



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=MjAyMjAyMjYxNzUzMjRfMTc0MTk%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. ↗
- 13 out of 28 identifiers in the sample were found in Reactome, where 335 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 MjAyMjAyMjYxNzUzMjRfMTc0MTk%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
Apoptosis induced DNA fragmentation	2 / 17	7.63e-04	9.35e-04	0.363	2 / 12	8.79e-04
MECP2 regulates transcription of neuronal ligands	2 / 27	0.001	0.002	0.45	2 / 8	5.86e-04
Formyl peptide receptors bind formyl peptides and many other ligands	1 / 17	7.63e-04	0.043	0.55	1 / 3	2.20e-04
Formation of Senescence-Associated Heterochromatin Foci (SAHF)	2 / 128	0.006	0.044	0.55	1 / 2	1.47e-04
HCN channels	1 / 18	8.08e-04	0.046	0.55	1 / 2	1.47e-04
Cam-PDE 1 activation	1 / 20	8.98e-04	0.051	0.55	1 / 2	1.47e-04
cGMP effects	1 / 21	9.43e-04	0.053	0.55	3 / 4	2.93e-04
PDE3B signalling	1 / 25	0.001	0.063	0.55	1 / 2	1.47e-04
PKB-mediated events	1 / 25	0.001	0.063	0.55	1 / 2	1.47e-04
Adenylate cyclase activating pathway	1 / 29	0.001	0.073	0.55	1 / 4	2.93e-04
Advanced glycosylation endproduct receptor signaling	1 / 33	0.001	0.082	0.55	2 / 4	2.93e-04
PKA activation in glucagon signalling	1 / 35	0.002	0.087	0.55	1 / 2	1.47e-04
Nitric oxide stimulates guanylate cyclase	1 / 38	0.002	0.094	0.55	3 / 7	5.13e-04
TRAF6 mediated NF- κ B activation	1 / 38	0.002	0.094	0.55	1 / 4	2.93e-04
Zinc influx into cells by the SLC39 gene family	1 / 42	0.002	0.104	0.55	1 / 6	4.40e-04
PKA activation	1 / 45	0.002	0.111	0.55	2 / 4	2.93e-04
Scavenging by Class B Receptors	1 / 45	0.002	0.111	0.55	2 / 5	3.66e-04
CREB1 phosphorylation through the activation of Adenylate Cyclase	1 / 48	0.002	0.118	0.55	2 / 6	4.40e-04
RNA Polymerase II Transcription Initiation	1 / 49	0.002	0.12	0.55	3 / 3	2.20e-04
Effects of PIP2 hydrolysis	1 / 50	0.002	0.122	0.55	1 / 9	6.60e-04
Dissolution of Fibrin Clot	1 / 55	0.002	0.134	0.55	3 / 19	0.001
Glucagon signaling in metabolic regulation	1 / 59	0.003	0.143	0.55	1 / 6	4.40e-04
Metabolism of vitamin K	1 / 64	0.003	0.154	0.55	1 / 4	2.93e-04
Ca2+ pathway	3 / 272	0.012	0.158	0.55	5 / 27	0.002

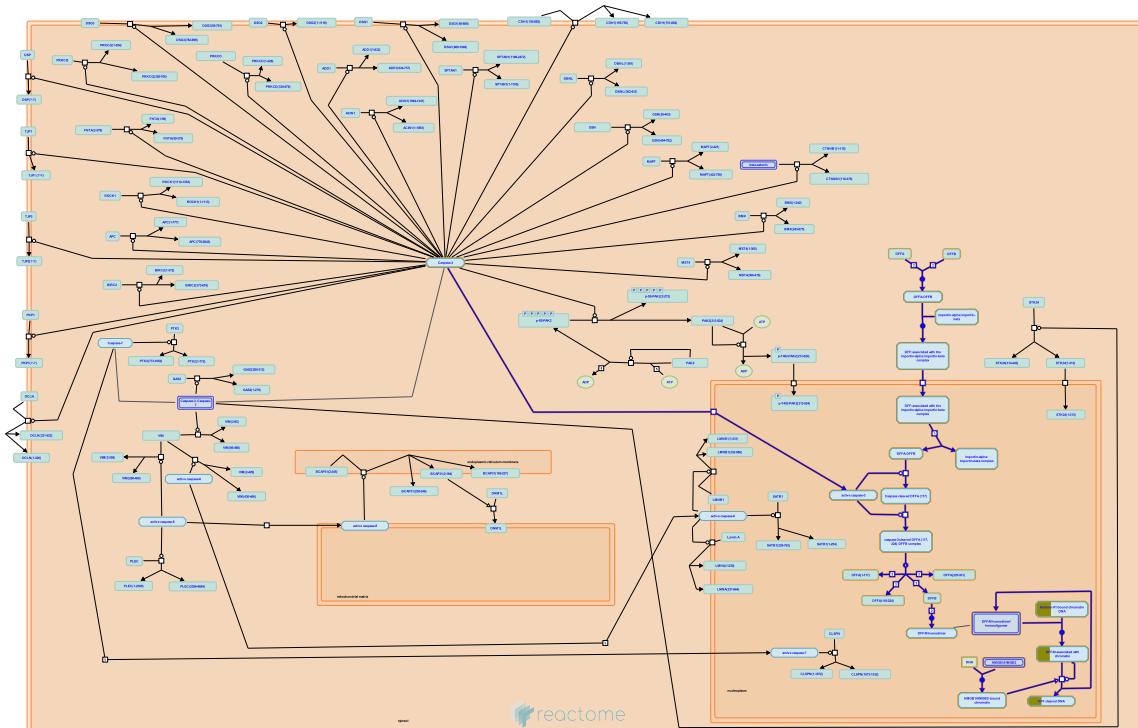
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
PKA-mediated phosphorylation of CREB	1 / 66	0.003	0.158	0.55	2 / 7	5.13e-04

* 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. Apoptosis induced DNA fragmentation (R-HSA-140342)



Cellular compartments: nucleoplasm, cytosol.

DNA fragmentation in response to apoptotic signals is achieved, in part, through the activity of apoptotic nucleases, termed DNA fragmentation factor (DFF) or caspase-activated DNase (CAD) (reviewed in Widlak and Garrard, 2005). In non-apoptotic cells, DFF is a nuclear heterodimer consisting of a 45 kD chaperone and inhibitor subunit (DFF45)/inhibitor of CAD (ICAD-L) and a 40 kD nuclease subunit (DFF40/CAD) (Liu et al. 1997, 1998; Enari et al. 1998). During apoptosis, activated caspase-3 or -7 cleave DFF45/ICAD releasing active DFF40/CAD nuclease. The activity of DFF is tightly controlled at multiple stages. During translation, DFF45/ICAD, Hsp70, and Hsp40 proteins play a role in insuring the appropriate folding of DFF40 during translation (Sakahira and Nagata, 2002). The nuclease activity of DFF40 is enhanced by the chromosomal proteins histone H1, Topoisomerase II and HMGB1/2 (Widlak et al., 2000). In addition, the inhibitors (DFF45/35; ICAD-S/L) are produced in stoichiometric excess (Widlak et al., 2003).

References

- Widlak P & Garrard WT (2005). Discovery, regulation, and action of the major apoptotic nucleases DFF40/CAD and endonuclease G. *J Cell Biochem*, 94, 1078-87. [🔗](#)
- Li P, Wang X, Widlak P & Garrard WT (2000). Cleavage preferences of the apoptotic endonuclease DFF40 (caspase-activated DNase or nuclease) on naked DNA and chromatin substrates. *J Biol Chem*, 275, 8226-32. [🔗](#)

Garrard W, Liu X, Wang X, Widlak P & Zou H (1999). Activation of the apoptotic endonuclease DFF40 (caspase-activated DNase or nuclease). Oligomerization and direct interaction with histone H1. *J Biol Chem*, 274, 13836-40. [🔗](#)

Cary RB, Lanuszewska J, Widlak P & Garrard WT (2003). Subunit structures and stoichiometries of human DNA fragmentation factor proteins before and after induction of apoptosis. *J Biol Chem*, 278, 26915-22. [🔗](#)

Yokoyama H, Nagata S, Okawa K, Enari M, Iwamatsu A & Sakahira H (1998). A caspase-activated DNase that degrades DNA during apoptosis, and its inhibitor ICAD. *Nature*, 391, 43-50. [🔗](#)

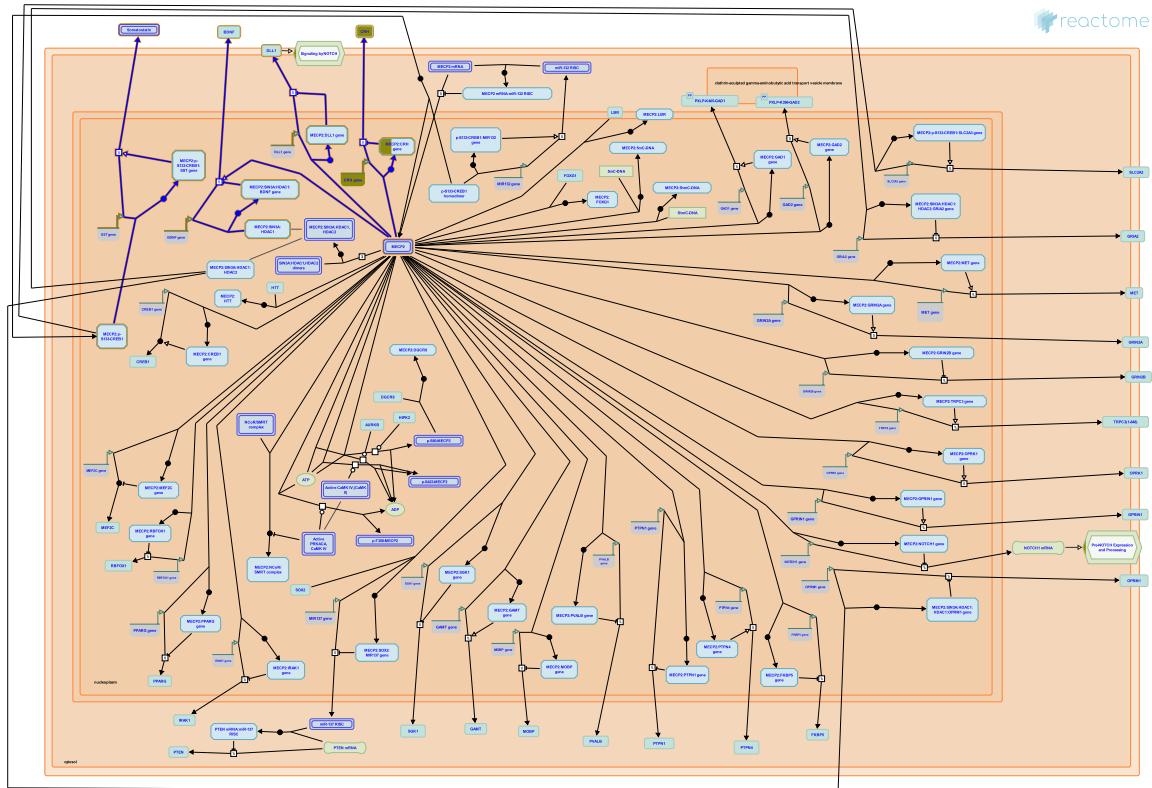
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2008-04-25	Reviewed	Widlak P
2008-04-25	Authored	Matthews L
2008-05-18	Revised	Matthews L
2008-05-18	Edited	Matthews L
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id
HIST1H1D	P16402, P16403

2. MECP2 regulates transcription of neuronal ligands ([R-HSA-9022702](#))



Ligands regulated by MECP2 include BDNF (reviewed by Li and Pozzo Miller 2014, and KhorshidAhmad et al. 2016), CRH (McGill et al. 2006, Samaco et al. 2012), SST (Somatostatin) (Chahrour et al. 2008), and DLL1 (Li et al. 2014).

References

- Mandel-Brehm C, Samaco RC, Zoghbi HY, McGill BE, Shaw CA & McGraw CM (2012). Crh and Oprm1 mediate anxiety-related behavior and social approach in a mouse model of MECP2 duplication syndrome. *Nat. Genet.*, 44, 206-11. [🔗](#)
- Carson JP, Bundle SF, Zoghbi HY, McGill BE, Yaylaoglu MB & Thaller C (2006). Enhanced anxiety and stress-induced corticosterone release are associated with increased Crh expression in a mouse model of Rett syndrome. *Proc. Natl. Acad. Sci. U.S.A.*, 103, 18267-72. [🔗](#)
- Zhong X, Jin P, Chau KF, Maslia J, Kong G, Chi J, ... Zhao X (2014). Cell cycle-linked MeCP2 phosphorylation modulates adult neurogenesis involving the Notch signalling pathway. *Nat Commun*, 5, 5601. [🔗](#)
- Qin J, Jung SY, Wong ST, Zoghbi HY, Shaw C, Chahrour M & Zhou X (2008). MeCP2, a key contributor to neurological disease, activates and represses transcription. *Science*, 320, 1224-9. [🔗](#)
- Gangadaran S, Lakowski TM, KhorshidAhmad T, Cortes C, Namaka M & Acosta C (2016). Transcriptional Regulation of Brain-Derived Neurotrophic Factor (BDNF) by Methyl CpG Binding Protein 2 (MeCP2): a Novel Mechanism for Re-Myelination and/or Myelin Repair Involved in the Treatment of Multiple Sclerosis (MS). *Mol. Neurobiol.*, 53, 1092-107. [🔗](#)

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Date	Action	Author
2017-09-25	Created	Orlic-Milacic M

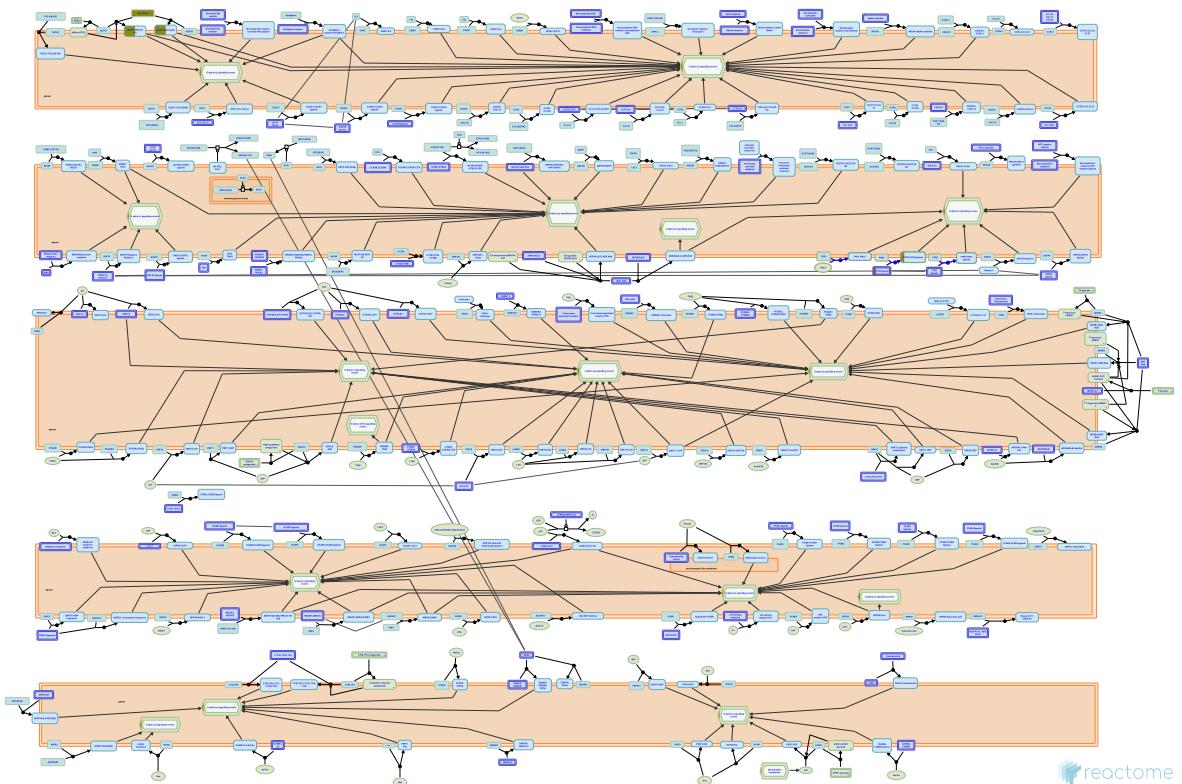
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2017-10-03	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Modified	Orlic-Milacic M
2018-08-08	Edited	Orlic-Milacic M

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

Input	UniProt Id
CRH	P06850

Input	Ensembl Id
CRH	ENSG00000147571

3. Formyl peptide receptors bind formyl peptides and many other ligands (R-HSA-444473)



Cellular compartments: plasma membrane.

The formyl peptide receptor (FPR) was defined pharmacologically in 1976 as a high affinity binding site on the surface of neutrophils for the peptide N-formyl-methionine-leucine-phenylalanine (fMLF). FPR was cloned in 1990 and the cDNA used as a probe to identify two additional genes, FPRL1 and FPRL2. The three genes form a cluster on 19q13.3. All are coupled to the Gi family of G proteins.

All 3 receptors can be activated by formyl peptides but also display affinities for a range of structurally diverse ligands.

References

Communi D, Migeotte I & Parmentier M (2006). Formyl peptide receptors: a promiscuous subfamily of G protein-coupled receptors controlling immune responses. Cytokine Growth Factor Rev, 17, 501-19. ↗

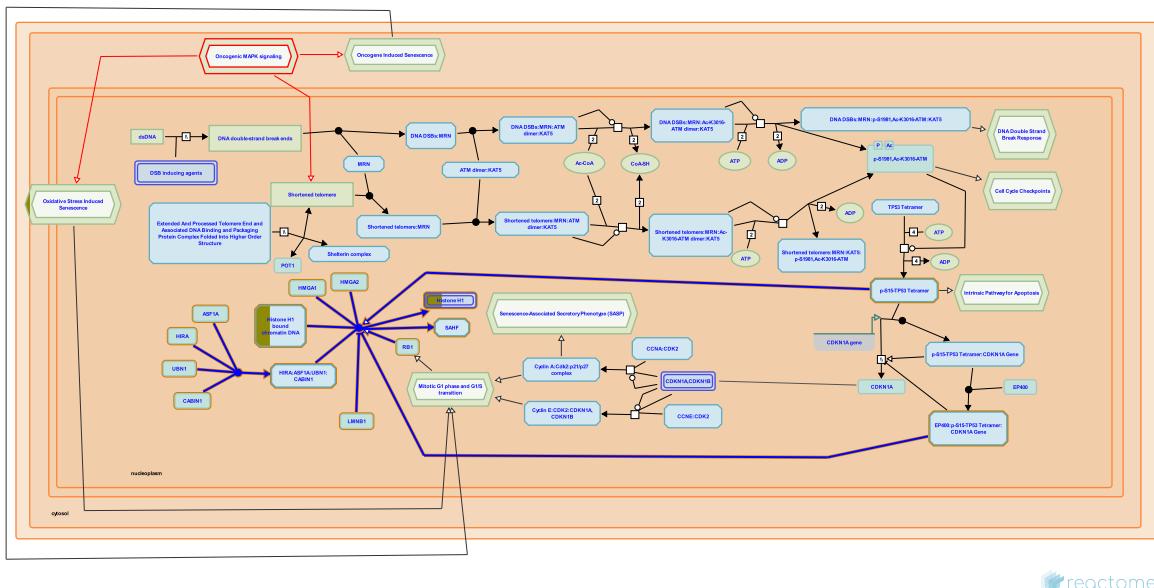
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2009-10-23	Created	Jupe S
2009-12-12	Reviewed	D'Eustachio P
2010-03-01	Edited	Jupe S
2021-11-26	Modified	Weiser JD

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

Input	UniProt Id
SAA1	P0DJI8

4. Formation of Senescence-Associated Heterochromatin Foci (SAHF) (R-HSA-2559584)



reactome

The process of DNA damage/telomere stress induced senescence culminates in the formation of senescence associated heterochromatin foci (SAHF). These foci represent facultative heterochromatin that is formed in senescent cells. They contribute to the repression of proliferation promoting genes and play an important role in the permanent cell cycle exit that characterizes senescence (Narita et al. 2003 and 2006). SAHF appear as compacted, punctate DAPI stained foci of DNA. Each chromosome is condensed into a single SAH focus, with telomeric and centromeric chromatin located predominantly at its periphery (Funayama et al. 2006, Zhang et al. 2007).

An evolutionarily conserved protein complex of HIRA, ASF1A, UBN1 and CABIN1 plays a crucial role in the SAHF formation. As cells approach senescence, HIRA, ASF1A, UBN1 and CABIN1 accumulate at the PML bodies (Zhang et al. 2005, Banumathy et al. 2009, Rai et al. 2011). PML bodies are punctate nuclear structures that contain PML protein and numerous other proteins and are proposed to be the sites of assembly of macromolecular regulatory complexes and protein modification (Fogal et al. 2000, Guo et al. 2000, Pearson et al. 2000). Recruitment of HIRA to PML bodies coincides with altered chromatin structure and deposition of macroH2A histone H2A variant onto chromatin. As cells become senescent, HIRA, ASF1A, UBN1 and CABIN1 relocate from PML bodies to SAHF. HIRA accumulation at PML bodies is RB1 and TP53 independent, but may require phosphorylation of HIRA serine S697 by GSK3B (Ye, Zerlanko, Kennedy et al. 2007). SAHF formation itself, however, requires functional RB1 and TP53 pathways (Ye, Zerlanko, Zhang et al. 2007).

SAHF contain H3K9Me mark, characteristic of transcriptionally silent chromatin, and HP1, macroH2A histone H2A variant and HMGA proteins are also components of SAHF (Narita et al. 2006), besides the HIRA:ASF1A:UBN1:CABIN1 complex. A yet unidentified H3K9Me histone methyltransferase may be recruited to SAHF by UBN1 (Banumathy et al. 2009). One of the functions of the HIRA:ASF1A:UBN1:CABIN1 complex is to deposit histone H3.3. variant to chromatin, which influences gene expression (Zhang et al. 2007, Rai et al. 2011).

Further studies are needed to fully elucidate the mechanism of SAHF formation and mechanism by which SAHF promote cell senescence.

References

- Sandy P, Fogal V, Pandolfi PP, Sternsdorf T, Del Sal G, Will H, ... Gostissa M (2000). Regulation of p53 activity in nuclear bodies by a specific PML isoform. *EMBO J.*, 19, 6185-95. [🔗](#)
- Erzberger JP, Ye X, Poustovoitov MV, Adams PD, Dunbrack RL, Santos HA, ... Berger JM (2005). Formation of MacroH2A-containing senescence-associated heterochromatin foci and senescence driven by ASF1a and HIRA. *Dev. Cell*, 8, 19-30. [🔗](#)
- Lowe SW, Nuñez S, Krizhanovsky V, Narita M, Narita M, Myers MP, ... Hearn SA (2006). A novel role for high-mobility group a proteins in cellular senescence and heterochromatin formation. *Cell*, 126, 503-14. [🔗](#)
- Ye X, Zhang R, Banumathy G, Zerlanko B, Adams PD & Kennedy A (2007). Downregulation of Wnt signaling is a trigger for formation of facultative heterochromatin and onset of cell senescence in primary human cells. *Mol. Cell*, 27, 183-96. [🔗](#)
- Ye X, Somaiah N, Zhang R, Zerlanko B, Salomoni P, Adams PD & Lipinski M (2007). Definition of pRB- and p53-dependent and -independent steps in HIRA/ASF1a-mediated formation of senescence-associated heterochromatin foci. *Mol. Cell. Biol.*, 27, 2452-65. [🔗](#)

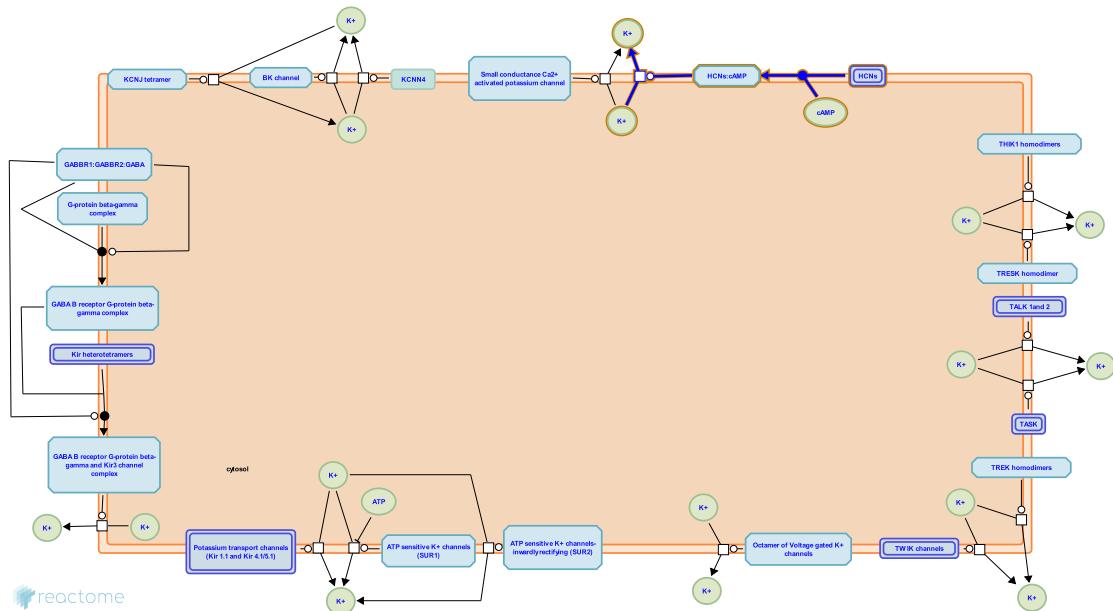
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2013-07-15	Edited	Matthews L, D'Eustachio P
2013-07-15	Authored	Orlic-Milacic M
2013-09-03	Reviewed	Samarajiwa S
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id
HIST1H1D	P16402, P16403

5. HCN channels (R-HSA-1296061)



Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are nonselective ligand-gated cation channels in the plasma membranes of heart and brain cells. HCN channels are sometimes referred to as "pacemaker channels" because they help to generate rhythmic activity within groups of heart and brain cells. They are highly expressed in spontaneously active cardiac regions, such as the sinoatrial node (SAN, the natural pacemaker region), the atrioventricular node (AVN) and the Purkinje fibres of conduction tissue. HCN channels are encoded by four genes (HCN1, 2, 3, 4) and are widely expressed throughout the heart and the central nervous system. HCN channels are homotetramers of four subunits and conduct a Na⁺ and K⁺ current with a permeability of 1:4. The mixed sodium-potassium current activates upon hyperpolarization at voltages in the diastolic range (normally from $\sim 60/\sim 70$ mV to ~ 40 mV). At the end of a sinoatrial action potential, the membrane repolarizes below $\sim 40/\sim 50$ mV, the "funny current" is activated and supplies inward current, which is responsible for starting the diastolic depolarization phase (DD); by this mechanism, the funny current controls the rate of spontaneous activity of sinoatrial myocytes, hence the cardiac rate. HCN channels are involved in controlling the rhythmic activity of pacemaker current in authythmic cells in heart and neuronal processes such as dendritic integration and synaptic transmission.

References

- Bottelli G, DiFrancesco D, Milanesi R, Baruscotti M & DiFrancesco JC (2010). HCN-related channelopathies. *Pflugers Arch*, 460, 405-15. [\[CrossRef\]](#)
- Biel M, Wahl-Schott C, Michalakis S & Zong X (2009). Hyperpolarization-activated cation channels: from genes to function. *Physiol Rev*, 89, 847-85. [\[CrossRef\]](#)

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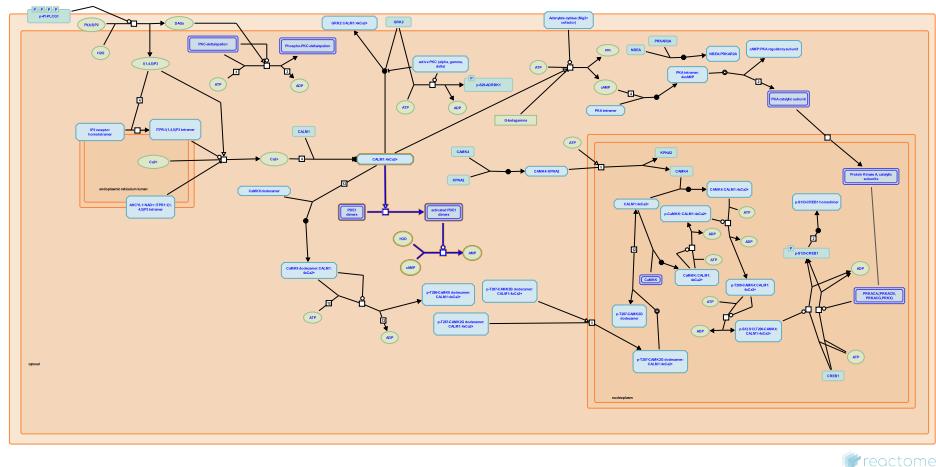
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Date	Action	Author
2011-05-19	Authored	Mahajan SS
2011-05-19	Created	Mahajan SS
2011-05-23	Edited	Mahajan SS
2021-11-26	Modified	Weiser JD

Interactors found in this pathway (1)

Input	ChEBI Id	Interacts with	Input	ChEBI Id	Interacts with
PRKG1	P00516-2	17489			

6. Cam-PDE 1 activation (R-HSA-111957)



Cellular compartments: cytosol.

Human Ca²⁺/calmodulin-dependent phosphodiesterase PDE1 is activated by the binding of calmodulin in the presence of Ca(2+). PDE1 has three subtypes PDE1A, PDE1B and PDE1C and their role is to hydrolyze both cGMP and cAMP. Their role is to antagonize the increased concentration of the intracellular second messengers determined by the synthetic activity of the adenylate cyclase enzymes thus governing intracellular cAMP dynamics in response to changes in the cytosolic Ca²⁺ concentration. PDE1 are mainly cytosolic but different isoforms are expressed in different tissues.

References

Sharma RK, Shrivastav A, Lakshmikuttyamma A, Das SB & Selvakumar P (2006). Regulation of calmodulin-stimulated cyclic nucleotide phosphodiesterase (PDE1): review. Int J Mol Med, 18, 95-105. [\[link\]](#)

Sharma RK, Raju RV & Kakkar R (1999). Calmodulin-dependent cyclic nucleotide phosphodiesterase (PDE1). Cell Mol Life Sci, 55, 1164-86. [\[link\]](#)

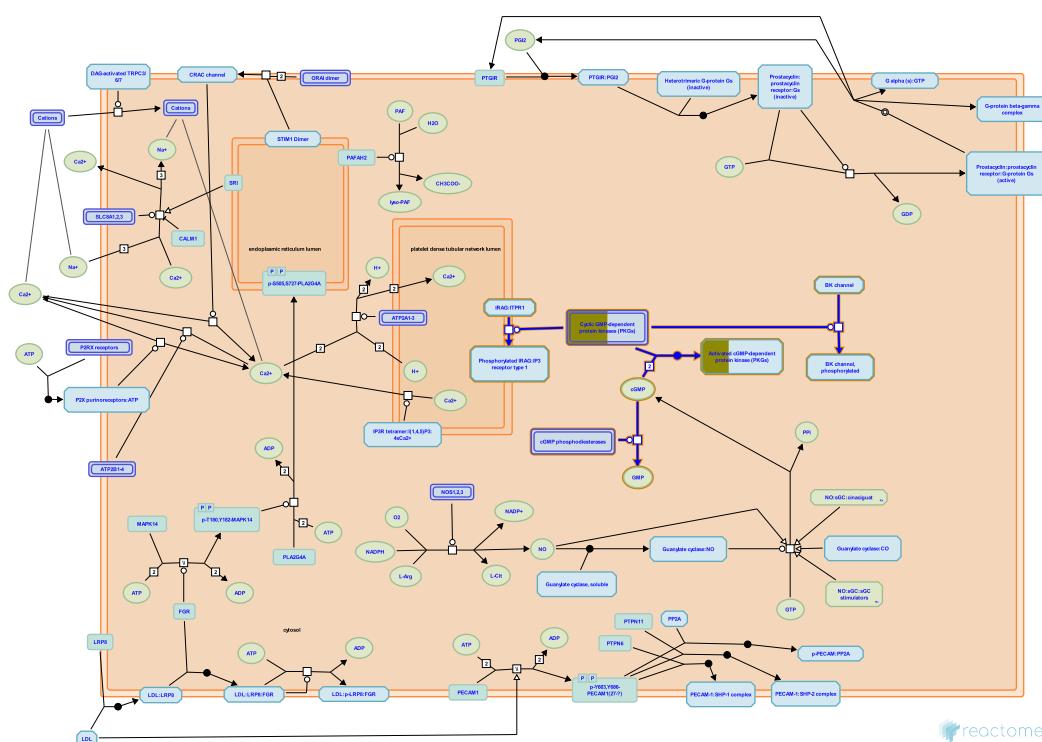
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2004-03-26	Created	Schmidt EE
2004-03-31	Authored	Jassal B, Le Novere N
2008-11-06	Edited	Jassal B
2008-11-06	Reviewed	Castagnoli L
2022-01-09	Modified	Weiser JD

Interactors found in this pathway (1)

Input	ChEBI Id	Interacts with	Input	ChEBI Id	Interacts with
PRKG1	P00516-2	17489			

7. cGMP effects (R-HSA-418457)



Cellular compartments: cytosol.

Cyclic guanosine monophosphate (cGMP) is an important secondary messenger synthesized by guanylate cyclases. cGMP has effects on phosphodiesterases (PDE), ion-gated channels, and the cGMP-dependent protein kinases (cGK, Protein Kinase G or PKG). It is involved in regulation of several physiological functions including vasodilation, platelet aggregation and neurotransmission. Elevation of intracellular cGMP activates PKG (Haslam et al. 1999) which regulates several intracellular molecules and pathways including the vasodilator-stimulated phosphoprotein (VASP) (Hallbrugge et al. 1990) and the ERK pathway (Hood and Granger 1998, Li et al. 2001). cGMP mediates nitric oxide (NO)-induced vascular smooth muscle relaxation (Furchtgott and Vanhoutte 1989). Phosphodiesterase 5 (PDE5) hydrolyzes cGMP; the PDE5 inhibitor sildenafil (Viagra) increases intracellular cGMP and thereby can be used as a treatment for erectile dysfunction (Corbin and Francis 1999). The role of the cGMP and PKG in platelet activation was controversial as increases in platelet cGMP levels were observed in response to both platelet agonists (thrombin, ADP or collagen) and inhibitors (NO donors such as sodium nitroprusside), but it is currently accepted that PKG inhibits platelet activation (Haslam et al. 1999). Consistent with this, nitric oxide (NO) donors that inhibit platelet activation enhance intracellular cGMP (Haslam et al. 1999). cGMP also plays an important stimulatory role in GPIb-IX-mediated platelet activation. Platelet responses to cGMP have been proposed to be biphasic, consisting of an early stimulatory response that promotes platelet activation followed by a delayed platelet inhibition that serves to limit the size of platelet aggregates (Li et al 2003).

References

- Murad F, Warner TD, Sheng H & Mitchell JA (1994). Effects of cyclic GMP on smooth muscle relaxation. *Adv Pharmacol*, 26, 171-94. [View](#)

Hofmann F, Mälsch A, Walter U, Lohmann SM, Mänzel T & Feil R (2003). Physiology and pathophysiology of vascular signaling controlled by guanosine 3',5'-cyclic monophosphate-dependent protein kinase [corrected]. Circulation, 108, 2172-83. [🔗](#)

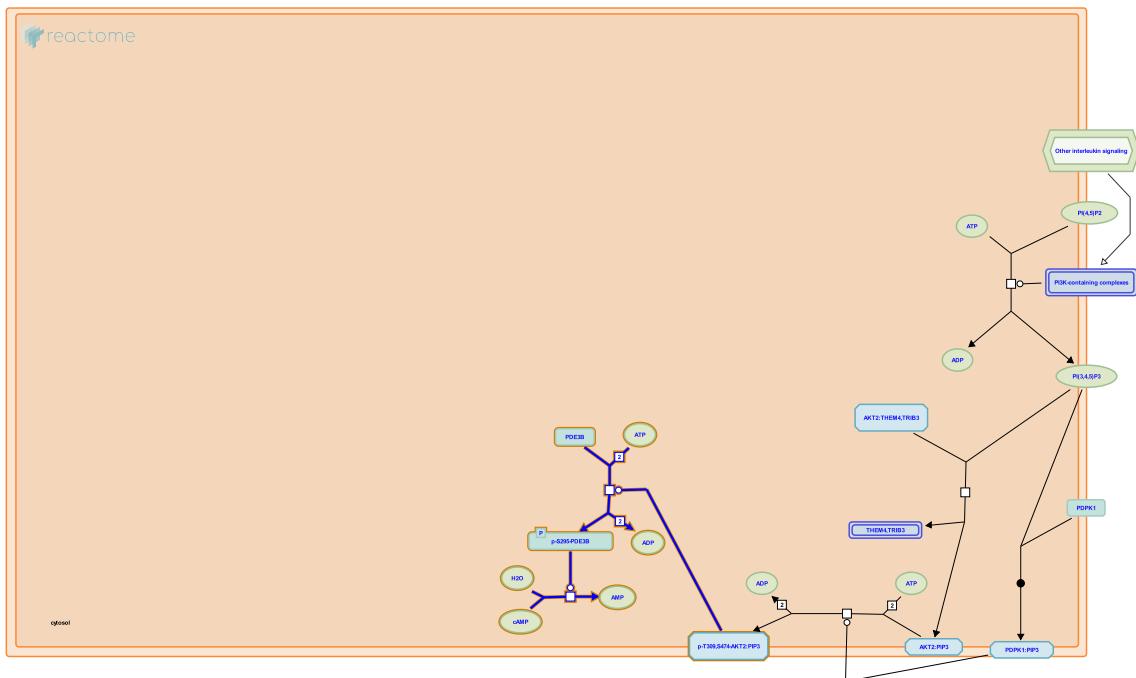
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2009-06-03	Authored	Akkerman JW
2010-06-07	Edited	Jupe S
2010-06-07	Reviewed	Kunapuli SP
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id
PRKG1	Q13976-1

8. PDE3B signalling (R-HSA-165160)



AKT (PKB) is recruited to the plasma membrane by binding phosphatidylinositol (3,4,5)-trisphosphate (PIP3). AKT is then activated by phosphorylation. Activated AKT in turn phosphorylates Phosphodiesterase 3B (PDE3B) which hydrolyzes 3',5'-cyclic AMP (cAMP) (reviewed in Manning and Toker 2017).

References

Manning BD & Toker A (2017). AKT/PKB Signaling: Navigating the Network. *Cell*, 169, 381-405. [View](#)

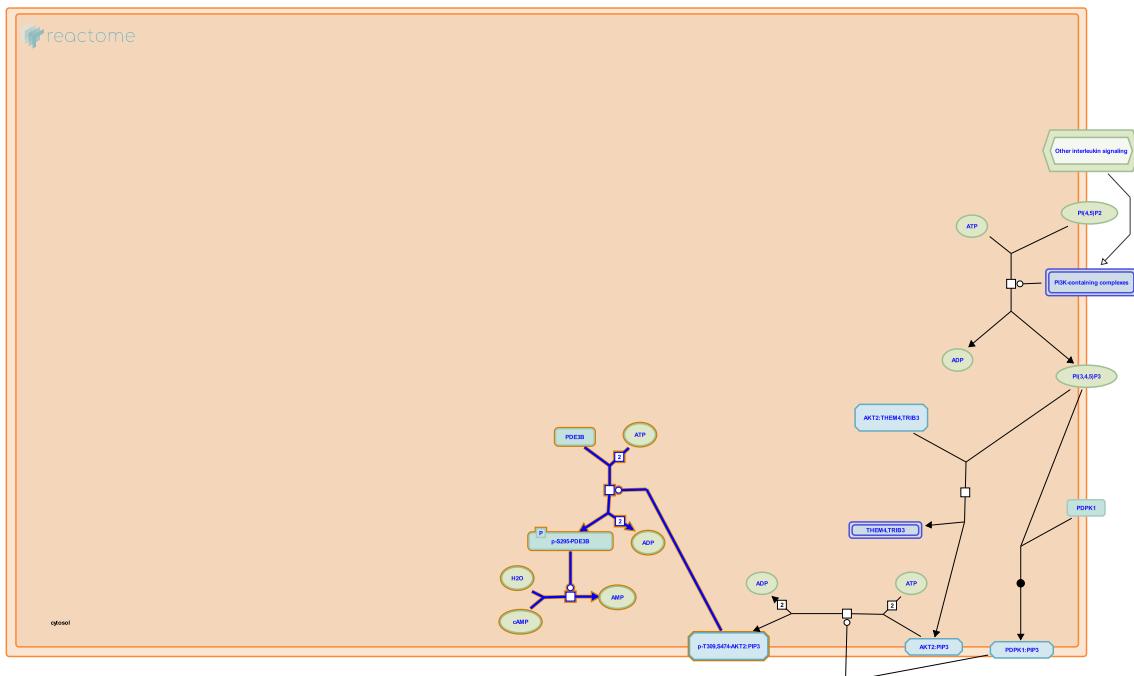
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2021-11-28	Modified	Weiser JD

Interactors found in this pathway (1)

Input	ChEBI Id	Interacts with	Input	ChEBI Id	Interacts with
PRKG1	P00516-2	17489			

9. PKB-mediated events (R-HSA-109703)



PKB and PDK1 are activated via membrane-bound PIP3. Activated PDK1 phosphorylates PKB, which in turn phosphorylates PDE3B. The latter hydrolyses cAMP to 5'AMP, depleting cAMP pools.

References

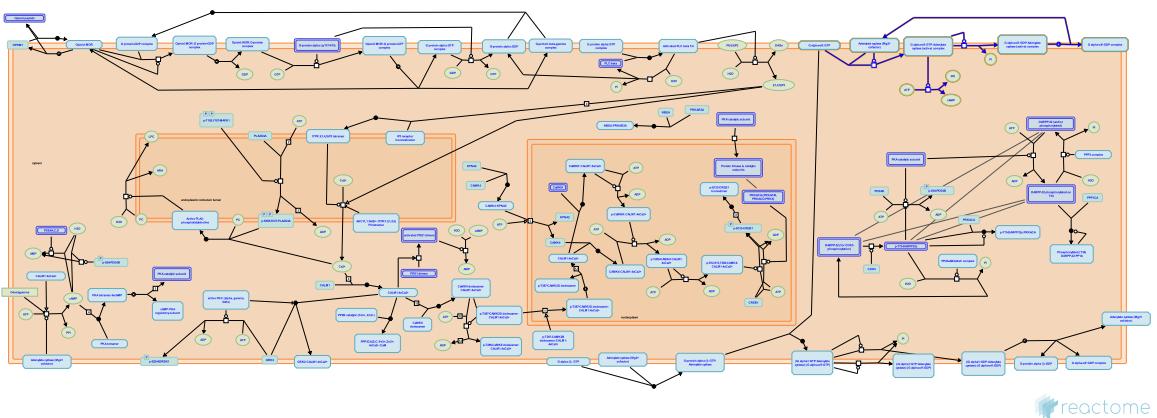
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2005-05-09	Authored	Tatoud R, Scott J
2021-11-28	Modified	Weiser JD

Interactors found in this pathway (1)

Input	ChEBI Id	Interacts with	Input	ChEBI Id	Interacts with
PRKG1	P00516-2	17489			

10. 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](#)

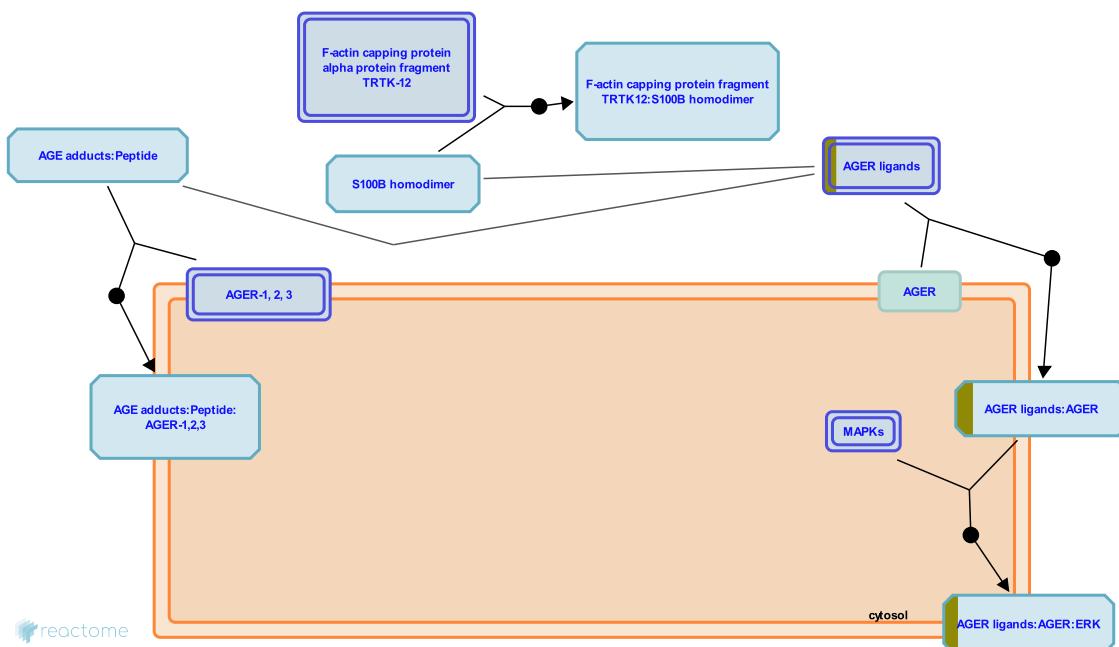
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Date	Action	Author
2004-03-31	Authored	Jassal B, Le Novere N
2006-01-10	Created	Jassal B
2008-11-06	Edited	Jassal B
2008-11-06	Reviewed	Castagnoli L
2021-11-27	Modified	Weiser JD

Interactors found in this pathway (1)

Input	ChEBI Id	Interacts with	Input	ChEBI Id	Interacts with
PRKG1	P00516-2	17489			

11. Advanced glycosylation endproduct receptor signaling (R-HSA-879415)



Cellular compartments: plasma membrane, extracellular region.

Advanced Glycosylation End- product-specific Receptor (AGER) also known as Receptor for Advanced Glycation End-products (RAGE) is a multi-ligand membrane receptor belonging to the immunoglobulin superfamily. It is considered to be a Pattern Recognition Receptor (Liliensiek et al. 2004). It recognizes a large variety of modified proteins known as advanced glycation/glycosylation endproducts (AGEs), a heterogenous group of structures that are generated by the Maillard reaction, a consequence of long-term incubation of proteins with glucose (Ikeda et al. 1996). Their accumulation is associated with diabetes, atherosclerosis, renal failure and ageing (Schmidt et al. 1999). The most prevalent class of AGE in vivo are N(6)-carboxymethyllysine (NECML) adducts (Kislinger et al. 1991). In addition to AGEs, AGER is a signal transduction receptor for amyloid-beta peptide (Ab) (Yan et al. 1996), mediating Ab neurotoxicity and promoting Ab influx into the brain. AGER also responds to the proinflammatory S100/calgranulins (Hofmann et al. 1999) and High mobility group protein B1 (HMGB1/Amphoterin/DEF), a protein linked to neurite outgrowth and cellular motility (Hori et al. 1995).

The major inflammatory pathway stimulated by AGER activation is NF κ B. Though the signaling cascade is unclear, several pieces of experimental data suggest that activation of AGER leads to sustained activation and upregulation of NF κ B, measured as NF κ B translocation to the nucleus, and increased levels of de novo synthesized NF κ B (Bierhaus et al. 2001). As this is clearly an indirect effect it is represented here as positive regulation of NF κ B translocation to the nucleus. AGER can bind ERK1/2 and thereby activate the MAPK and JNK cascades (Bierhaus et al. 2005).

References

Humpert PM, Wendt T, Arnold B, Stern DM, Chavakis T, Bierhaus A, ... Nawroth PP (2005). Understanding RAGE, the receptor for advanced glycation end products. *J Mol Med*, 83, 876-86. [🔗](#)

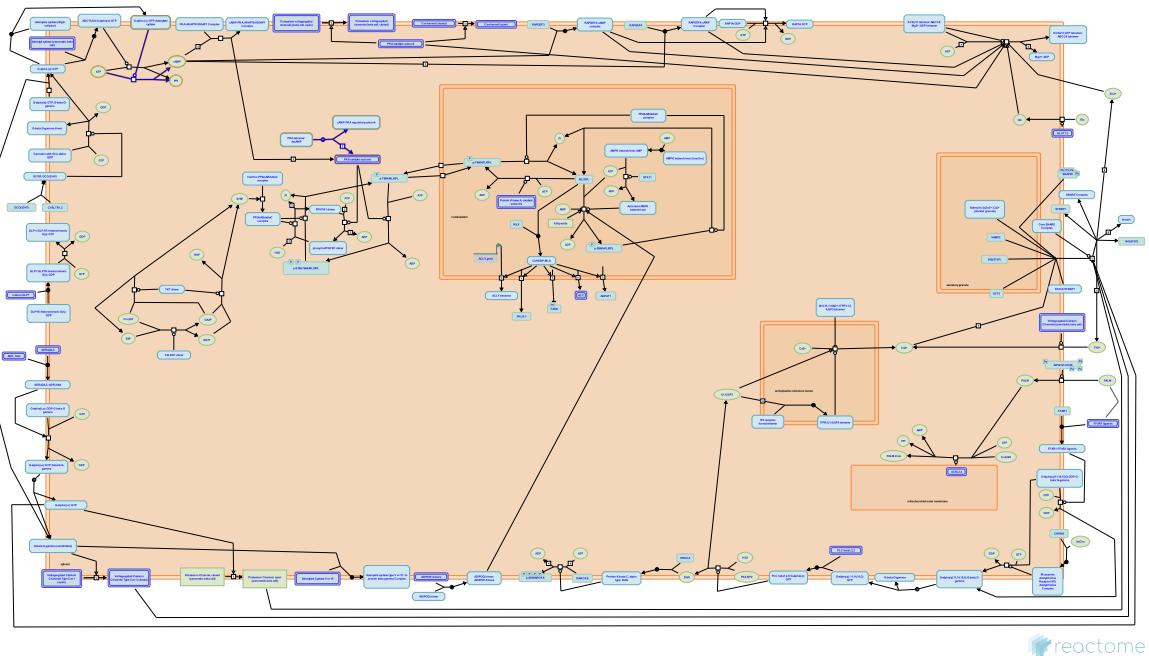
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Date	Action	Author
2010-06-01	Authored	Jupe S
2010-06-17	Created	Jupe S
2010-09-01	Edited	Jupe S
2010-11-09	Reviewed	Yan SD
2021-11-27	Modified	Weiser JD

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

Input	UniProt Id
SAA1	P0DJI8

12. 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

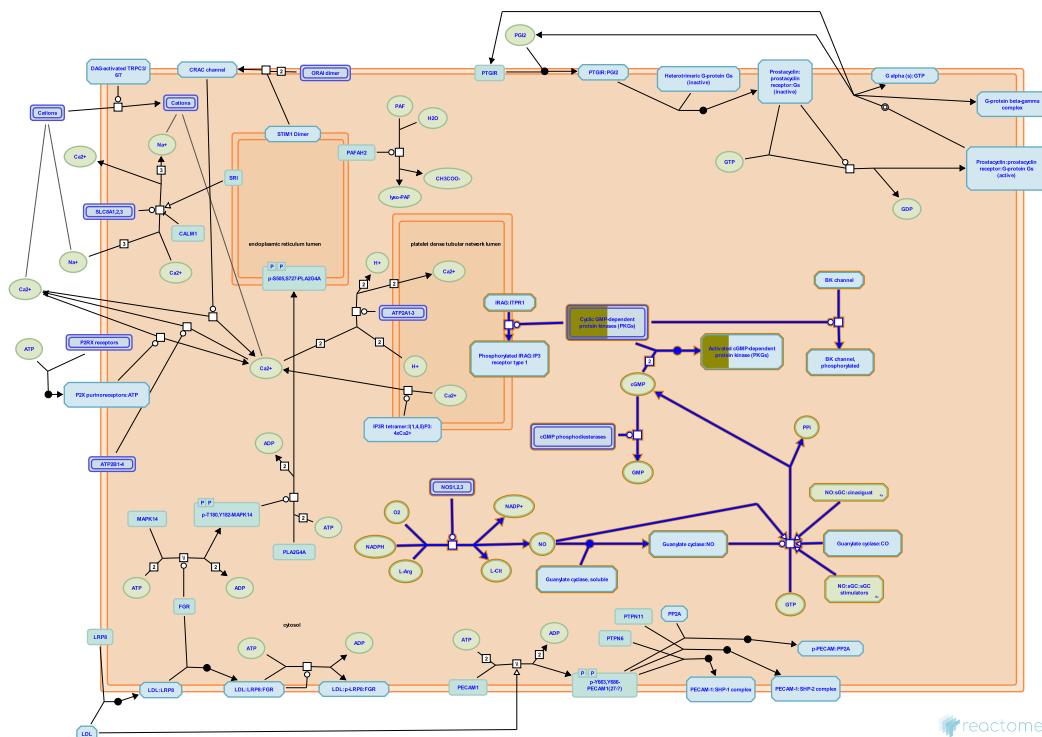
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Date	Action	Author
2005-05-19	Authored	Gopinathrao G, D'Eustachio P
2005-05-19	Created	Gopinathrao G
2021-11-28	Modified	Weiser JD

Interactors found in this pathway (1)

Input	ChEBI Id	Interacts with	Input	ChEBI Id	Interacts with
PRKG1	P00516-2	17489			

13. Nitric oxide stimulates guanylate cyclase (R-HSA-392154)



Cellular compartments: cytosol.

Nitric Oxide (NO) inhibits smooth muscle cell proliferation and migration, oxidation of low-density lipoproteins, and platelet aggregation and adhesion. It can stimulate vasodilatation of the endothelium, disaggregation of preformed platelet aggregates and inhibits activated platelet recruitment to the aggregate. NO is synthesized from L-arginine by a family of isoformic enzymes known as nitric oxide synthase (NOS). Three isoforms, namely endothelial, neuronal, and inducible NOS (eNOS, nNOS, and iNOS, respectively), have been identified. The eNOS isoform is found in the endothelium and platelets. NO regulation of cyclic guanosine-3,5-monophosphate (cGMP), via activation of soluble guanylate cyclase, is the principal mechanism of negative control over platelet activity. Defects in this control mechanism have been associated with platelet hyperaggregability and associated thrombosis.

References

Koesling D & Friebe A (2003). Regulation of nitric oxide-sensitive guanylyl cyclase. Circ Res, 93, 96-105. [View](#)

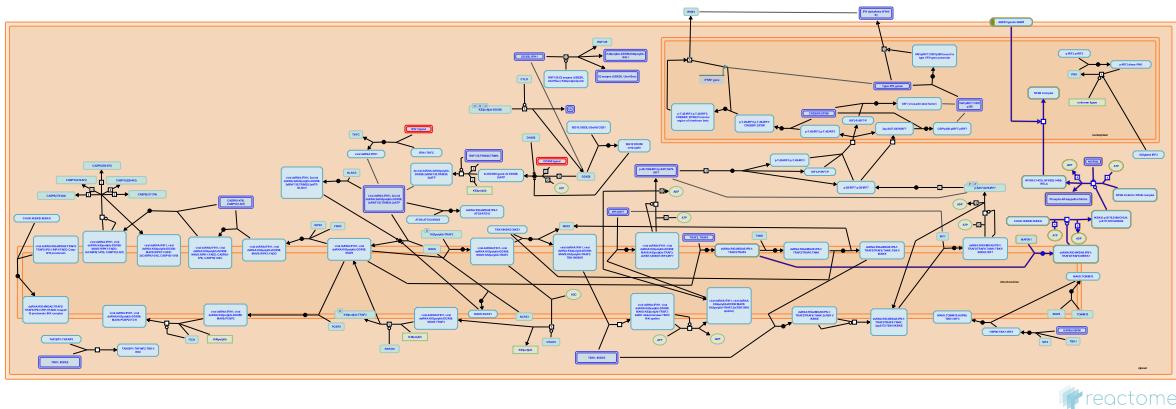
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Date	Action	Author
2009-02-27	Created	Jupe S
2009-06-03	Authored	Akkerman JW
2010-06-07	Edited	Jupe S
2010-06-07	Reviewed	Kunapuli SP
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id
PRKG1	Q13976-1

14. TRAF6 mediated NF-kB activation (R-HSA-933542)



Cellular compartments: cytosol, mitochondrial outer membrane.

The TRAF6/TAK1 signal activates a canonical IKK complex, resulting in the activation of NF- κ B as well as MAPK cascades leading to the activation of AP-1. Although TRAF6/TAK1 has been implicated in Toll like receptor (TLR) mediated cytokine production, the involvement of these molecules in the regulation of type I IFN induction mediated by RIG-I/MDA5 pathway is largely unknown. According to the study done by Yoshida et al RIG-I/IPS-1 pathway requires TRAF6 and MAP3K, MEKK1 to activate NF- κ B and MAP Kinases for optimal induction of type I IFNs.

References

Kobayashi T, Kawai T, Yoshioka T, Yoshida H, Takaesu G, Yoshida R, ... Okamoto F (2008). TRAF6 and MEKK1 play a pivotal role in the RIG-I-like helicase antiviral pathway. *J Biol Chem*, 283, 36211-20. [🔗](#)

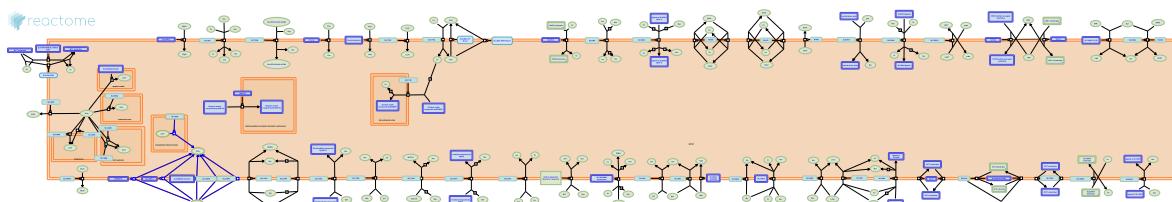
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Date	Action	Author
2010-08-02	Edited	Garapati P V
2010-08-02	Authored	Garapati P V
2010-08-16	Created	Garapati P V
2010-10-30	Reviewed	Akira S, Kawai T
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
SAA1	P0DJI8

15. Zinc influx into cells by the SLC39 gene family (R-HSA-442380)



The SLC39 gene family encode zinc transporters belonging to the ZIP (Zrt-, Irt-like proteins) family of metal ion transporters. All ZIPs transport metal ions into the cytoplasm of cells, be it across cellular membranes or from intracellular compartments. To date, there are 14 human SLC39 genes that encode the zinc transporters hZIP1-14. There are 9 members which belong to a subfamily of the ZIPs called the LZTs (LIV-1 subfamily of ZIP zinc transporters) (Taylor KM and Nicholson RI, 2003). Of these 14 proteins, four (hZIP9, 11, 12 and 13) have no function determined yet (Eide DJ, 2004).

References

Eide DJ (2004). The SLC39 family of metal ion transporters. *Pflugers Arch*, 447, 796-800. [🔗](#)

Taylor KM & Nicholson RI (2003). The LZT proteins; the LIV-1 subfamily of zinc transporters. *Biochim Biophys Acta*, 1611, 16-30. [🔗](#)

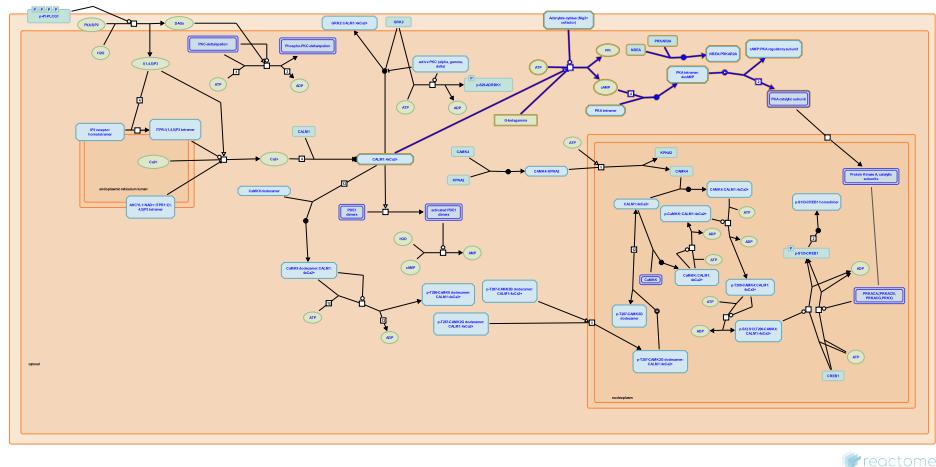
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Date	Action	Author
2009-09-25	Edited	Jassal B
2009-09-25	Authored	Jassal B
2009-09-25	Created	Jassal B
2009-11-12	Reviewed	He L
2021-11-28	Modified	Weiser JD

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
KIAA1644	Q3SXP7	Q92504			

16. PKA activation (R-HSA-163615)



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](#)

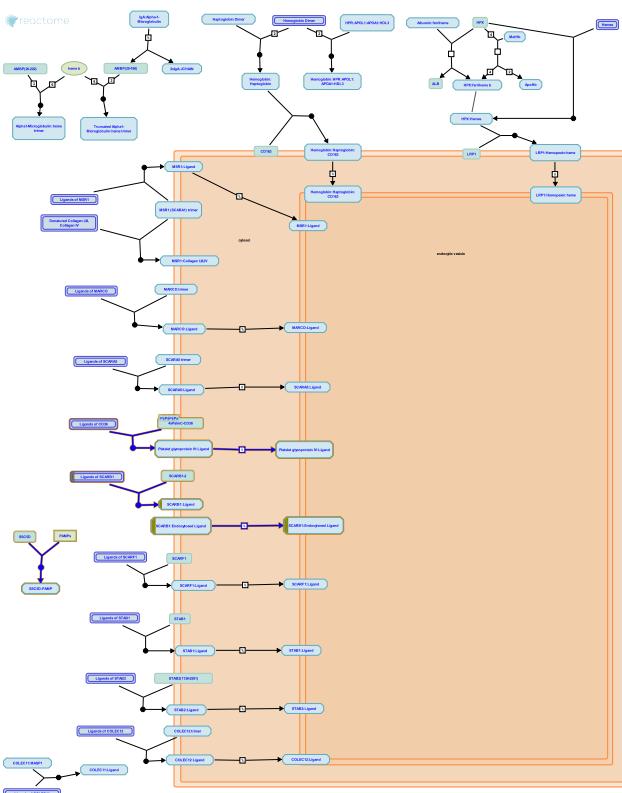
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Date	Action	Author
2004-03-31	Authored	Jassal B, Le Novere N
2005-05-03	Created	Schmidt EE
2008-11-06	Edited	Jassal B
2008-11-06	Reviewed	Castagnoli L
2022-01-09	Modified	Weiser JD

Interactors found in this pathway (1)

Input	ChEBI Id	Interacts with	Input	ChEBI Id	Interacts with
PRKG1	P00516-2	17489			

17. Scavenging by Class B Receptors (R-HSA-3000471)



Cellular compartments: plasma membrane, extracellular region, endocytic vesicle membrane.

Class B receptors have two transmembrane domains separated by an extracellular loop (reviewed in Adachi and Tsujimoto 2006, Areschoug and Gordon 2009).

References

Adachi H & Tsujimoto M (2006). Endothelial scavenger receptors. *Prog. Lipid Res.*, 45, 379-404. ↗

Gordon S & Areschoug T (2009). Scavenger receptors: role in innate immunity and microbial pathogenesis. *Cell. Microbiol.*, 11, 1160-9. ↗

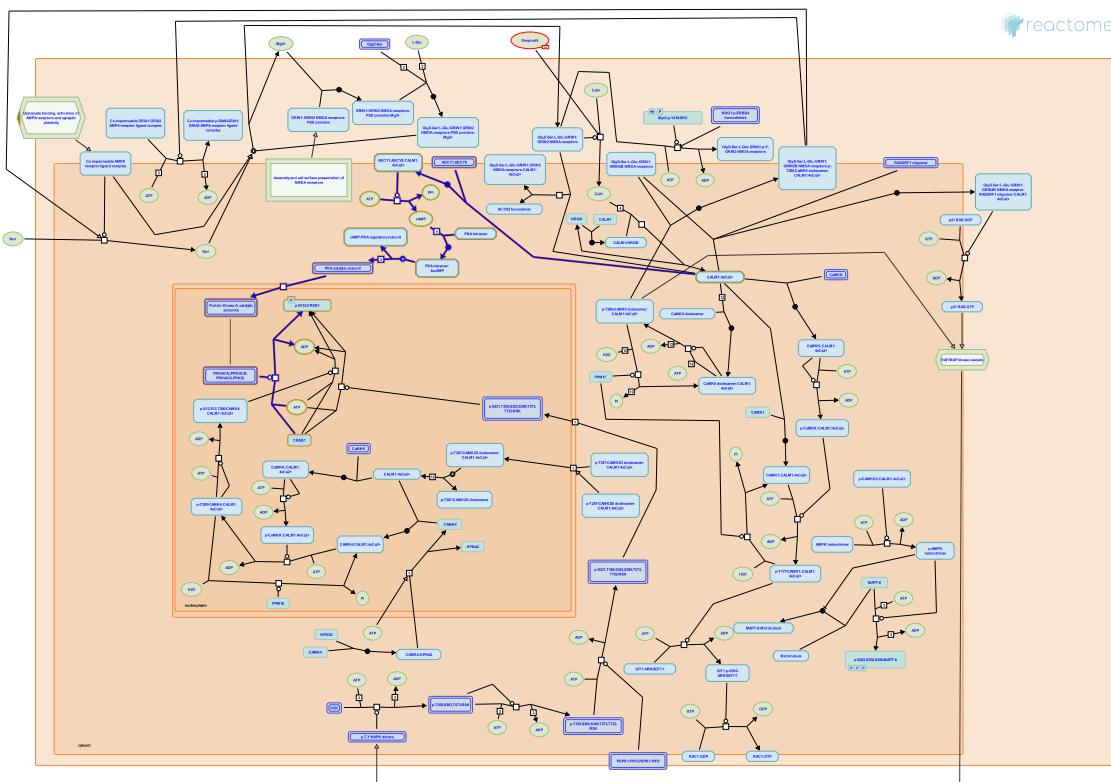
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Date	Action	Author
2013-01-27	Edited	May B
2013-01-27	Authored	May B
2013-01-28	Created	May B
2013-03-22	Reviewed	Neyen C
2013-03-22	Authored	Neyen C
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
SAA1	P0DJI8

18. CREB1 phosphorylation through the activation of Adenylate Cyclase (R-HSA-442720)



Cellular compartments: nucleoplasm, plasma membrane, cytosol.

Ca²⁺ influx through activated NMDA receptors in the post synaptic neurons activates adenylate cyclase-mediated signal transduction, leading to the activation of PKA and phosphorylation and activation of CREB1 induced transcription (Masada et al. 2012, Chetkovich et al. 1991, Chetkovich and Sweatt 1993

References

Vikis HG, Lu Y, Liu Y, You M & James MA (2009). RGS17, an overexpressed gene in human lung and prostate cancer, induces tumor cell proliferation through the cyclic AMP-PKA-CREB pathway. *Cancer Res*, 69, 2108-16. [\[link\]](#)

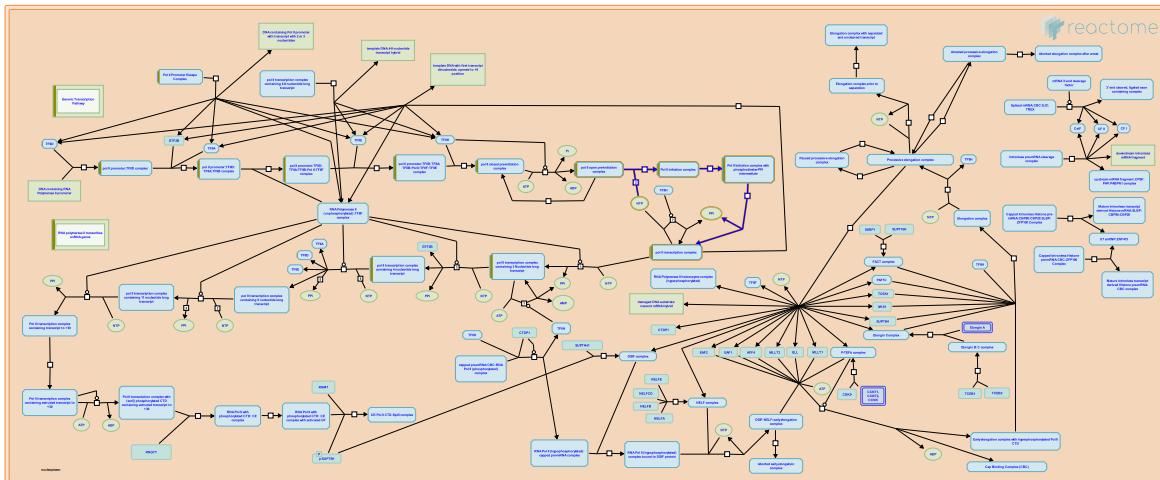
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Date	Action	Author
2009-09-29	Created	Mahajan SS
2009-10-29	Authored	Mahajan SS
2009-11-18	Reviewed	Tukey D
2009-11-19	Edited	Gillespie ME
2018-10-11	Revised	Orlic-Milacic M
2018-11-02	Reviewed	Hansen KB, Yi F
2018-11-07	Edited	Orlic-Milacic M
2022-01-09	Modified	Weiser JD

Interactors found in this pathway (1)

Input	ChEBI Id	Interacts with	Input	ChEBI Id	Interacts with
PRKG1	P00516-2	17489			

19. RNA Polymerase II Transcription Initiation (R-HSA-75953)



Cellular compartments: nucleoplasm.

Formation of the open complex exposes the template strand to the catalytic center of the RNA polymerase II enzyme. This facilitates formation of the first phosphodiester bond, which marks transcription initiation. As a result of this, the TFIIB basal transcription factor dissociates from the initiation complex.

The open transcription initiation complex is unstable and can revert to the closed state. Initiation at this stage requires continued (d)ATP-hydrolysis by TFIIH. Dinucleotide transcripts are not stably associated with the transcription complex. Upon dissociation they form abortive products. The transcription complex is also sensitive to inhibition by small oligo-nucleotides.

Dinucleotides complementary to position -1 and +1 in the template can also direct first phosphodiester bond formation. This reaction is independent on the basal transcription factors TFIIE and TFIIH and does not involve open complex formation. This reaction is sensitive to inhibition by single-stranded oligonucleotides.

References

- Goodrich JA & Kugel JF (2002). Translocation after synthesis of a four-nucleotide RNA commits RNA polymerase II to promoter escape. *Mol Cell Biol*, 22, 762-73. [🔗](#)
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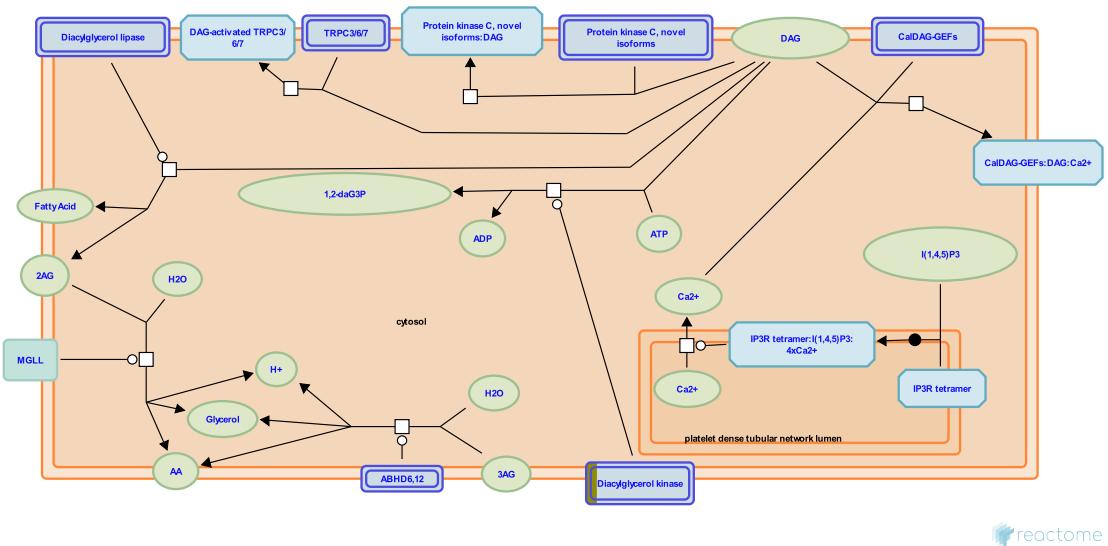
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Date	Action	Author
2003-09-11	Authored	Timmers HTM
2003-09-11	Created	Timmers HTM
2021-11-23	Edited	Joshi-Tope G
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id
TAF10	Q12962

20. Effects of PIP2 hydrolysis (R-HSA-114508)



Hydrolysis of phosphatidyl inositol-bisphosphate (PIP2) by phospholipase C (PLC) produces diacylglycerol (DAG) and inositol triphosphate (IP3). Both are potent second messengers. IP3 diffuses into the cytosol, but as DAG is a hydrophobic lipid it remains within the plasma membrane. IP3 stimulates the release of calcium ions from the smooth endoplasmic reticulum, while DAG activates the conventional and unconventional protein kinase C (PKC) isoforms, facilitating the translocation of PKC from the cytosol to the plasma membrane. The effects of DAG are mimicked by tumor-promoting phorbol esters. DAG is also a precursor for the biosynthesis of prostaglandins, the endocannabinoid 2-arachidonoylglycerol and an activator of a subfamily of TRP-C (Transient Receptor Potential Canonical) cation channels 3, 6, and 7.

References

- Mellor H & Parker PJ (1998). The extended protein kinase C superfamily. *Biochem J*, 332, 281-92. [🔗](#)
- Carrasco S & Márquez I (2007). Diacylglycerol, when simplicity becomes complex. *Trends Biochem Sci*, 32, 27-36. [🔗](#)

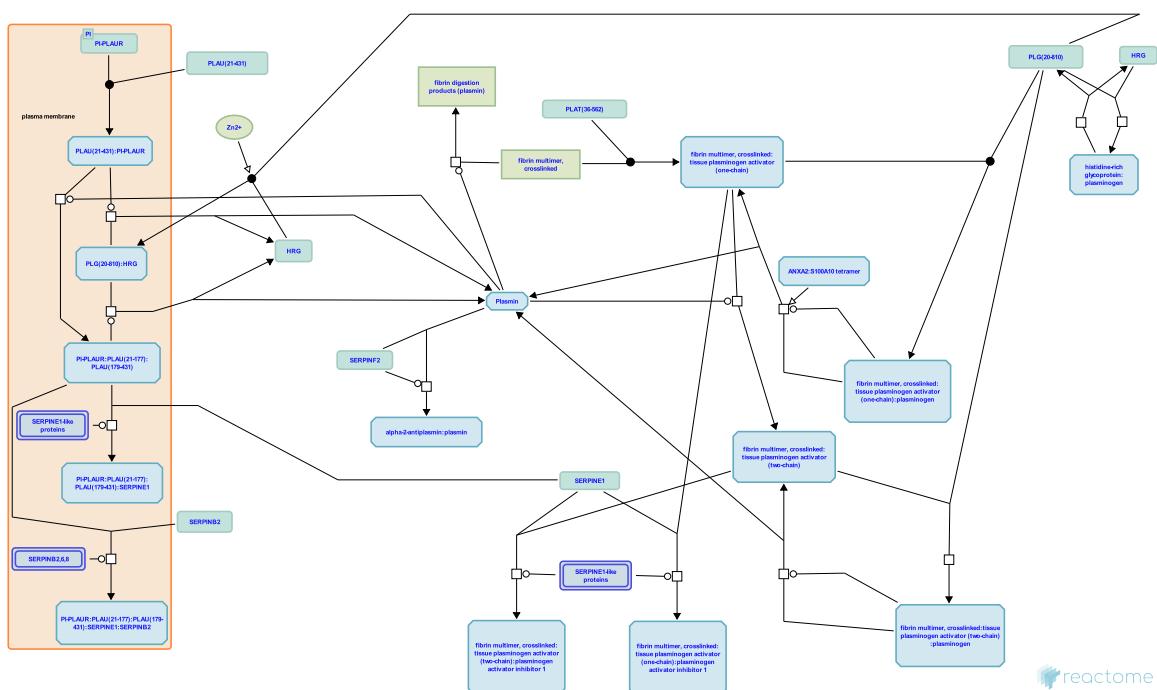
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Date	Action	Author
2004-09-25	Created	Farndale R, Pace NP, de Bono B
2009-09-09	Edited	Jupe S
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id
DGKQ	P52824

21. Dissolution of Fibrin Clot (R-HSA-75205)



The crosslinked fibrin multimers in a clot are broken down to soluble polypeptides by plasmin, a serine protease. Plasmin can be generated from its inactive precursor plasminogen and recruited to the site of a fibrin clot in two ways, by interaction with tissue plasminogen activator at the surface of a fibrin clot, and by interaction with urokinase plasminogen activator at a cell surface. The first mechanism appears to be the major one responsible for the dissolution of clots within blood vessels. The second, although capable of mediating clot dissolution, may normally play a major role in tissue remodeling, cell migration, and inflammation (Chapman 1997; Lijnen 2001).

Clot dissolution is regulated in two ways. First, efficient plasmin activation and fibrinolysis occur only in complexes formed at the clot surface or on a cell membrane - proteins free in the blood are inefficient catalysts and are rapidly inactivated. Second, both plasminogen activators and plasmin itself are inactivated by specific serpins, proteins that bind to serine proteases to form stable, enzymatically inactive complexes (Kohler and Grant 2000).

These events are outlined in the drawing: black arrows connect the substrates (inputs) and products (outputs) of individual reactions, and blue lines connect output activated enzymes to the other reactions that they catalyze.

References

- Lijnen HR (2001). Elements of the fibrinolytic system. *Ann N Y Acad Sci*, 936, 226-36. [🔗](#)
- Kohler HP & Grant PJ (2000). Plasminogen-activator inhibitor type 1 and coronary artery disease. *N Engl J Med*, 342, 1792-801. [🔗](#)
- Chapman HA (1997). Plasminogen activators, integrins, and the coordinated regulation of cell adhesion and migration. *Curr Opin Cell Biol*, 9, 714-24. [🔗](#)

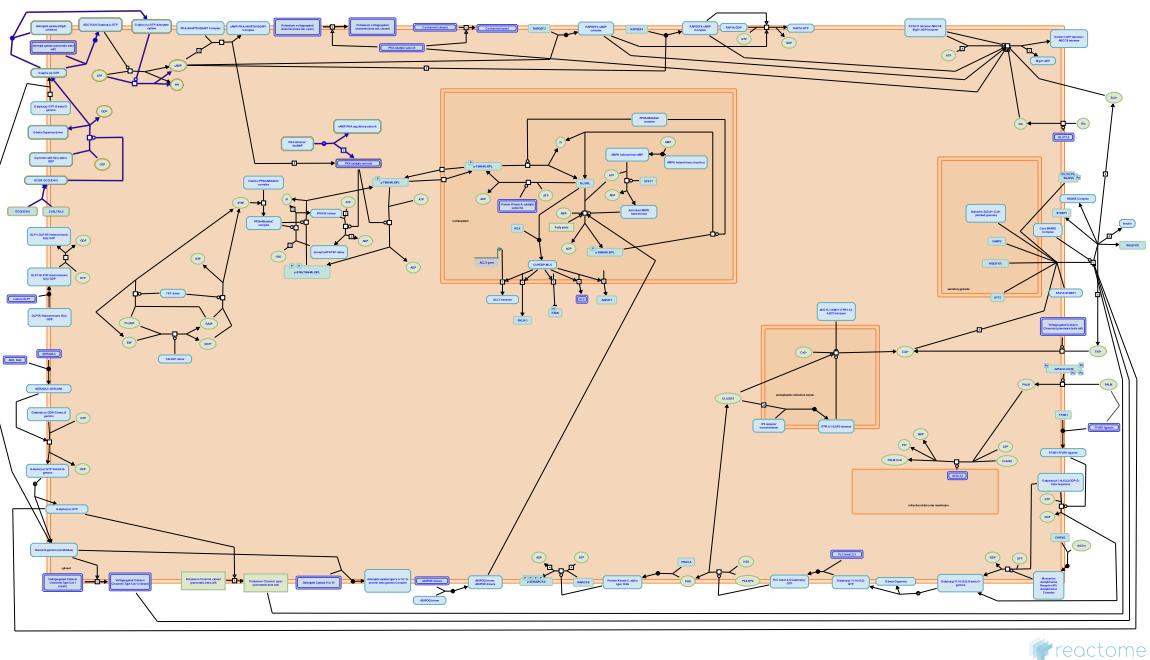
Edit history

Date	Action	Author
2008-01-11	Reviewed	Rush MG
2021-11-23	Edited	D'Eustachio P
2021-11-26	Modified	Weiser JD

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
ORM1	P02763	P05121			

22. Glucagon signaling in metabolic regulation (R-HSA-163359)



reactome

Glucagon and insulin are peptide hormones released from the pancreas into the blood, that normally act in complementary fashion to stabilize blood glucose concentration. When blood glucose levels rise, insulin release stimulates glucose uptake from the blood, glucose breakdown (glycolysis), and glucose storage as glycogen. When blood glucose levels fall, glucagon release stimulates glycogen breakdown and de novo glucose synthesis (gluconeogenesis), while inhibiting glycolysis and glycogen synthesis.

At a molecular level, the binding of glucagon to the extracellular face of its receptor causes conformational changes in the receptor that allow the dissociation and activation of subunits Gs and Gq. The activation of Gq leads to the activation of phospholipase C, production of inositol 1,4,5-triphosphate, and subsequent release of intracellular calcium. The activation of Gs leads to activation of adenylate cyclase, an increase in intracellular cAMP levels, and activation of protein kinase A (PKA). Active PKA phosphorylates key enzymes of glycogenolysis, glycogenesis, gluconeogenesis, and glycolysis, modifying their activities. These signal transduction events, and some of their downstream consequences, are illustrated below (adapted from Jiang and Zhang, 2003).

References

Zhang BB & Jiang G (2003). Glucagon and regulation of glucose metabolism. Am J Physiol Endocrinol Metab, 284, E671-8.

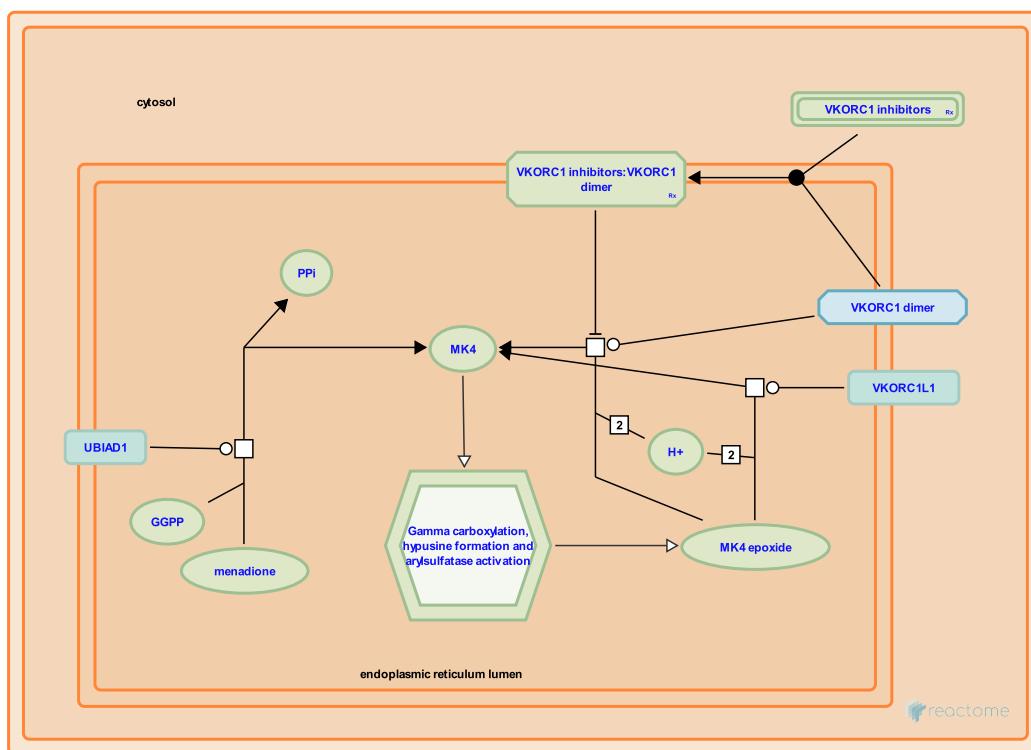
Edit history

Date	Action	Author
2005-04-28	Authored	Gopinathrao G
2005-04-28	Created	Gopinathrao G
2021-11-28	Modified	Weiser JD

Interactors found in this pathway (1)

Input	ChEBI Id	Interacts with	Input	ChEBI Id	Interacts with
PRKG1	P00516-2	17489			

23. Metabolism of vitamin K (R-HSA-6806664)



Vitamin K is a required co-factor in a single metabolic reaction, the gamma-carboxylation of glutamate residues of proteins catalyzed by GGCX (gamma-carboxyglutamyl carboxylase). Substrates of GGCX include blood clotting factors, osteocalcin (OCN), and growth arrest-specific protein 6 (GAS6) (Brenner et al. 1998). Vitamin K is derived from green leafy vegetables as phylloquinone and is synthesized by gut flora as menaquinone-7. These molecules are taken up by intestinal enterocytes with other lipids, packaged into chylomicrons, and delivered via the lymphatic and blood circulation to tissues of the body, notably hepatocytes and osteoblasts, via processes of lipoprotein trafficking (Shearer & Newman 2014; Shearer et al. 2012) described elsewhere in Reactome.

In these tissues, menadiol (reduced vitamin K3) reacts with geranylgeranyl pyrophosphate to form MK4 (vitamin K hydroquinone), the form of the vitamin required as cofactor for gamma-carboxylation of protein glutamate residues (Hirota et al. 2013). The gamma-carboxylation reactions, annotated elsewhere in Reactome as a part of protein metabolism, convert MK4 to its epoxide form, which is inactive as a cofactor. Two related enzymes, VKORC1 and VKORCL1, can each catalyze the reduction of MK4 epoxide to active MK4. VKORC1 activity is essential for normal operation of the blood clotting cascade and for osteocalcin function (Ferron et al. 2015). A physiological function for VKORCL1 has not yet been definitively established (Hammed et al. 2013; Tie et al. 2014).

References

- Suhara Y, Tsugawa N, Okano T, Wada A, Kamao M, Uchino Y, ... Okitsu T (2013). Menadione (vitamin K3) is a catabolic product of oral phylloquinone (vitamin K1) in the intestine and a circulating precursor of tissue menaquinone-4 (vitamin K2) in rats. *J. Biol. Chem.*, 288, 33071-80. [🔗](#)
- Shearer MJ & Newman P (2014). Recent trends in the metabolism and cell biology of vitamin K with special reference to vitamin K cycling and MK-4 biosynthesis. *J. Lipid Res.*, 55, 345-62. [🔗](#)

Booth SL, Shearer MJ & Fu X (2012). Vitamin K nutrition, metabolism, and requirements: current concepts and future research. *Adv Nutr*, 3, 182-95. [\[View\]](#)

Wu SM, Stafford DW, Sanchez-Vega B, Lanir N, Solera J & Brenner B (1998). A missense mutation in gamma-glutamyl carboxylase gene causes combined deficiency of all vitamin K-dependent blood coagulation factors. *Blood*, 92, 4554-9. [\[View\]](#)

Matagrin B, Lattard V, Prouillac C, Spohn G, Hammed A & Benoit E (2013). VKORC1L1, an enzyme rescuing the vitamin K 2,3-epoxide reductase activity in some extrahepatic tissues during anticoagulation therapy. *J. Biol. Chem.*, 288, 28733-42. [\[View\]](#)

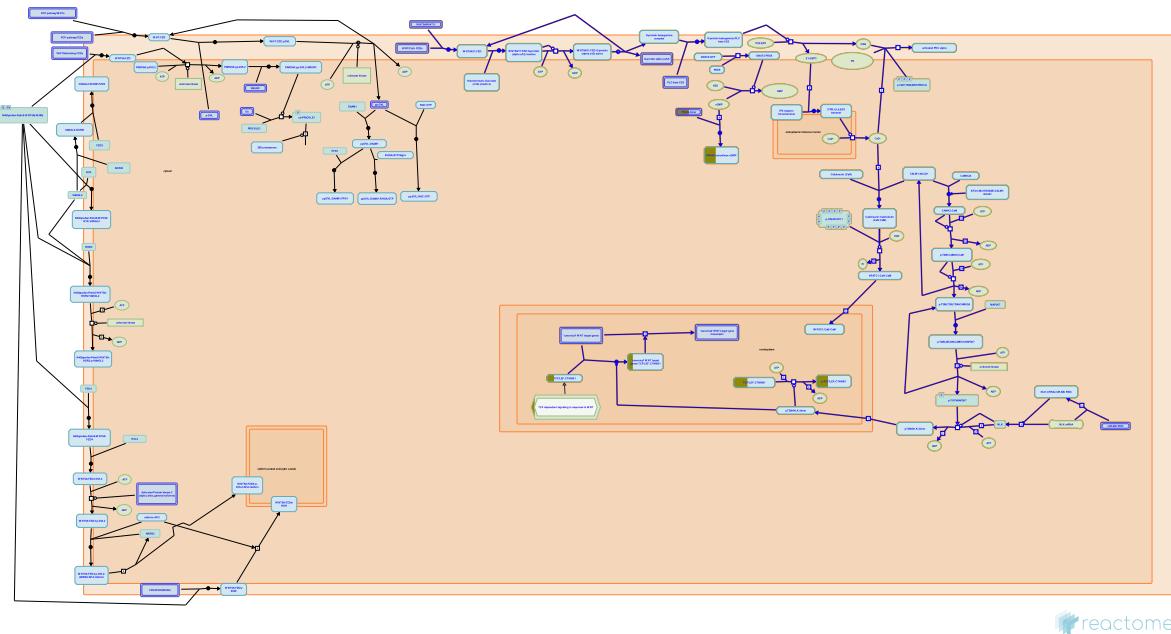
Edit history

Date	Action	Author
2015-10-23	Created	D'Eustachio P
2015-11-02	Edited	D'Eustachio P
2015-11-02	Reviewed	Jassal B
2015-11-02	Authored	D'Eustachio P
2021-11-27	Modified	Weiser JD

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
AGT	P01019	Q8N0U8			

24. Ca²⁺ pathway (R-HSA-4086398)



Cellular compartments: cytosol, plasma membrane.

A number of so called non-canonical WNT ligands have been shown to promote intracellular calcium release upon FZD binding. This beta-catenin-independent WNT pathway acts through heterotrimeric G proteins and promotes calcium release through phosphoinositol signaling and activation of phosphodiesterase (PDE). Downstream effectors include the calcium/calmodulin-dependent kinase II (CaMK2) and PKC (reviewed in De, 2011). The WNT Ca²⁺ pathway is important in dorsoventral polarity, convergent extension and organ formation in vertebrates and also has roles in negatively regulating 'canonical' beta-catenin-dependent transcription. Non-canonical WNT Ca²⁺ signaling is also implicated in inflammatory response and cancer (reviewed in Kohn and Moon, 2005; Sugimura and Li, 2010).

References

- Li L & Sugimura R (2010). Noncanonical Wnt signaling in vertebrate development, stem cells, and diseases. *Birth Defects Res. C Embryo Today*, 90, 243-56. [🔗](#)
- Moon RT & Kohn AD (2005). Wnt and calcium signaling: beta-catenin-independent pathways. *Cell Calcium*, 38, 439-46. [🔗](#)
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Edit history

Date	Action	Author
2013-08-08	Authored	Rothfels K
2013-08-08	Created	Rothfels K
2013-10-07	Edited	Matthews L
2013-11-13	Reviewed	Kikuchi A
2021-11-28	Modified	Weiser JD

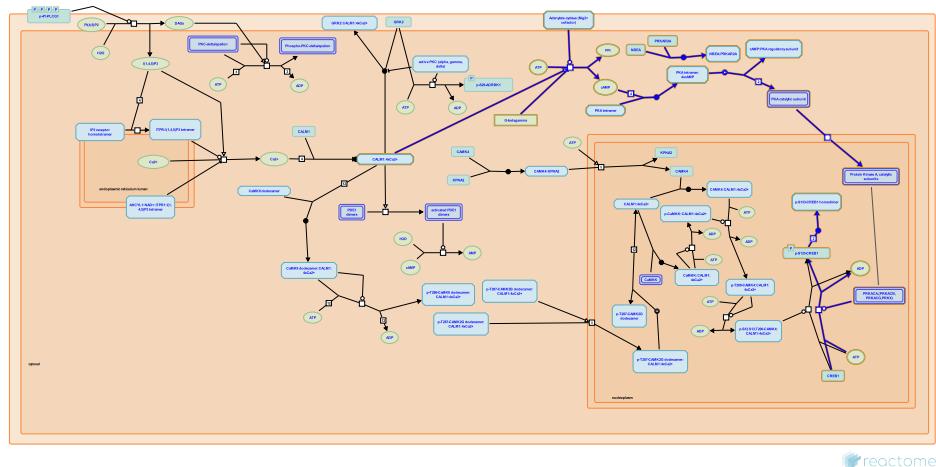
2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
LEF1	Q9UJU2	PRKG1	Q13976

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
TMEM176B	Q3YBM2	P17252			

25. PKA-mediated phosphorylation of CREB (R-HSA-111931)



Cellular compartments: nucleoplasm, plasma membrane, cytosol.

Cyclic adenosine 3',5'-monophosphate (cAMP) induces gene transcription through activation of cAMP-dependent protein kinase (PKA), and subsequent phosphorylation of the transcription factor cAMP response element-binding protein, CREB, at serine-133.

References

Moens U, Delghandi MP & Johannessen M (2005). The cAMP signalling pathway activates CREB through PKA, p38 and MSK1 in NIH 3T3 cells. *Cell Signal*, 17, 1343-51. [View](#)

Moens U, Delghandi MP & Johannessen M (2004). What turns CREB on?. *Cell Signal*, 16, 1211-27. [View](#)

Edit history

Date	Action	Author
2004-03-25	Created	Schmidt EE
2004-03-31	Authored	Jassal B, Le Novere N
2008-11-06	Edited	Jassal B
2008-11-06	Reviewed	Castagnoli L
2021-11-28	Modified	Weiser JD

Interactors found in this pathway (1)

Input	ChEBI Id	Interacts with	Input	ChEBI Id	Interacts with
PRKG1	P00516-2	17489			

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.

13 of the submitted entities were found, mapping to 22 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AGT	P01019	CRH	P06850	DGKQ	P52824
DLGAP3	O95886	HIST1H1D	P16402, P16403	LEF1	Q9UJU2
ORM1	P02763, Q8N138	PCK2	Q16822	PRKG1	Q13976-1
SAA1	P0DJI8	TAF10	Q12962	TFF1	P04155
VGF	O15240				

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
AGT	ENSG00000135744	CRH	ENSG00000147571	SAA1	ENSG00000173432
TFF1	ENSG00000160182	VGF	ENSG00000128564		

Interactors (18)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
AGT	P01019	Q8N0U8	CDCA7	Q9BWT1	P42858
CHRDL2	Q6WN34-2	O75093	DLGAP3	O95886	Q08379
JRK	O75564-2	Q96MT3	KIAA1644	Q3SXP7	Q92504
LEF1	Q9UJU2	P35222	MYBPHL	A2RUH7	Q15078
ORM1	P02763	P05121	PCK2	Q16822	Q9BXC9
PID1	Q7Z2X4	Q8N9N5	SIX3	O95343	Q92570
SMOC1	Q9H4F8-2	Q92570	TAF10	Q12962	Q92831
TFF1	P04155	Q6UX41	TMEM176B	Q3YBM2	P17252
VGF	EBI-10042615	P05412			
Input	ChEBI Id	Interacts with	Input	ChEBI Id	Interacts with
PRKG1	P00516-2	17489			

7. Identifiers not found

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

ANKRD26P1	ARVCF	BAI2	CCDC65	DLL3	FIZ1	GAB3	LCN10
LOC100506134	LOC389332	RBM24	SHISA7	SUGT1P3	TOR2A	TSIX	