin acts via cell surface Protease Activated Receptors (PARs). PARs are G-protein coupled receptors activated by a proteolytic cleavage in an extracellular loop (Vu, 1991) (3). Activated PARs signal via G alpha q (4) and via the beta:gamma component of the G-protein (5). Both stimulate PLC giving rise to PIP2 hydrolysis and consequent activation of PI3K (6). PLCgamma2 activation also gives rise to IP3 (7) which stimulates the IP3 receptor (8) leading to increased intracellular calcium. Platelet activation further results in the scramblase-mediated transport of negatively-charged phospholipids to the platelet surface. These phospholipids provide a catalytic surface (with the charge provided by phosphatidylserine and phosphatidylethanolamine) for the tenase complex (formed by the activated forms of the blood coagulation factors factor VIII and factor I).

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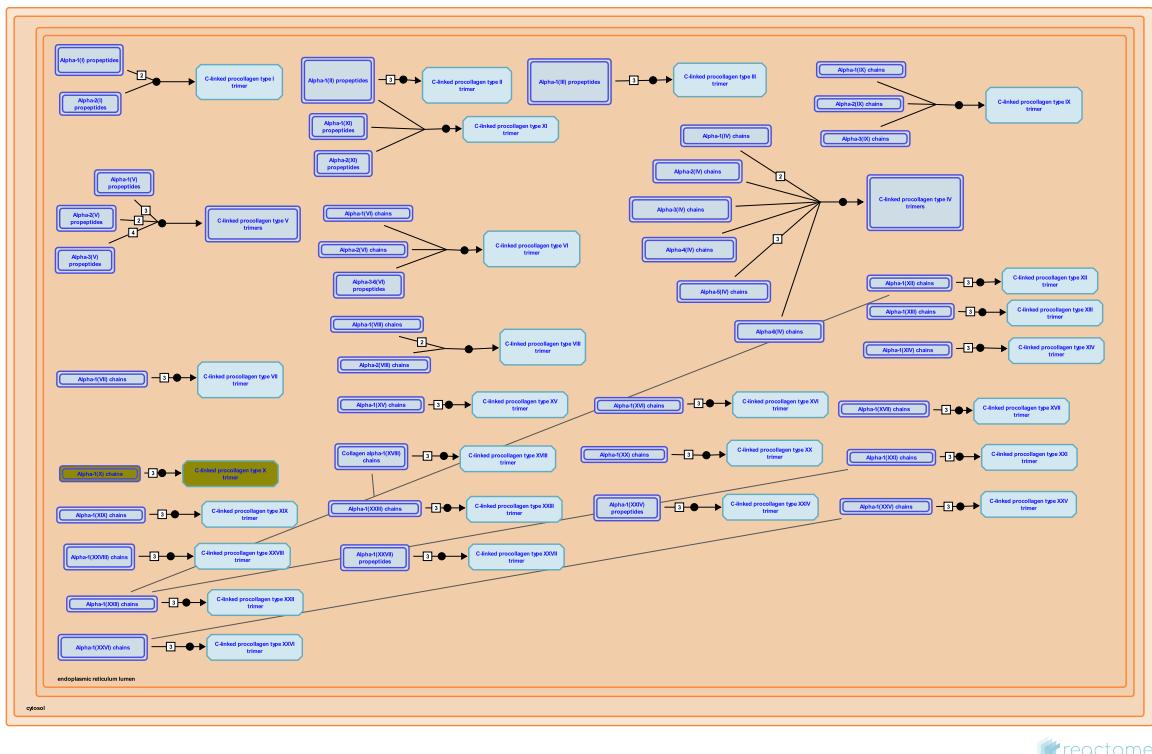
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Date	Action	Author
2004-08-13	Authored	de Bono B
2004-09-25	Created	Farndale R, Pace NP, de Bono B
2010-06-07	Revised	Jupe S
2010-06-07	Reviewed	Kunapuli SP
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
DGKQ	P52824	F13A1	P00488
ORM1	P02763	ORM2	P19652

## 22. Collagen chain trimerization (R-HSA-8948216)



The C-propeptides of collagen propeptide chains are essential for the association of three peptide chains into a trimeric but non-helical procollagen. This initial binding event determines the composition of the trimer, brings the individual chains into the correct register and initiates formation of the triple helix at the C-terminus, which then proceeds towards the N-terminus in a zipper-like fashion (Engel & Prockop 1991). Most early refolding studies were performed with collagen type III, which contains a disulfide linkage at the C-terminus of its triple helix (Bächinger et al. 1978, Bruckner et al. 1978) that acts as a permanent linker even after removal of the non-collagenous domains.

Mutations within the C-propeptides further suggest that they are crucial for the correct interaction of the three polypeptide chains and for subsequent correct folding (refs. in Boudko et al. 2011).

## References

Byers PH, Bornstein P, Click EM & Harper E (1975). Interchain disulfide bonds in procollagen are located in a large nontriple-helical COOH-terminal domain. Proc Natl Acad Sci U S A, 72, 3009-13. [View](#)

Timpl R, Brückner P, Engel J & Bächinger HP (1978). The role of cis-trans isomerization of peptide bonds in the coil leads to and comes from triple helix conversion of collagen. Eur J Biochem, 90, 605-13. [View](#)

## Edit history

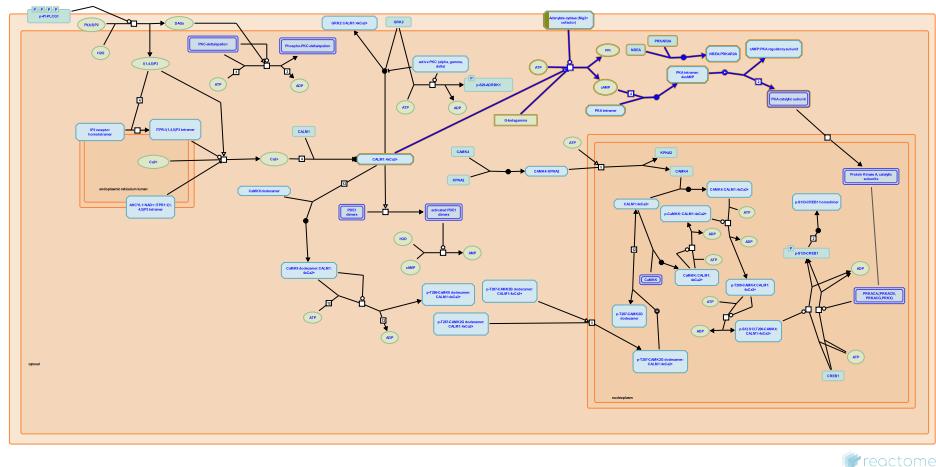
Date	Action	Author
2012-04-11	Authored	Jupe S
2012-05-24	Reviewed	Canty-Laird EG
2016-11-03	Edited	Jupe S

Date	Action	Author
2016-11-11	Created	Jupe S
2021-11-27	Modified	Weiser JD

**1 submitted entities found in this pathway, mapping to 1 Reactome entities**

Input	UniProt Id
COL10A1	Q03692

## 23. PKA activation (R-HSA-163615)



reactome

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

A number of inactive tetrameric PKA holoenzymes are produced by the combination of homo- or heterodimers of the different regulatory subunits associated with two catalytic subunits. When cAMP binds to two specific binding sites on the regulatory subunits, these undergo a conformational change that causes the dissociation of a dimer of regulatory subunits bound to four cAMP from two monomeric, catalytically active PKA subunits.

## References

Taylor SS, Buechler JA & Yonemoto W (1990). cAMP-dependent protein kinase: framework for a diverse family of regulatory enzymes. *Annu Rev Biochem*, 59, 971-1005. [View](#)

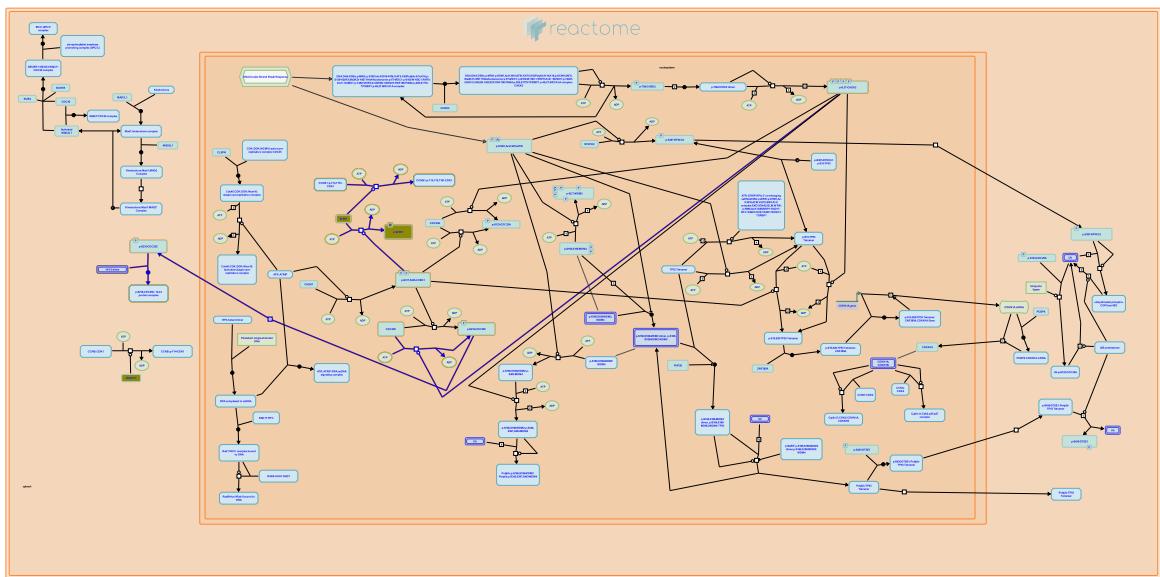
## Edit history

Date	Action	Author
2004-03-31	Authored	Jassal B, Le Novere N
2005-05-03	Created	Schmidt EE
2008-11-06	Edited	Jassal B
2008-11-06	Reviewed	Castagnoli L
2022-01-09	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
ADCY4	Q8NFM4

## 24. Chk1/Chk2(Cds1) mediated inactivation of Cyclin B:Cdk1 complex (R-HSA-75035)



DNA damage induced activation of the checkpoint kinases Chk1/Chk2(Cds1) results in the conversion and/or maintenance of CyclinB:Cdc2 complex in its Tyrosine 15 phosphorylated (inactive) state. Cdc2 activity is regulated by a balance between the phosphorylation and dephosphorylation by the Wee1/Myt1 kinase and Cdc25 phosphatase. Inactivation of the Cyclin B:Cdc2 complex likely involves both inactivation of Cdc25 and/or stimulation of Wee1/Myt1 kinase activity.

## References

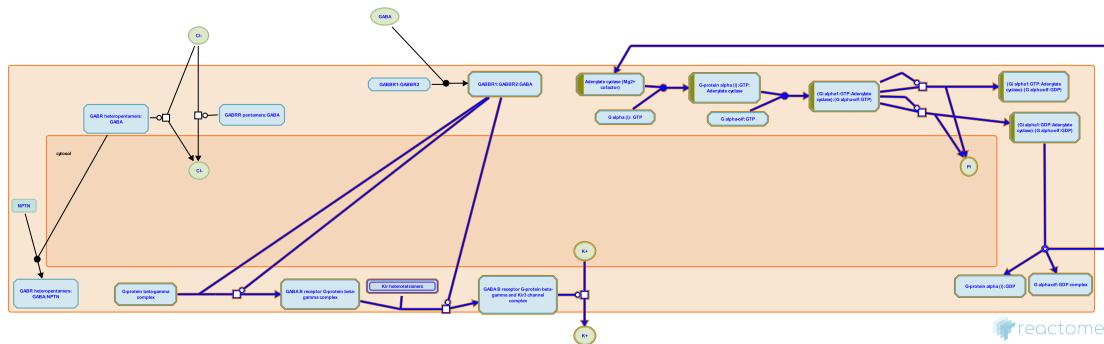
### Edit history

Date	Action	Author
2003-08-05	Authored	Matthews L
2003-10-31	Created	Matthews L
2021-11-28	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
WEE1	P30291

## 25. Activation of GABAB receptors (R-HSA-991365)



**Cellular compartments:** extracellular region, cytosol.

GABA B receptors are metabotropic receptors that are functionally linked to C type G protein coupled receptors.?

GABA B receptors are activated upon ligand binding. The GABA B1 subunit binds ligand and GABA B2 subunit modulates the activity of adenylate cyclase via the intracellular loop.?

GABA B receptors show inhibitory activity via Galpha/G0 subunits via the inhibition of adenylate cyclase or via the activity of Gbeta/gamma subunits that mediate the inhibition of voltage gated Ca<sup>2+</sup> channels.

## References

Slesinger PA & Padgett CL (2010). GABAB receptor coupling to G-proteins and ion channels. *Adv Pharmacol*, 58, 123-47. [View](#)

## Edit history

Date	Action	Author
2008-11-27	Reviewed	Restituito S
2010-11-03	Created	Mahajan SS
2010-11-08	Authored	Mahajan SS
2010-11-25	Edited	D'Eustachio P
2021-11-27	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
ADCY4	Q8NFM4

## 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.

**12 of the submitted entities were found, mapping to 18 Reactome entities**

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ADCY4	Q8NFM4	ATP8A2	Q9NTI2	COL10A1	Q03692
DGKQ	P52824	F13A1	P00488	HJURP	Q8NCD3
HLA-DQA1	P01909, P20036	HLA-DRB5	Q30154	ORM1	P02763
ORM2	P19652	WEE1	P30291, Q99640	ZNF331	Q9NQX6

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
F13A1	ENSG00000124491	HLA-DQA1	ENSG00000196735	HLA-DRB5	ENSG00000198502

### Interactors (12)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
ADCY4	Q8NFM4	P37231	CLEC1A	Q8NC01	O15552
COL10A1	Q03692	Q8N9N5	ERP27	Q96DN0	P29692
F13A1	P00488	Q6NXG1	HJURP	Q8NCD3	P62805
HLA-DQA1	P01909	P04233	ORM1	P02763	P05121
ORM2	Q06144	Q96BA8	SIX3	O95343	Q92570
WEE1	P30291	P31946	ZNF331	Q9NQX6	O15397

## 7. Identifiers not found

These 15 identifiers were not found neither mapped to any entity in Reactome.

AGPAT4-IT1	ANKRD26P1	BAI2	CALY	FAIM2	GPR6	LCN10	LOC100128568
LOC643650	MIRLET7BHG	MSMB	POSTN	RBM24	SHISA7	TSIX	