



Pathway Analysis Report

Multi-sample analysis

This report contains the pathway analysis results for the submitted sample 'Multi-sample analysis'. Analysis was performed against Reactome version 77 on 17/07/2021. The web link to these results is:

[https://www.reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMTA3MTcxNTQ4MDZfMzM1OTQ%
3D](https://www.reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMTA3MTcxNTQ4MDZfMzM1OTQ%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:

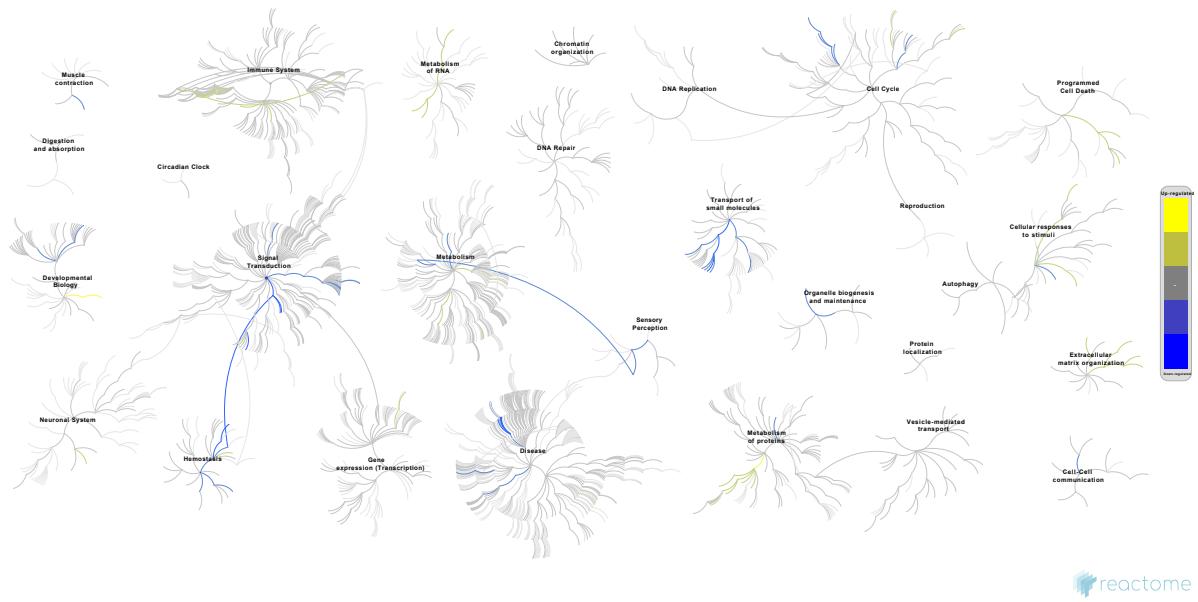
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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 a gene set analysis method: A method that tests for differential expression directly on the pathway level. Camera uses linear models for the differential expression analysis. This has the advantage that it can take confounding parameters (for example the patient) into consideration. ↗
- 602 out of 651 identifiers in the sample were found in Reactome, where 1376 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent. ↗
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAyMTA3MTcxNTQ4MDZfMzM1OTQ%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
Plasma lipoprotein remodeling	13 / 54	0.004	3.67e-05	0.022	17 / 30	0.002
Platelet degranulation	64 / 139	0.01	1.03e-04	0.022	8 / 11	8.14e-04
Response to elevated platelet cytosolic Ca2+	64 / 146	0.01	1.03e-04	0.022	8 / 14	0.001
Signaling by RAF1 mutants	12 / 49	0.003	1.36e-04	0.022	6 / 7	5.18e-04
Signaling by high-kinase activity BRAF mutants	13 / 44	0.003	1.41e-04	0.022	4 / 6	4.44e-04
MAP2K and MAPK activation	13 / 49	0.003	1.41e-04	0.022	8 / 12	8.88e-04
HDL remodeling	9 / 24	0.002	1.47e-04	0.022	11 / 13	9.62e-04
p130Cas linkage to MAPK signaling for integrins	9 / 22	0.002	1.53e-04	0.022	3 / 3	2.22e-04
Keratinization	8 / 226	0.016	1.79e-04	0.022	17 / 34	0.003
Formation of the cornified envelope	8 / 138	0.009	1.79e-04	0.022	10 / 27	0.002
Translation	16 / 339	0.023	1.85e-04	0.022	31 / 99	0.007
Signaling by moderate kinase activity BRAF mutants	14 / 54	0.004	2.43e-04	0.022	7 / 7	5.18e-04
Signaling downstream of RAS mutants	14 / 54	0.004	2.43e-04	0.022	7 / 7	5.18e-04
Paradoxical activation of RAF signaling by kinase inactive BRAF	14 / 54	0.004	2.43e-04	0.022	7 / 7	5.18e-04
Signaling by RAS mutants	14 / 54	0.004	2.43e-04	0.022	7 / 9	6.66e-04
Plasma lipoprotein assembly, remodeling, and clearance	20 / 98	0.007	4.16e-04	0.036	60 / 84	0.006
GRB2:SOS provides linkage to MAPK signaling for Integrins	10 / 20	0.001	5.08e-04	0.039	2 / 2	1.48e-04
Integrin signaling	10 / 39	0.003	5.08e-04	0.039	24 / 24	0.002
Signaling by BRAF and RAF1 fusions	14 / 73	0.005	0.001	0.073	5 / 5	3.70e-04
Chylomicron assembly	8 / 14	9.63e-04	0.001	0.073	5 / 5	3.70e-04
Oncogenic MAPK signaling	15 / 93	0.006	0.001	0.095	38 / 46	0.003
Chylomicron remodeling	7 / 17	0.001	0.002	0.095	3 / 3	2.22e-04
NR1H3 & NR1H2 regulate gene expression linked to cholesterol transport and efflux	7 / 66	0.005	0.002	0.095	6 / 40	0.003
NR1H2 and NR1H3-mediated signaling	7 / 85	0.006	0.002	0.095	6 / 60	0.004

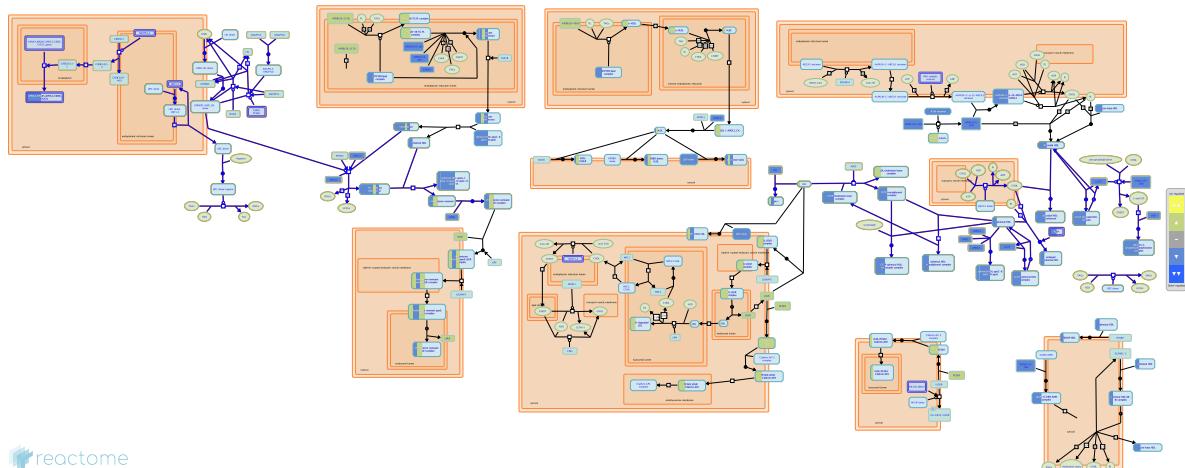
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Platelet activation, signaling and aggregation	76 / 291	0.02	0.002	0.095	72 / 116	0.009

* 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. Plasma lipoprotein remodeling (R-HSA-8963899)



As chylomicrons circulate in the body, they acquire molecules of apolipoproteins C and E, and through interaction with endothelial lipases can lose a large fraction of their triacylglycerol. These changes convert them to chylomicron remnants which bind to LDL receptors, primarily on the surfaces of liver cells, clearing them from the circulation. This whole sequence of events is rapid: the normal lifespan of a chylomicron is 30 - 60 minutes (Redgrave 2004).

As they circulate, VLDL are acted on by lipoprotein lipases on the endothelial surfaces of blood vessels, liberating fatty acids and glycerol to be taken up by tissues and converting the VLDL first to intermediate density lipoproteins (IDL) and then to low density lipoproteins (LDL) (Gibbons et al. 2004).

HDL remodeling includes the conversion of HDL-associated cholesterol to cholesterol esters (remodeling of spherical HDL), the transfer of HDL lipids to target cells with the regeneration of pre-beta HDL (lipid-poor apoA-I), and the conversion of pre-beta HDL to discoidal HDL (Rye et al. 1999).

References

- Gibbons GF, Wiggins D, Brown AM & Hebbachi AM (2004). Synthesis and function of hepatic very-low-density lipoprotein. Biochem. Soc. Trans., 32, 59-64. [🔗](#)
- Redgrave TG (2004). Chylomicron metabolism. Biochem. Soc. Trans., 32, 79-82. [🔗](#)
- Rye KA, Clay MA & Barter PJ (1999). Remodelling of high density lipoproteins by plasma factors. Atherosclerosis, 145, 227-38. [🔗](#)

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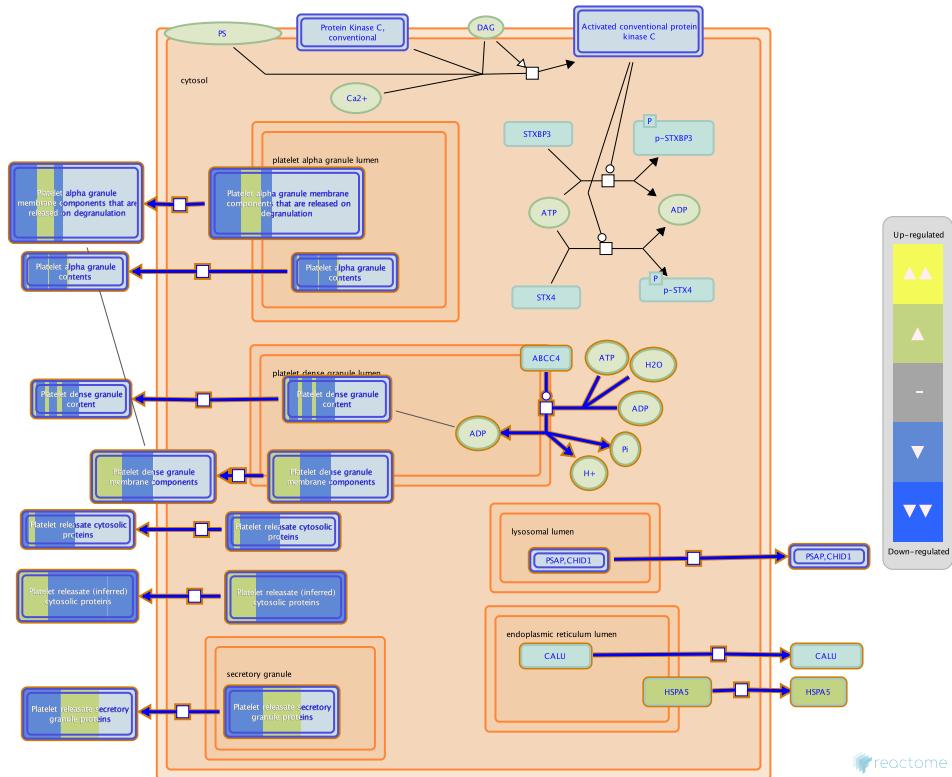
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2006-02-20	Edited	D'Eustachio P
2006-02-20	Authored	D'Eustachio P

Date	Action	Author
2016-01-27	Reviewed	Jassal B
2017-02-14	Created	D'Eustachio P
2021-05-22	Modified	Shorser S

Entities found in this pathway (12)

Input	UniProt Id	Camera_ms...
P02652	P02652	-1.00e+00
P04114	P04114	1
P04180	P04180	-1.00e+00
P02655	P02655	-1.00e+00
P06727	P06727	-1.00e+00
P08519	P08519	-1.00e+00
P02656	P02656	-1.00e+00
P02647	P02647	-1.00e+00
P02768	P02768	-1.00e+00
P11597	P11597	-1.00e+00
P02649	P02649	-1.00e+00
P55058	P55058-1, P55058-2	-1.00e+00

2. 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

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

Coppinger JA, Cagney G, Toomey S, Kislinger T, Belton O, McRedmond JP, ... Maguire PB (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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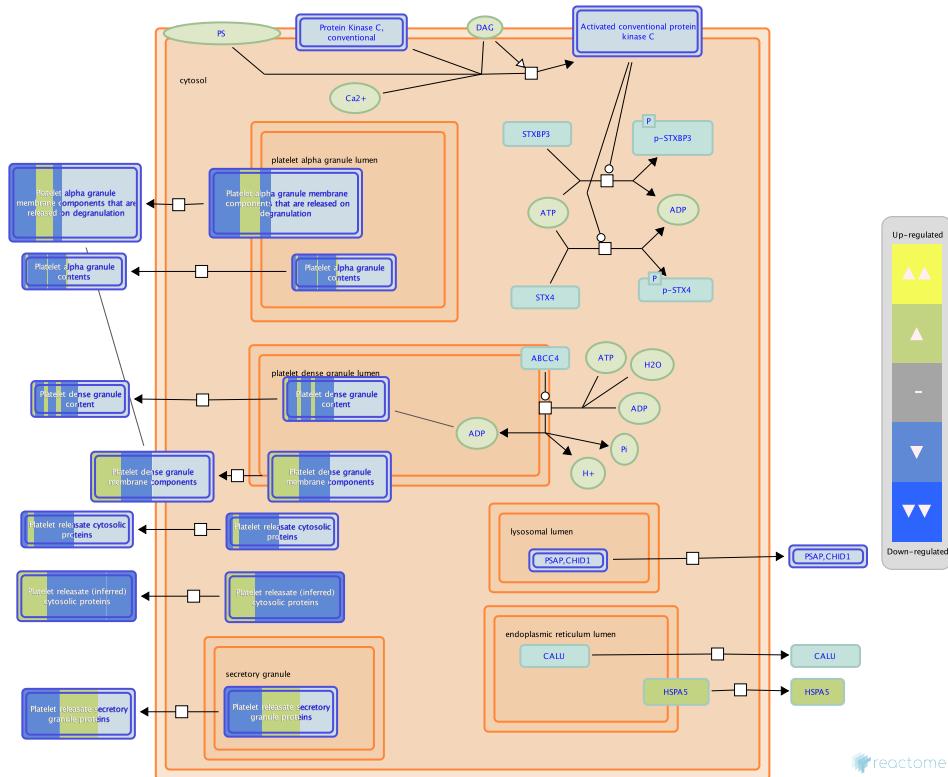
Date	Action	Author
2004-09-25	Created	Farndale R, Pace NP, de Bono B
2021-05-22	Modified	Shorser S

Entities found in this pathway (64)

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P07737	P07737	1
Q13103	Q13103	1
P10909	P10909	-1.00e+00
Q9Y490	Q9Y490	-1.00e+00
Q01518	Q01518	-1.00e+00
Q92520	Q92520	-1.00e+00
P05155	P05155	-1.00e+00
Q99969	Q99969	-1.00e+00
P02647	P02647	-1.00e+00
P02768	P02768	-1.00e+00
P00746	P00746	1
P16284	P16284	1
P00747	P00747	-1.00e+00
Q6YHK3	Q6YHK3	1
P08514	P08514	-1.00e+00
P12814	P12814	-1.00e+00
P02775	P02775	-1.00e+00
P04075	P04075	1
P07225	P07225	-1.00e+00
P05121	P05121	-1.00e+00
P01042	P01042	-1.00e+00
P04275	P04275	-1.00e+00
P49908	P49908	1
P01009	P01009	-1.00e+00
P12259	P12259	-1.00e+00
Q06033	Q06033	-1.00e+00
O75083	O75083	-1.00e+00
P01011	P01011	-1.00e+00
P29622	P29622	-1.00e+00
P00441	P00441	-1.00e+00
P07996	P07996	-1.00e+00
P02787	P02787	1
P00488	P00488	-1.00e+00
Q13201	Q13201	-1.00e+00
P01137	P01137	-1.00e+00
P08567	P08567	-1.00e+00
P05452	P05452	-1.00e+00
P13473	P13473	1
P18206	P18206	-1.00e+00
O00391	O00391	-1.00e+00
P23528	P23528	-1.00e+00

Input	UniProt Id	Camera_ms...
P16109	P16109	-1.00e+00
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P37802	P37802	-1.00e+00
Q08380	Q08380	-1.00e+00
Q86UX7	Q86UX7	-1.00e+00
Q14624	Q14624	-1.00e+00
P01023	P01023	-1.00e+00
Q9NXH8	Q9NXH8	1
P05106	P05106	-1.00e+00
P00451	P00451	-1.00e+00
P02675	P02675	-1.00e+00
P02751	P02751	-1.00e+00
P02679	P02679	-1.00e+00
P62937	P62937	-1.00e+00
P04217	P04217	-1.00e+00
P21333	P21333	-1.00e+00
P02671	P02671	-1.00e+00
P08697	P08697	-1.00e+00
O94919	O94919	1
Q96C24	Q96C24	-1.00e+00
P11021	P11021	1

3. Response to elevated platelet cytosolic Ca²⁺ (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 PIP₂ to form 1,2 Diacylglycerol (DAG) and 1,4,5-inositol trisphosphate (IP₃). IP₃ opens Ca²⁺ channels in the platelet dense tubular system, raising intracellular Ca²⁺ 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 Ca²⁺. Platelets contain several PKC isoforms that can be activated by DAG and/or Ca²⁺ (Chang 1997).

References

Walker TR & Watson SP (1993). Synergy between Ca²⁺ 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
2021-05-22	Modified	Shorser S

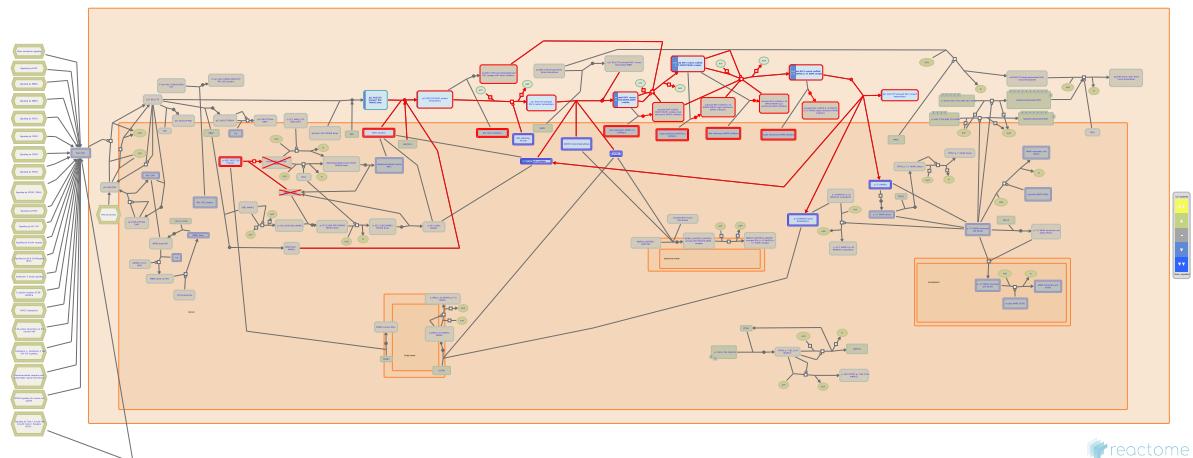
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Q16610	Q16610	-1.00e+00

Input	UniProt Id	Camera_ms...
P07737	P07737	1
Q13103	Q13103	1
P10909	P10909	-1.00e+00
Q9Y490	Q9Y490	-1.00e+00
Q01518	Q01518	-1.00e+00
Q92520	Q92520	-1.00e+00
P05155	P05155	-1.00e+00
Q99969	Q99969	-1.00e+00
P02647	P02647	-1.00e+00
P02768	P02768	-1.00e+00
P00746	P00746	1
P16284	P16284	1
P00747	P00747	-1.00e+00
Q6YHK3	Q6YHK3	1
P08514	P08514	-1.00e+00
P12814	P12814	-1.00e+00
P02775	P02775	-1.00e+00
P04075	P04075	1
P07225	P07225	-1.00e+00
P05121	P05121	-1.00e+00
P01042	P01042	-1.00e+00
P04275	P04275	-1.00e+00
P49908	P49908	1
P01009	P01009	-1.00e+00
P12259	P12259	-1.00e+00
Q06033	Q06033	-1.00e+00
O75083	O75083	-1.00e+00
P01011	P01011	-1.00e+00
P29622	P29622	-1.00e+00
P00441	P00441	-1.00e+00
P07996	P07996	-1.00e+00
P02787	P02787	1
P00488	P00488	-1.00e+00
Q13201	Q13201	-1.00e+00
P01137	P01137	-1.00e+00
P08567	P08567	-1.00e+00
P05452	P05452	-1.00e+00
P13473	P13473	1
P18206	P18206	-1.00e+00
O00391	O00391	-1.00e+00
P23528	P23528	-1.00e+00
P16109	P16109	-1.00e+00
P02749	P02749	1
P37802	P37802	-1.00e+00
Q08380	Q08380	-1.00e+00
Q86UX7	Q86UX7	-1.00e+00
Q14624	Q14624	-1.00e+00
P01023	P01023	-1.00e+00
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P05106	P05106	-1.00e+00

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P62937	P62937	-1.00e+00
P04217	P04217	-1.00e+00
P21333	P21333	-1.00e+00
P02671	P02671	-1.00e+00
P08697	P08697	-1.00e+00
O94919	O94919	1
Q96C24	Q96C24	-1.00e+00
P11021	P11021	1

4. Signaling by RAF1 mutants (R-HSA-9656223)



Diseases: Noonan syndrome, cancer, Costello syndrome, LEOPARD syndrome, hypertrophic cardiomyopathy.

RAF1, also known as CRAF, is mutated in a number of germline RASopathies including Noonan Syndrome, Costello Syndrome and others, and also at low frequency in a number of cancers (reviewed in Rauen, 2013; Samatar and Poulikakos, 2015). Activating mutations cluster around conserved region 2 (CR2) which is required for regulation of the protein and the activation segment in CR3 (reviewed in Rauen, 2013).

References

Rauen KA (2013). The RASopathies. Annu Rev Genomics Hum Genet, 14, 355-69. [\[link\]](#)

Samatar AA & Poulikakos PI (2014). Targeting RAS-ERK signalling in cancer: promises and challenges. Nat Rev Drug Discov, 13, 928-42. [\[link\]](#)

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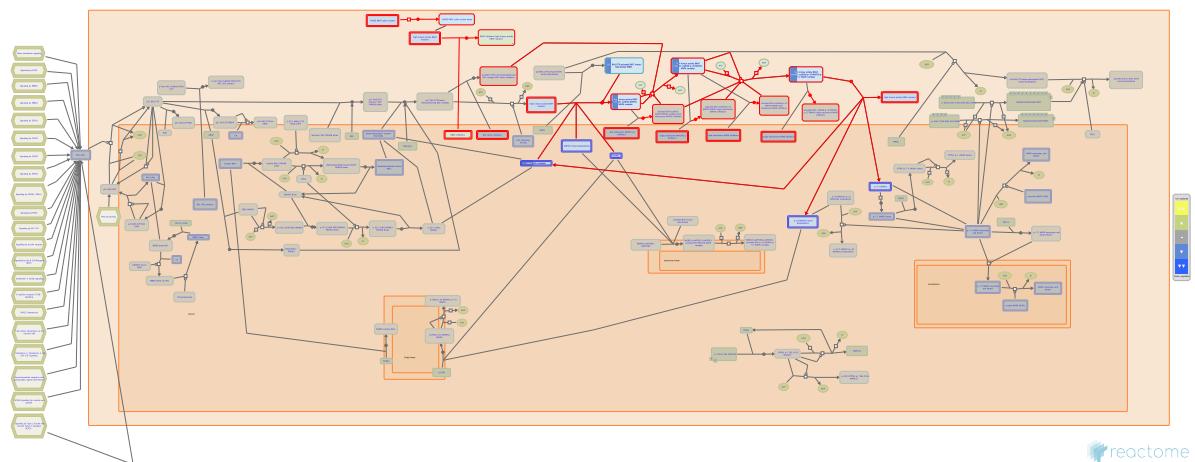
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2019-10-25	Authored	Rothfels K
2020-05-04	Reviewed	Gavathiotis E
2020-05-26	Edited	Rothfels K
2021-05-31	Modified	Shorser S

Entities found in this pathway (12)

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P08514	P08514	-1.00e+00
P02751	P02751	-1.00e+00
P18206	P18206	-1.00e+00
P60709	P60709	-1.00e+00
P31946	P31946	-1.00e+00
P02679	P02679	-1.00e+00

Input	UniProt Id	Camera_ms...
Q9Y490	Q9Y490	-1.00e+00
P02671	P02671	-1.00e+00
P61224	P61224	-1.00e+00
P04275	P04275	-1.00e+00

5. Signaling by high-kinase activity BRAF mutants (R-HSA-6802948)



Diseases: cancer.

BRAF is mutated in about 8% of human cancers, with high prevalence in hairy cell leukemia, melanoma, papillary thyroid and ovarian carcinomas, colorectal cancer and a variety of other tumors (Davies et al, 2002; reviewed in Samatar and Poulikakos, 2014). Most BRAF mutations fall in the activation loop region of the kinase or the adjacent glycine rich region. These mutations promote increased kinase activity either by mimicking the effects of activation loop phosphorylations or by promoting the active conformation of the enzyme (Davies et al, 2002; Wan et al, 2004). Roughly 90% of BRAF mutants are represented by the single missense mutation BRAF V600E (Davies et al, 2002; Wan et al, 2004). Other highly active kinase mutants of BRAF include BRAF G469A and BRAF T599dup. G469 is in the glycine rich region of the kinase domain which plays a role in orienting ATP for catalysis, while T599 is one of the two conserved regulatory phosphorylation sites of the activation loop. Each of these mutants has highly enhanced basal kinase activities, phosphorylates MEK and ERK in vitro and in vivo and is transforming when expressed in vivo (Davies et al, 2002; Wan et al, 2004; Eisenhardt et al, 2011). Further functional characterization shows that these highly active mutants are largely resistant to disruption of the BRAF dimer interface, suggesting that they are able to act as monomers (Roring et al, 2012; Brummer et al, 2006; Freeman et al, 2013; Garnett et al, 2005). Activating BRAF mutations occur for the most part independently of RAS activating mutations, and RAS activity levels are generally low in BRAF mutant cells. Moreover, the kinase activity of these mutants is only slightly elevated by coexpression of G12V KRAS, and biological activity of the highly active BRAF mutants is independent of RAS binding (Brummer et al, 2006; Wan et al, 2004; Davies et al, 2002; Garnett et al, 2005). Although BRAF V600E is inhibited by RAF inhibitors such as vemurafenib, resistance frequently develops, in some cases mediated by the expression of a splice variant that lacks the RAS binding domain and shows elevated dimerization compared to the full length V600E mutant (Poulikakos et al, 2011; reviewed in Lito et al, 2013).

References

- Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, ... Futreal PA (2002). Mutations of the BRAF gene in human cancer. *Nature*, 417, 949-54. [🔗](#)
- Samatar AA & Poulikakos PI (2014). Targeting RAS-ERK signalling in cancer: promises and challenges. *Nat Rev Drug Discov*, 13, 928-42. [🔗](#)

Wan PT, Garnett MJ, Roe SM, Lee S, Niculescu-Duvaz D, Good VM, ... Marais R (2004). Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. *Cell*, 116, 855-67. 

Eisenhardt AE, Olbrich H, Röring M, Janzarik W, Anh TN, Cin H, ... Brummer T (2011). Functional characterization of a BRAF insertion mutant associated with pilocytic astrocytoma. *Int. J. Cancer*, 129, 2297-303. 

Röring M, Herr R, Fiala GJ, Heilmann K, Braun S, Eisenhardt AE, ... Brummer T (2012). Distinct requirement for an intact dimer interface in wild-type, V600E and kinase-dead B-Raf signalling. *EMBO J.*, 31, 2629-47. 

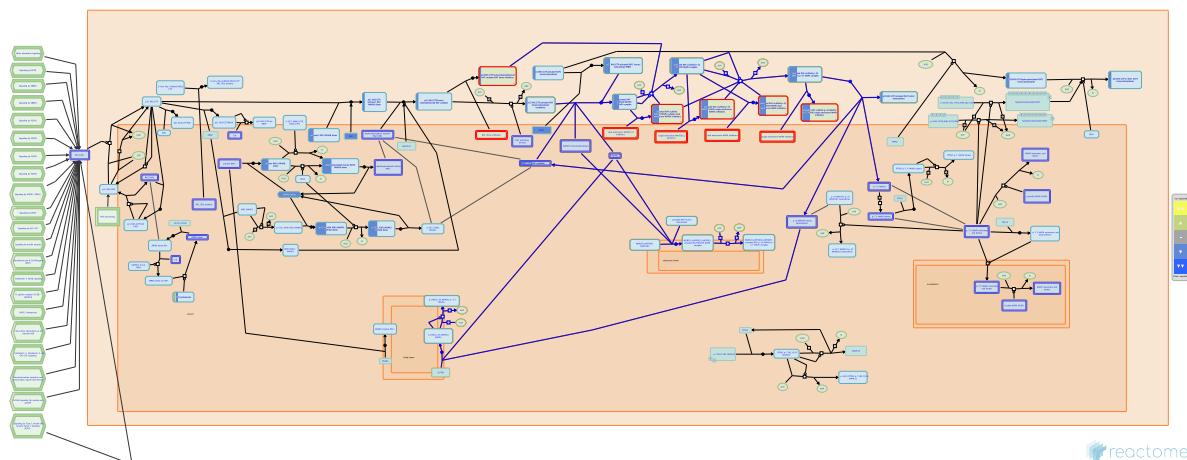
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2015-08-10	Authored	Rothfels K
2015-10-02	Created	Rothfels K
2016-08-05	Reviewed	Stephens RM
2021-05-31	Modified	Shorser S

Entities found in this pathway (13)

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P60709	P60709	-1.00e+00
P31946	P31946	-1.00e+00
P02679	P02679	-1.00e+00
Q9Y490	Q9Y490	-1.00e+00
P02671	P02671	-1.00e+00
P61224	P61224	-1.00e+00
P04275	P04275	-1.00e+00
P18206	P18206	-1.00e+00
P30086	P30086	-1.00e+00

6. MAP2K and MAPK activation (R-HSA-5674135)



Activated RAF proteins are restricted substrate kinases whose primary downstream targets are the two MAP2K proteins, MAPK2K1 and MAP2K2 (also known as MEK1 and MEK2) (reviewed in Roskoski, 2010, Roskoski, 2012a). Phosphorylation of the MAP2K activation loop primes them to phosphorylate the primary effector of the activated MAPK pathway, the two MAPK proteins MAPK3 and MAPK1 (also known as ERK1 and 2). Unlike their upstream counterparts, MAPK3 and MAPK1 catalyze the phosphorylation of hundreds of cytoplasmic and nuclear targets including transcription factors and regulatory molecules (reviewed in Roskoski, 2012b). Activation of MAP2K and MAPK proteins downstream of activated RAF generally occurs in the context of a higher order scaffolding complex that regulates the specificity and localization of the pathway (reviewed in Brown and Sacks, 2009; Matallanas et al, 2011).

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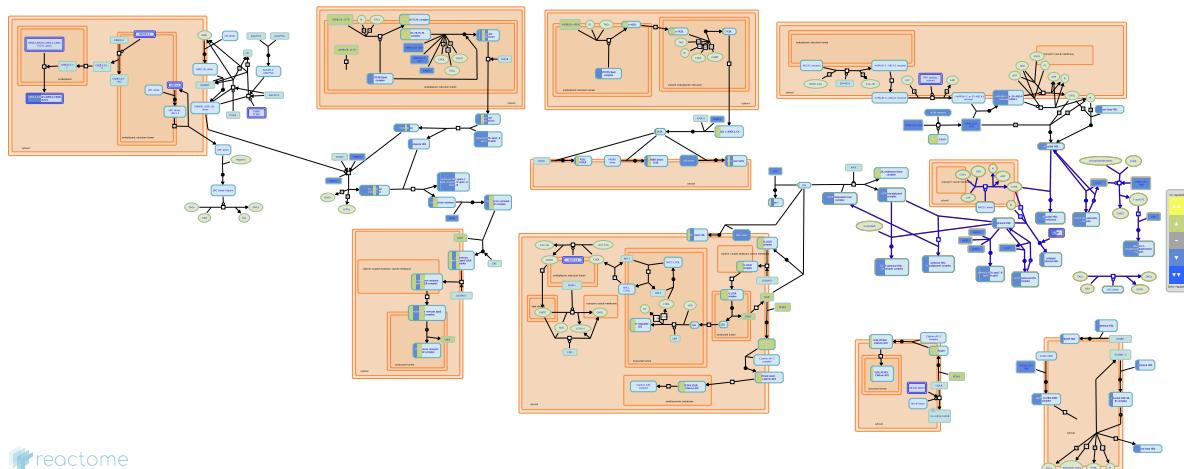
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2015-02-12	Edited	Rothfels K
2015-04-29	Reviewed	Roskoski R Jr
2021-05-31	Modified	Shorser S

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P61224	P61224	-1.00e+00
P04275	P04275	-1.00e+00
P18206	P18206	-1.00e+00
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7. HDL remodeling (R-HSA-8964058)



HDL (high-density lipoprotein) particles play a central role in the reverse transport of cholesterol, the process by which cholesterol in tissues other than the liver is returned to the liver for conversion to bile salts and excretion from the body and provided to tissues such as the adrenals and gonads for steroid hormone synthesis (Tall et al. 2008).

ABCG1 mediates the movement of intracellular cholesterol to the extracellular face of the plasma membrane where it is accessible to circulating HDL (Vaughan & Oram 2005). Spherical (mature) HDL particles can acquire additional molecules of free cholesterol (CHOL) and phospholipid (PL) from cell membranes.

At the HDL surface, LCAT (lecithin-cholesterol acyltransferase) associates strongly with HDL particles and, activated by apoA-I, catalyzes the reaction of cholesterol and phosphatidylcholine to yield cholesterol esterified with a long-chain fatty acid and 2-lysophosphatidylcholine. The hydrophobic cholesterol ester reaction product is strongly associated with the HDL particle while the 2-lysophosphatidylcholine product is released. Torcetrapib associates with a molecule of CETP and a spherical HDL particle to form a stable complex, thus trapping CETP and inhibiting CETP-mediated lipid transfer between HDL and LDL (Clark et al. 2006).

Spherical HDL particles can bind apoC-II, apoC-III and apoE proteins.

References

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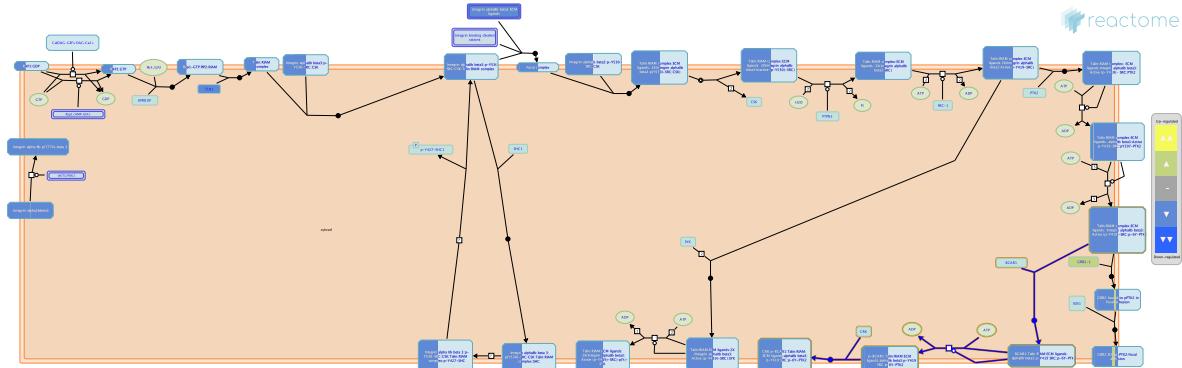
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Date	Action	Author
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2017-02-15	Created	D'Eustachio P
2021-05-31	Modified	Shorser S

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P11597	P11597	-1.00e+00
P02649	P02649	-1.00e+00
P55058	P55058-1, P55058-2	-1.00e+00

8. p130Cas linkage to MAPK signaling for integrins (R-HSA-372708)



Integrin signaling is linked to the MAP kinase pathway by recruiting p130cas and Crk to the FAK/Src activation complex.

References

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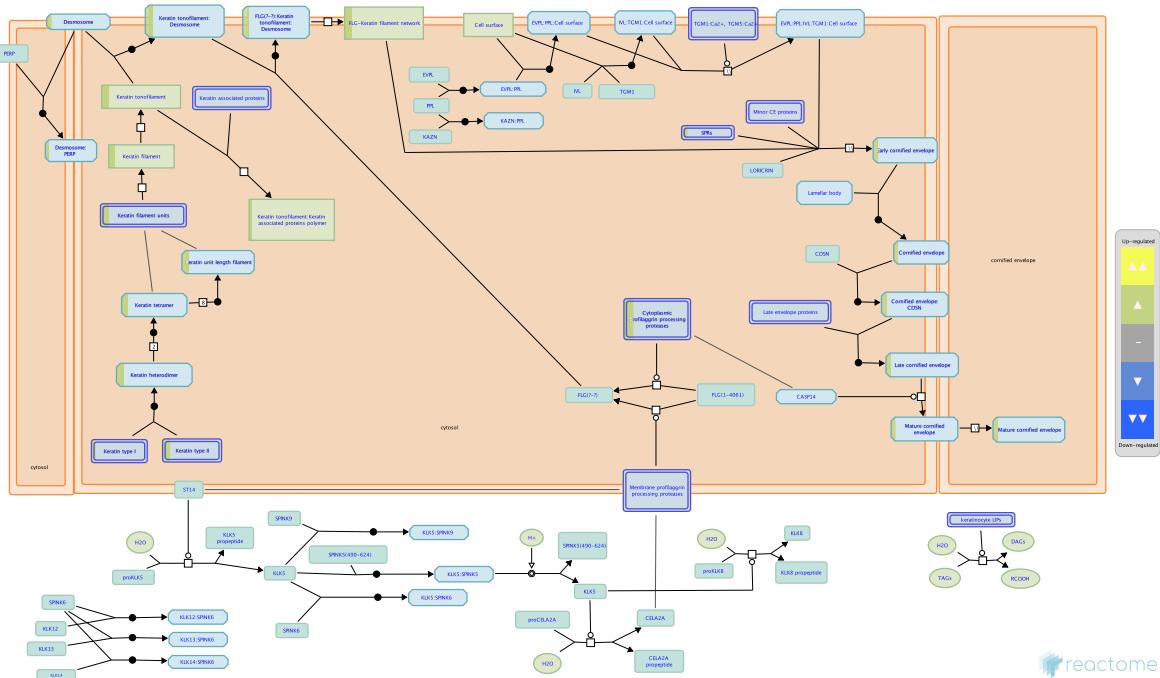
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2008-06-27	Created	Garapati P V
2008-09-16	Reviewed	Shattil SJ
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P61224	P61224	-1.00e+00
P04275	P04275	-1.00e+00

9. Keratinization (R-HSA-6805567)



Keratins are the major structural protein of vertebrate epidermis, constituting up to 85% of a fully differentiated keratinocyte (Fuchs 1995). Keratins belong to a superfamily of intermediate filament (IF) proteins that form alpha-helical coiled-coil dimers, which associate laterally and end-to-end to form approximately 10 nm diameter filaments. Keratin filaments are heteropolymeric, formed from equal amounts of acidic type I and basic /neutral type 2 keratins. Humans have 54 keratin genes (Schweitzer et al. 2006). They have highly specific expression patterns, related to the epithelial type and stage of differentiation. Roughly half of human keratins are specific to hair follicles (Langbein & Schweizer 2005). Keratin filaments bundle into tonofilaments that span the cytoplasm and bind to desmosomes and other cell membrane structures (Waschke 2008). This reflects their primary function, maintaining the mechanical stability of individual cells and epithelial tissues (Moll et al. 2008).

References

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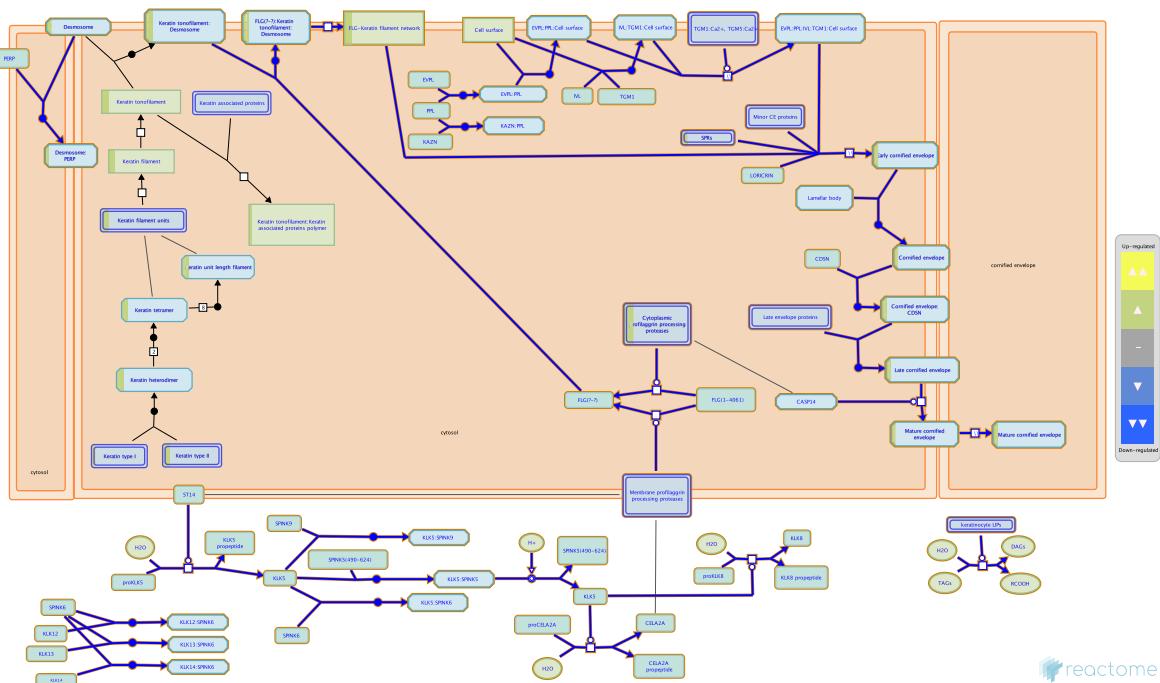
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2021-05-22	Modified	Shorser S

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P19013	P19013	1
P07384	P07384	1
P04264	P04264	1

10. Formation of the cornified envelope ([R-HSA-6809371](#))



As keratinocytes progress towards the upper epidermis, they undergo a unique process of cell death termed cornification (Eckhart et al. 2013). This involves the crosslinking of keratinocyte proteins such as loricrin and involucrin by transglutaminases and the breakdown of the nucleus and other organelles by intracellular and secreted proteases (Eckhart et al. 2000, Denecker et al. 2008). This process is strictly regulated by the Ca²⁺ concentration gradient in the epidermis (Esholtz et al. 2014). Loricrin and involucrin are encoded in 'Epidermal Differentiation Complex' linked to a large number of genes encoding nonredundant components of the CE (Kypriotou et al. 2012, Niehues et al. 2016). Keratinocytes produce specialized proteins and lipids which are used to construct the cornified envelope (CE), a heavily crosslinked submembranous layer that confers rigidity to the upper epidermis, allows keratin filaments to attach to any location in the cell membrane (Kirfel et al. 2003) and acts as a water-impermeable barrier. The CE has two functional parts: covalently cross-linked proteins (10 nm thick) that comprise the backbone of the envelope and covalently linked lipids (5 nm thick) that coat the exterior (Eckert et al. 2005). Desmosomal components are crosslinked to the CE to form corneodesmosomes, which bind cornified cells together (Ishida-Yamamoto et al. 2011). Mature terminally differentiated cornified cells consist mostly of keratin filaments covalently attached to the CE embedded in lipid lamellae (Kalinin et al. 2002). The exact composition of the cornified envelope varies between epithelia (Steinert et al. 1998); the relative amino-acid composition of the proteins used may determine differential mechanical properties (Kartasova et al. 1996).

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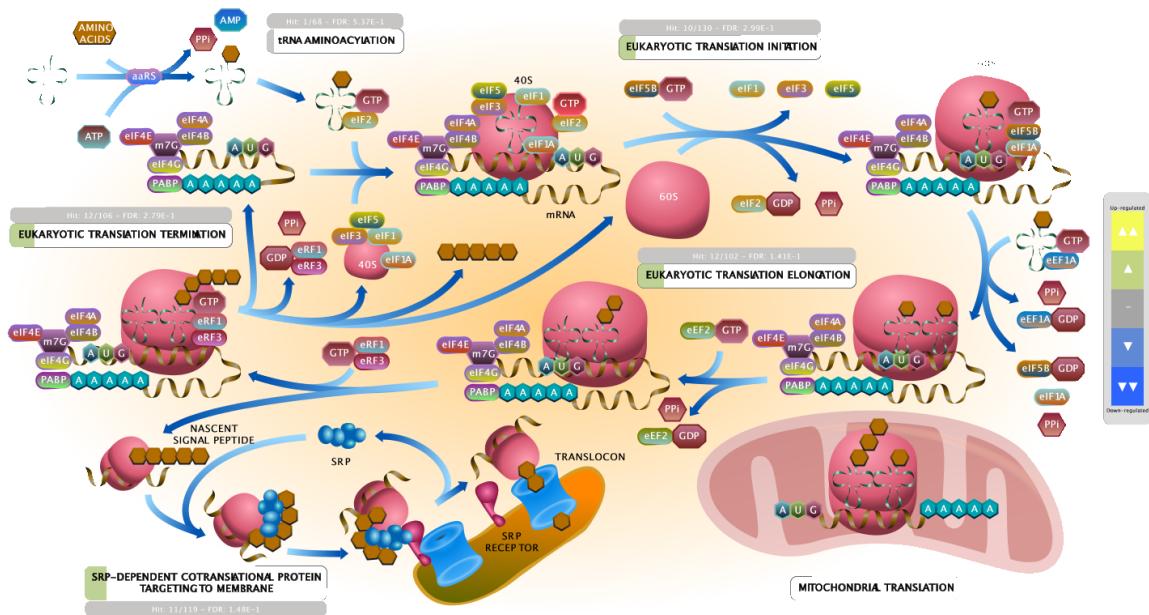
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2016-08-12	Reviewed	Blumenberg M
2021-05-22	Modified	Shorser S

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P19013	P19013	1
P07384	P07384	1
P04264	P04264	1

11. Translation (R-HSA-72766)



Protein synthesis is accomplished through the process of translation of an mRNA sequence into a polypeptide chain. This process can be divided into three distinct stages: initiation, elongation and termination. During the initiation phase, the two subunits of the ribosome are brought together to the translation start site on the mRNA where the polypeptide chain is to begin. Extension of the polypeptide chain occurs when a specific aminoacyl-tRNA, as determined by the template mRNA, binds an elongating ribosome. The protein chain is released from the ribosome when any one of three stop codons in the relevant reading frame on the mRNA is reached. Individual reactions at each one of these stages are catalyzed by a number of initiation, elongation and release factors, respectively.

Proteins destined for the endoplasmic reticulum (ER) contain a short sequence of hydrophobic amino acid residues (approximately 20 residues) at their N-termini. Upon protrusion of the signal sequence from the translating ribosome, the signal sequence is bound by the cytosolic signal recognition particle (SRP), translation is temporarily halted, and the SRP:nascent peptide:ribosome complex then docks with a SRP receptor complex on the ER membrane. There the nascent peptide:ribosome complex is transferred from the SRP complex to a translocon complex embedded in the ER membrane and reoriented so that the nascent polypeptide protrudes through a pore in the translocon into the ER lumen. Translation now resumes, the signal peptide is cleaved from the polypeptide by signal peptidase as the signal peptide emerges into the ER, and elongation proceeds with the growing polypeptide oriented into the ER lumen.

The 13 proteins encoded by the mitochondrial genome are translated within the mitochondrion by mitochondrial ribosomes (mitoribosomes) at the matrix face of the inner mitochondrial membrane. Mitochondrial translation reflects both the bacterial origin of the organelle and subsequent divergent evolution during symbiosis. Mitoribosomes have shorter rRNAs, mitochondria-specific proteins, and rearranged protein positions. Mitochondrial mRNAs have either no untranslated leaders or very short untranslated leaders of 1-3 nucleotides. Translation begins with N-formylmethionine, as in bacteria, and continues with cycles of aminoacyl-tRNA:TUFM:GTP binding, GTP hydrolysis and dissociation of TUFM:GDP. All 13 proteins encoded by the mitochondrial genome are hydrophobic inner membrane proteins which are inserted cotranslationally into the membrane by an interaction with OXA1L. Translation is terminated when MTRF1L:GTP recognizes a UAA or UAG codon at the A-site of the mitoribosome. The translated polypeptide is released and MRRF and GFM2:GTP act to dissociate the 55S ribosome into 28S and 39S subunits.

References

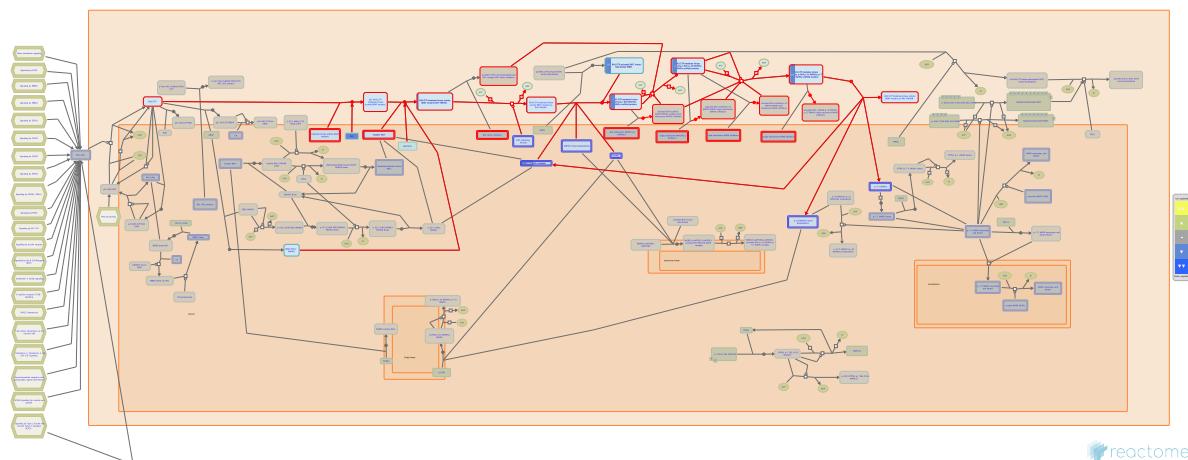
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2004-09-08	Revised	Kinzy TG
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2013-11-25	Edited	Tello-Ruiz MK, Matthews L, Gopinathrao G, Gillespie ME
2021-05-18	Reviewed	Hinnebusch AG, Sonenberg N, Hershey JW
2021-05-22	Modified	Shorser S

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P36578	P36578	1
P13798	P13798	1
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12. Signaling by moderate kinase activity BRAF mutants (R-HSA-6802946)



reactome

Diseases: cancer.

In addition to the highly prevalent and activating V600E BRAF mutations, numerous moderately activating and less common mutations have also been identified in human cancers (Forbes et al, 2015). Unlike the case for their highly activating counterparts, signaling through these mutant versions of BRAF depends both upon RAS binding and RAF dimerization (Wan et al, 2004; Freeman et al, 2013; Roring et al, 2012; reviewed in Lito et al, 2013; Lavoie and Therrien, 2015)

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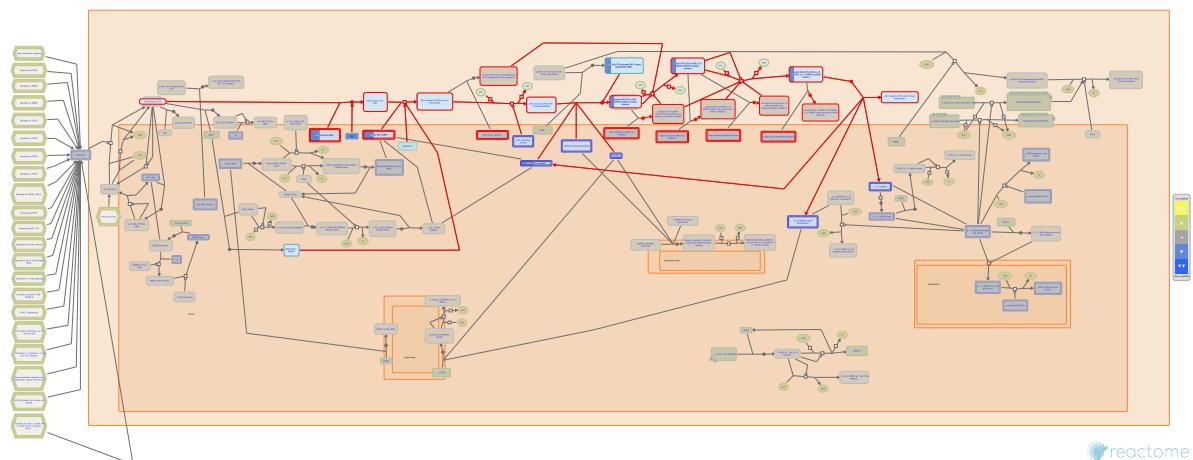
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2021-05-31	Modified	Shorser S

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P02671	P02671	-1.00e+00
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P04275	P04275	-1.00e+00
P18206	P18206	-1.00e+00
P30086	P30086	-1.00e+00
P35232	P35232	-1.00e+00

13. Signaling downstream of RAS mutants (R-HSA-9649948)



Diseases: cancer.

Disease-causing mutations in RAS favour the active RAS:GTP bound form and yield constitutively active forms of the protein (reviewed in Prior et al, 2011; Maertens and Cichowski, 2014). Mutations in RAS contribute to cellular proliferation, transformation and survival by activating the MAPK signaling pathway, the AKT pathway and the RAL GDS pathway, among others (reviewed in Stephen et al, 2014; Pylayeva-Gupta et al, 2011)

References

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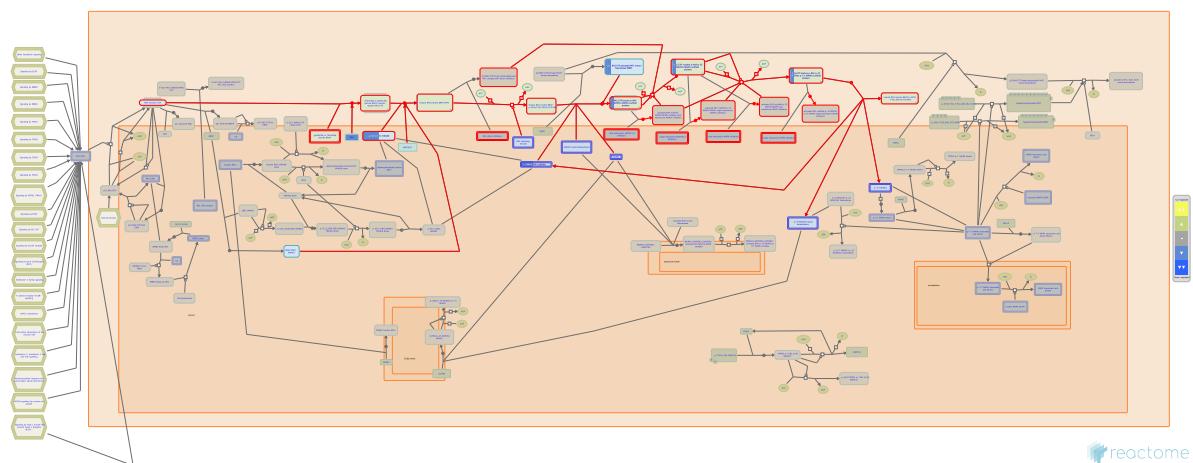
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P35232	P35232	-1.00e+00

14. Paradoxical activation of RAF signaling by kinase inactive BRAF (R-HSA-6802955)



Diseases: cancer.

While BRAF-specific inhibitors inhibit MAPK/ERK activation in the presence of the BRAF V600E mutant, paradoxical activation of ERK signaling has been observed after treatment of cells with inhibitor in the presence of WT BRAF (Wan et al, 2004; Garnett et al, 2005; Heidorn et al, 2010; Hazivassiliou et al, 2010; Poulikakos et al, 2010). This paradoxical ERK activation is also seen in cells expressing kinase-dead or impaired versions of BRAF such as D594V, which occur with low frequency in some cancers (Wan et al, 2004; Heidorn et al, 2010). Unlike BRAF V600E, which occurs exclusively of activating RAS mutations, kinase-impaired versions of BRAF are coincident with RAS mutations in human cancers, and indeed, paradoxical activation of ERK signaling in the presence of inactive BRAF is enhanced in the presence of oncogenic RAS (Heidorn et al, 2010; reviewed in Holderfield et al, 2014). Although the details remain to be worked out, paradoxical ERK activation in the presence of inactive BRAF appears to rely on enhanced dimerization with and transactivation of CRAF (Heidorn et al, 2010; Hazivassiliou et al, 2010; Poulikakos et al, 2010; Roring et al, 2012; Rajakulendran et al, 2009; Holderfield et al, 2013; Freeman et al, 2013; reviewed in Roskoski, 2010; Samatar and Poulikakos, 2014; Lavoie and Therrien, 2015). RAF inhibitors can promote association of RAF-RAS interaction and enhanced RAF dimerization through disruption of intramolecular interactions between the kinase domain and its N-terminal regulatory region. Moreover, specific BRAF inhibitors can only occupy one protomer within the transactivated BRAF dimer due to negative co-operativity leading to paradoxical ERK activation. (Karoulia et al, 2016; Jin et al, 2017, reviewed in Karoulia et al, 2017).

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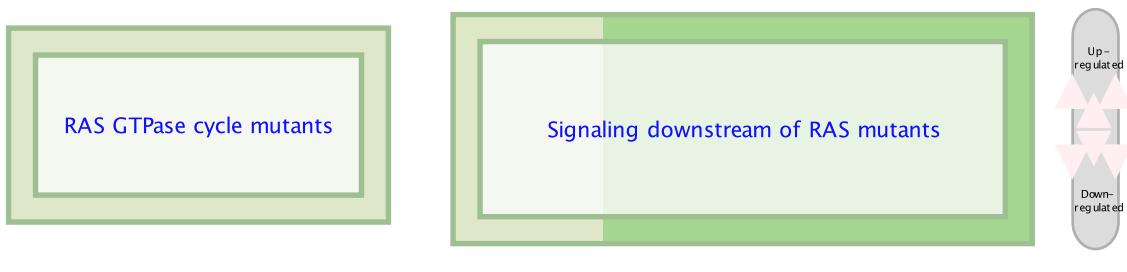
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P61224	P61224	-1.00e+00
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P18206	P18206	-1.00e+00
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15. Signaling by RAS mutants ([R-HSA-6802949](#))



 [reactome](#)

Diseases: cancer, Noonan syndrome.

Members of the RAS gene family were the first oncogenes to be identified, and mutations in RAS are present in ~20-30% of human cancers (reviewed in Prior et al, 2012). Mutations in the KRAS gene are the most prevalent, and are found with high frequency in colorectal cancer, non-small cell lung cancer and pancreatic cancer, among others. The reasons for the lower prevalence of HRAS and NRAS mutations in human cancers are not fully understood, but may reflect gene-specific functions as well as differential codon usage and spatio-temporal regulation (reviewed in Prior et al, 2012; Stephen et al, 2014; Pylayeva-Gupta et al, 2011). Activating RAS mutations contribute to cellular proliferation, transformation and survival by activating the MAPK signaling pathway, the AKT pathway and the RAL GDS pathway, among others (reviewed in Stephen et al, 2014; Pylayeva-Gupta et al, 2011).

Although the frequency and distribution varies between RAS genes and cancer types, the vast majority of activating RAS mutations occur at one of three residues - G12, G13 and Q61. Mutations at these sites favour the RAS:GTP bound form and yield constitutively active versions of the protein (reviewed in Prior et al, 2012).

References

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- Pylayeva-Gupta Y, Grabocka E & Bar-Sagi D (2011). RAS oncogenes: weaving a tumorigenic web. *Nat. Rev. Cancer*, 11, 761-74. [🔗](#)

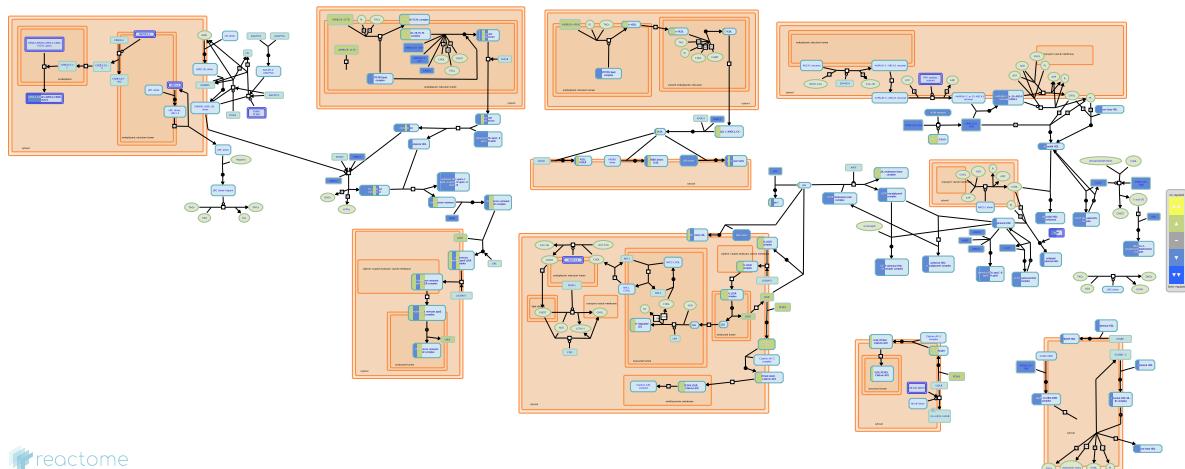
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P08514	P08514	-1.00e+00
P02751	P02751	-1.00e+00
P60709	P60709	-1.00e+00
P31946	P31946	-1.00e+00
P02679	P02679	-1.00e+00
Q9Y490	Q9Y490	-1.00e+00
P02671	P02671	-1.00e+00
P61224	P61224	-1.00e+00
P04275	P04275	-1.00e+00
P18206	P18206	-1.00e+00
P30086	P30086	-1.00e+00
P35232	P35232	-1.00e+00

16. Plasma lipoprotein assembly, remodeling, and clearance (R-HSA-174824)



Because of their hydrophobicity, lipids are found in the extracellular spaces of the human body primarily in the form of lipoprotein complexes. **Chylomicrons** form in the small intestine and transport dietary lipids to other tissues in the body. **Very low density lipoproteins (VLDL)** form in the liver and transport triacylglycerol synthesized there to other tissues of the body. As they circulate, VLDL are acted on by lipoprotein lipases on the endothelial surfaces of blood vessels, liberating fatty acids and glycerol to be taken up by tissues and converting the VLDL first to **intermediate density lipoproteins (IDL)** and then to **low density lipoproteins (LDL)**. IDL and LDL are cleared from the circulation via a specific cell surface receptor, found in the body primarily on the surfaces of liver cells. **High density lipoprotein (HDL)** particles, initially formed primarily by the liver, shuttle several kinds of lipids between tissues and other lipoproteins. Notably, they are responsible for the so-called reverse transport of cholesterol from peripheral tissues to LDL for return to the liver.

Three aspects of lipoprotein function are currently annotated in Reactome: **chylomicron-mediated lipid transport**, **LDL endocytosis and degradation**, and **HDL-mediated lipid transport**, each divided into assembly, remodeling, and clearance subpathways.

References

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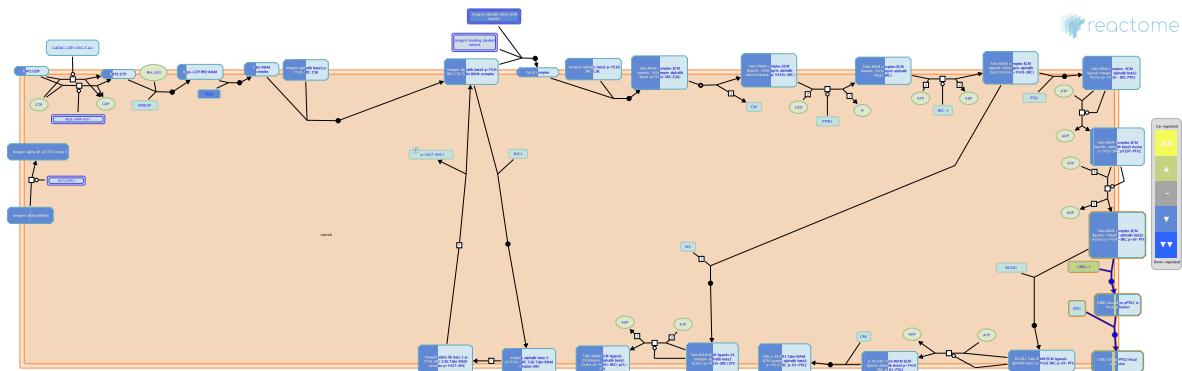
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2016-01-27	Reviewed	Jassal B
2017-02-14	Revised	D'Eustachio P
2021-05-22	Modified	Shorser S

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P08519	P08519	-1.00e+00
P02656	P02656	-1.00e+00
Q86X29	Q86X29	-1.00e+00
P01130	P01130	1
Q8NBP7	Q8NBP7	1
P04180	P04180	-1.00e+00
P02647	P02647	-1.00e+00
P02768	P02768	-1.00e+00
P11597	P11597	-1.00e+00
P02649	P02649	-1.00e+00
P55058	P55058-1, P55058-2	-1.00e+00
P13497	P13497-3	1

17. GRB2:SOS provides linkage to MAPK signaling for Integrins (R-HSA-354194)



Integrin signaling is linked to the MAP kinase pathway by recruiting Grb2 to the FAK1/SRC activation complex.

References

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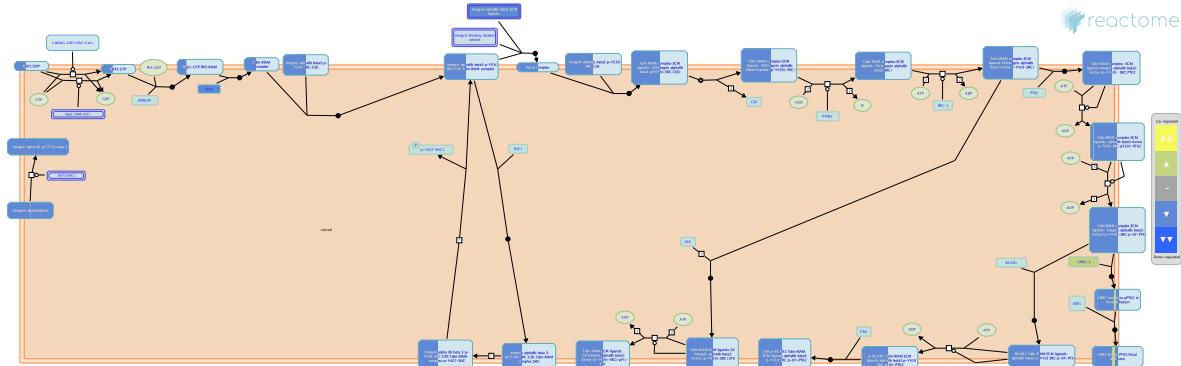
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2008-09-16	Reviewed	Shattil SJ
2021-05-31	Modified	Shorser S

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P62993	P62993-1	1
P02671	P02671	-1.00e+00
P61224	P61224	-1.00e+00
P04275	P04275	-1.00e+00

18. Integrin signaling (R-HSA-354192)



Integrins are a major family of cell surface receptors that modulate cell adhesion, migration, proliferation and survival through interaction with the extracellular matrix (ECM) and the actin cytoskeleton. Integrins are type 1 transmembrane proteins that exist at the cell surface as heterodimers of alpha and beta subunits, of which there are 18 and 8 different isoforms, respectively, in human cells. In addition to their mechanical role in mediating contact between the ECM and the cytoskeleton, integrins also modulate intracellular signaling pathways governing cytoskeletal rearrangements and pro-survival and mitogenic signaling (reviewed in Hehlgans et al, 2007; Harburger and Calderwood, 2009; Ata and Antonescu, 2017).

In this pathway, we describe signaling through integrin alphaIIb beta3 as a representative example.

At the sites of vascular injury bioactive molecules such as thrombin, ADP, collagen, fibrinogen and thrombospondin are generated, secreted or exposed. These stimuli activate platelets, converting the major platelet integrin alphaIIb beta3 from a resting state to an active conformation, in a process termed integrin priming or 'inside-out signalling'. Integrin activation refers to the change required to enhance ligand-binding activity. The activated alphaIIb beta3 interacts with the fibrinogen and links platelets together in an aggregate to form a platelet plug. AlphaIIb beta3 bound to fibrin generates more intracellular signals (outside-in signalling), causing further platelet activation and platelet-plug retraction.

In the resting state the alpha and beta tails are close together. This interaction keeps the membrane proximal regions in a bent conformation that maintains alphaIIb beta3 in a low affinity state.

Integrin alphaIIb beta3 is released from its inactive state by interaction with the protein talin. Talin interacts with the beta3 cytoplasmic domain and disrupts the salt bridge between the alpha and beta chains. This separation in the cytoplasmic regions triggers the conformational change in the extracellular domain that increases its affinity to fibrinogen.

Much of talin exists in an inactive cytosolic pool, and the Rap1 interacting adaptor molecule (RIAM) is implicated in talin activation and translocation to beta3 integrin cytoplasmic domain.

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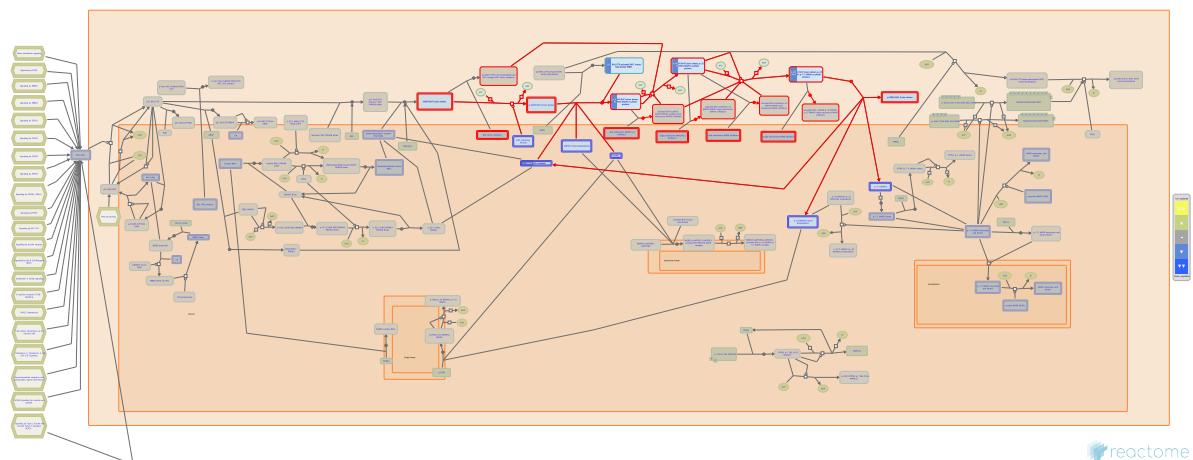
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2021-05-31	Modified	Shorser S

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P62993	P62993-1	1
P02671	P02671	-1.00e+00
P61224	P61224	-1.00e+00
P04275	P04275	-1.00e+00

19. Signaling by BRAF and RAF1 fusions (R-HSA-6802952)



Diseases: cancer.

In addition to the more prevalent point mutations, BRAF and RAF1 are also subject to activation as a result of translocation events that yield truncated or fusion products (Jones et al, 2008; Cin et al, 2011; Palanisamy et al, 2010; Ciampi et al, 2005; Stransky et al, 2014; Hutchinson et al, 2013; Zhang et al, 2013; Lee et al, 2012; Ricarte-Filho et al, 2013; reviewed in Lavoie and Therrien et al, 2015). In general these events put the C-terminal kinase domain of BRAF or RAF1 downstream of an N-terminal sequence provided by a partner protein. This removes the N-terminal region of the RAF protein, relieving the autoinhibition imposed by this region of the protein. In addition, some but not all of the fusion partner proteins have been shown to contain coiled-coil or other dimerization domains. Taken together, the fusion proteins are thought to dimerize constitutively and activate downstream signaling (Jones et al, 2008; Lee et al, 2012; Hutchinson et al, 2013; Ciampi et al, 2005; Cin et al, 2011; Stransky et al, 2014).

References

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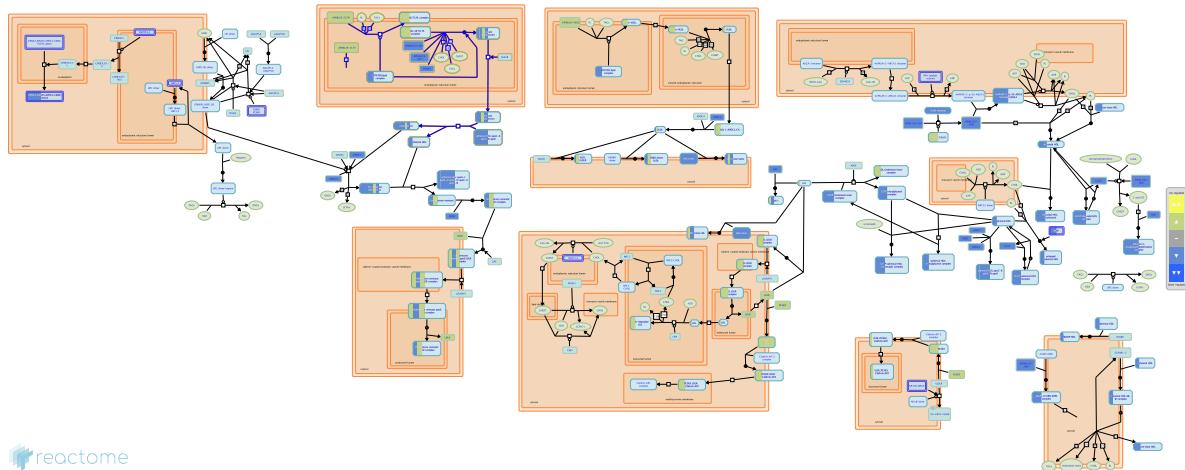
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2015-10-02	Created	Rothfels K
2016-08-05	Reviewed	Stephens RM
2021-05-31	Modified	Shorser S

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P02679	P02679	-1.00e+00
Q9Y490	Q9Y490	-1.00e+00
P02671	P02671	-1.00e+00
P61224	P61224	-1.00e+00
P04275	P04275	-1.00e+00
P18206	P18206	-1.00e+00
P30086	P30086	-1.00e+00

20. Chylomicron assembly (R-HSA-8963888)



Chylomicrons transport triacylglycerol, phospholipid, and cholesterol derived from dietary lipid from the small intestine to other tissues of the body. Each chylomicron assembles around a single molecule of apolipoprotein B-48 (Phillips et al. 1997) which at the time the particle leaves the intestine and enters the lymphatic circulation is complexed with >200,000 molecules of triacylglycerol (TG), ~35,000 of phospholipid, ~11,000 of cholesterol ester, ~8,000 of free cholesterol, ~60 copies of apolipoprotein A-I, ~15 copies of apolipoprotein A-IV, and copies of apolipoprotein A-II (Bhattacharya and Redgrave 1981).

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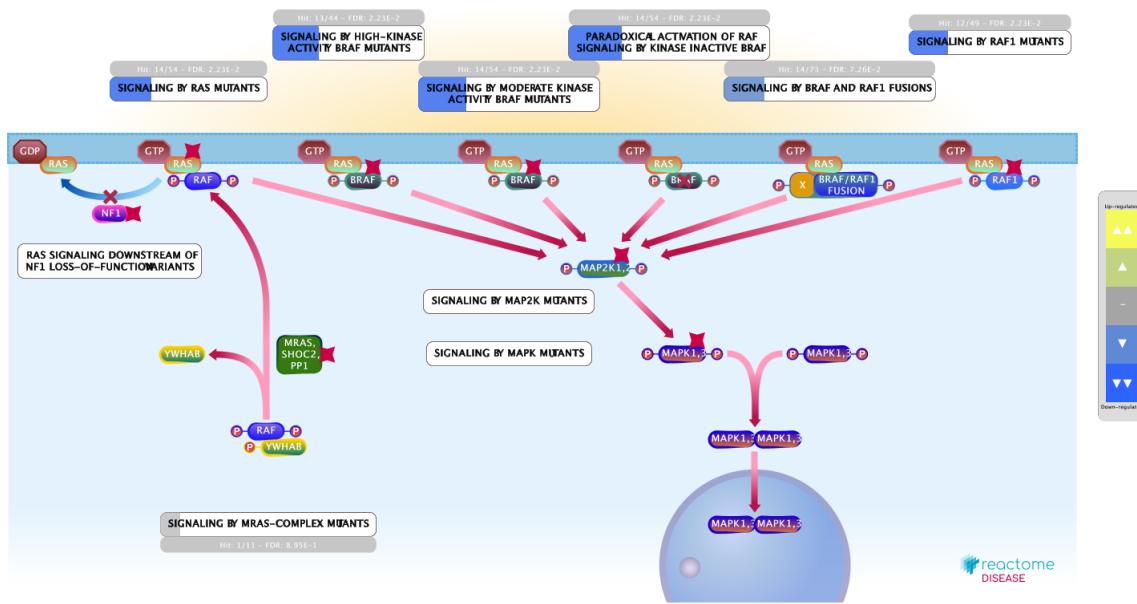
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2021-05-31	Modified	Shorser S

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P02656	P02656	-1.00e+00

Input	UniProt Id	Camera_ms...
P02647	P02647	-1.00e+00
P02649	P02649	-1.00e+00

21. Oncogenic MAPK signaling (R-HSA-6802957)



Diseases: cancer.

The importance of the RAS/RAF/MAPK cascade in regulating cellular proliferation, differentiation and survival is highlighted by the fact that components of the pathway are mutated with high frequency in a large number of human cancers. Activating mutations in RAS are found in approximately one third of human cancers, while ~8% of tumors express an activated form of BRAF. RAS pathway activation is also achieved in a smaller subset of cancers by loss-of-function mutations in negative regulators of RAS signaling, such as the RAS GAP NF1 (reviewed in Prior et al, 2012; Pylayeva-Gupta et al, 2011; Stephen et al, 2014; Lavoie and Therrien, 2015; Lito et al, 2013; Samatar and Poulikakos, 2014; Maertens and Cichowski, 2014).

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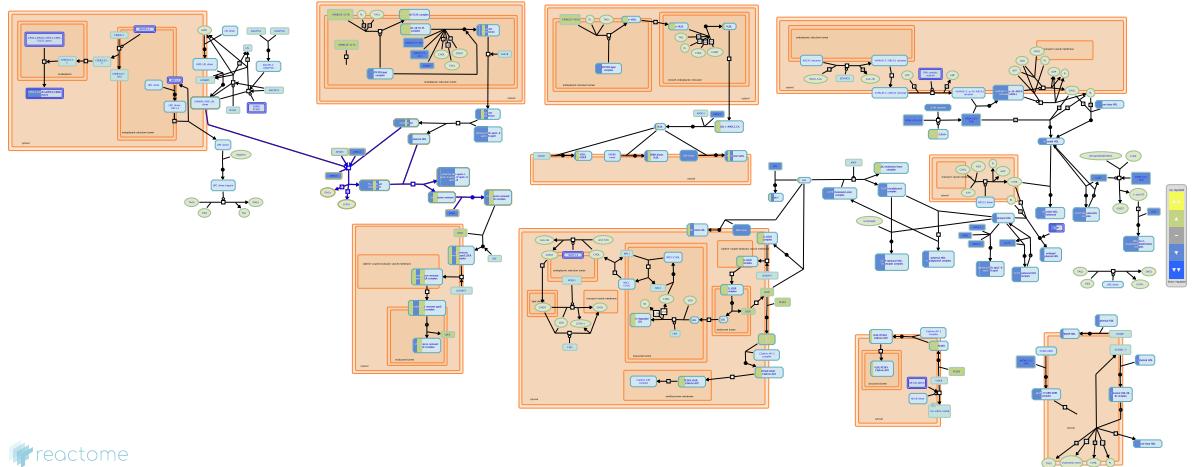
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2016-08-05	Reviewed	Stephens RM
2020-05-04	Reviewed	Gavathiotis E
2021-05-04	Modified	Matthews L

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P02545	P02545	1
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P02679	P02679	-1.00e+00
Q9Y490	Q9Y490	-1.00e+00
P02671	P02671	-1.00e+00
P61224	P61224	-1.00e+00
P04275	P04275	-1.00e+00
P18206	P18206	-1.00e+00
P30086	P30086	-1.00e+00
P35232	P35232	-1.00e+00

22. Chylomicron remodeling (R-HSA-8963901)



As chylomicrons circulate in the body, they acquire molecules of apolipoproteins C and E, and through interaction with endothelial lipases can lose a large fraction of their triacylglycerol. These changes convert them to chylomicron remnants which bind to LDL receptors, primarily on the surfaces of liver cells, clearing them from the circulation. This whole sequence of events is rapid: the normal lifespan of a chylomicron is 30 - 60 minutes (Redgrave 2004).

References

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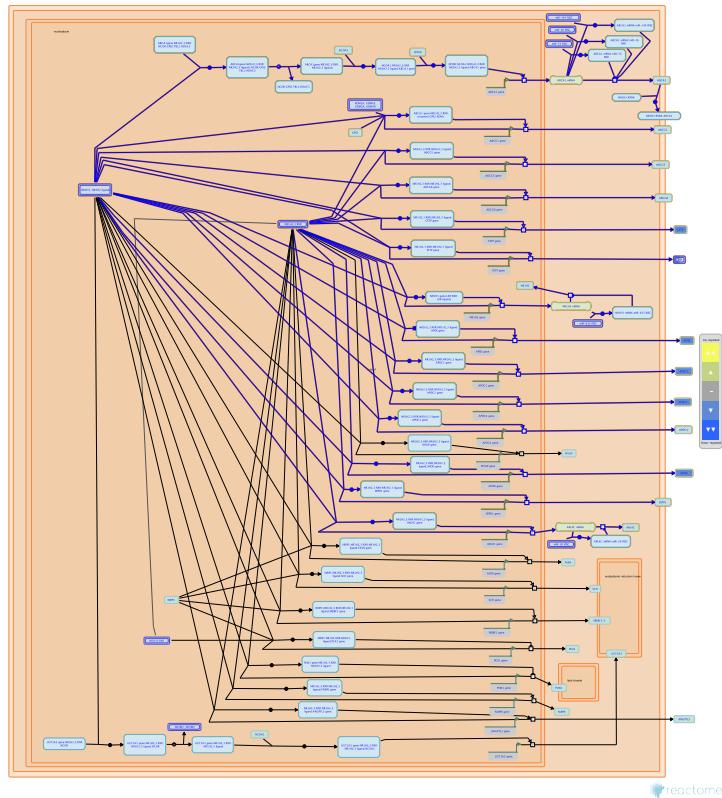
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P02656	P02656	-1.00e+00
P02647	P02647	-1.00e+00
P02649	P02649	-1.00e+00

23. NR1H3 & NR1H2 regulate gene expression linked to cholesterol transport and efflux ([R-HSA-9029569](#))



Cellular compartments: nucleoplasm.

The liver X receptors (LXRs), LXR (NR1H3) and LXR (NR1H2), are nuclear receptors that are activated by endogenous oxysterols, oxidized derivatives of cholesterol (Janowski BA et al. 1996). When cellular oxysterols accumulate as a result of increasing concentrations of cholesterol, NR1H2,3 induce the transcription of genes that protect cells from cholesterol overload (Zhao C & Dahlman-Wright K 2010; Ma Z et al. 2017). In peripheral cells such as macrophages, NR1H2 and NR1H3 increase cholesterol efflux by inducing expression of ATP-binding cassette subfamily A type 1 (ABCA1), ABCG1, and apolipoprotein APOE (Jakobsson T et al. 2009; Laffitte BA et al. 2001; Mak PA et al. 2002). In the intestine, LXR agonists decrease cholesterol absorption through induction of ABCA1, ABCG5, and ABCG8 (Repa JJ et al. 2000; Back SS et al. 2013). Cholesterol removal from non-hepatic peripheral cells, such as lipid-laden macrophages, and its delivery back to the liver for catabolism and excretion are processes collectively known as reverse cholesterol transport (RCT) (Francis GA 2010; Rosenson RS et al. 2012). This Reactome module describes the activation of several direct NR1H2,3 target genes that are closely associated with the RCT pathway, including genes encoding membrane lipid transporters, such ABCA1, ABCG1, ABCG5, ABCG8 and a cluster of apolipoprotein genes APOE, APOC1, APOC2 and APOC4 (Jakobsson T et al. 2009; Back SS et al. 2013; Mak PA et al. 2002).

References

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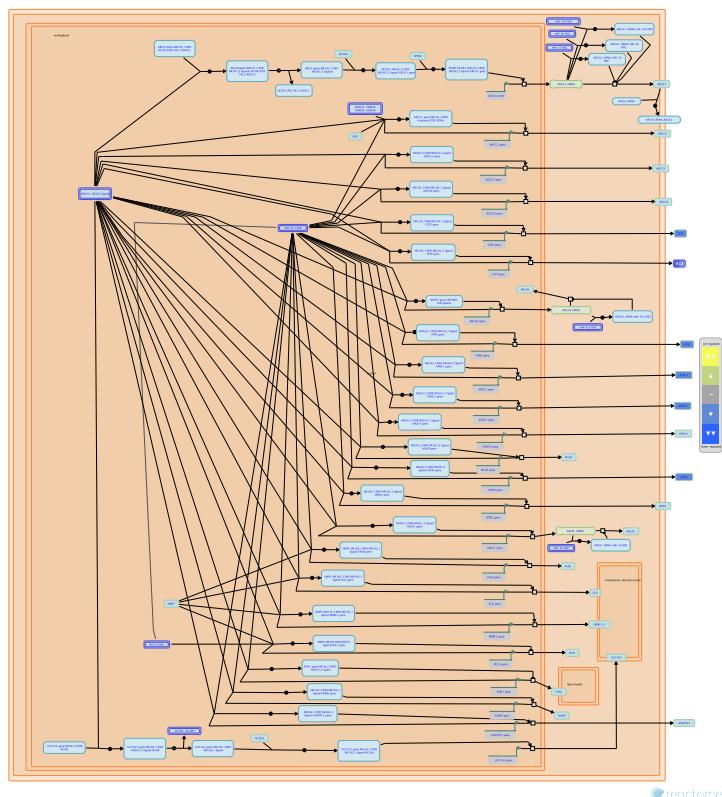
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P11597	P11597	-1.00e+00
P02649	P02649	-1.00e+00
P55058	P55058-1, P55058-2	-1.00e+00

24. NR1H2 and NR1H3-mediated signaling (R-HSA-9024446)



Cellular compartments: nucleoplasm.

The liver X receptors LXR (NR1H3) and LXR (NR1H2) are members of the nuclear receptor superfamily and function as ligand-activated transcription factors. The natural ligands of NR1H2 and NR1H3 are oxysterols (e.g., 24(S),25-epoxycholesterol, 24(S)-hydroxycholesterol (OH), 25-OH, and 27-OH) that are produced endogenously by enzymatic reactions, by reactive oxygen species (ROS)-dependent oxidation of cholesterol and by the alimentary processes (reviewed in: Jakobsson T et al. 2012; Huang C 2014; Komati R et al. 2017). It has been shown that these oxysterols bind directly to the ligand-binding domain of LXRs with Kd values ranging from 0.1 to 0.4 microM. 24(S), 25-epoxycholesterol was found to be the most potent endogenous agonist (Janowski BA et al. 1999). NR1H3 (LXR) and NR1H2 (LXR) showed similar affinities for these compounds (Janowski BA et al. 1999). In physiological conditions, oxysterols are formed in amounts proportional to cholesterol content in the cell and therefore the LXRs operate as cholesterol sensors to alter gene expression and protect the cells from cholesterol overload via: (1) inhibiting intestinal cholesterol absorption; (2) stimulating cholesterol efflux from cells to high-density lipoproteins through the ATP-binding cassette transporters ABCA1 and ABCG1; (3) activating the conversion of cholesterol to bile acids in the liver; and (4) activating biliary cholesterol and bile acid excretion (reviewed in: Wójcicka G et al. 2007; Baranowski M 2008; Laurencikiene J & Rydén M 2012; Edwards PA et al. 2002; Zelcer N & Tontonoz P 2006; Zhao C & Dahlman-Wright K 2010). In addition, LXR agonists enhance de novo fatty acid synthesis by stimulating the expression of a lipogenic transcription factor, sterol regulatory element-binding protein-1c (SREBP-1c), leading to the elevation of plasma triglycerides and hepatic steatosis (Wójcicka G et al. 2007; Baranowski M 2008; Laurencikiene J & Rydén M 2012). In addition to their function in lipid metabolism, NR1H2,3 have also been found to modulate immune and inflammatory responses in macrophages (Zelcer N & Tontonoz P 2006). The NR1H2 and NR1H3 molecules can be viewed as having four functional domains: (1) an amino-terminal ligand-independent activation function domain (AF-1), which may stimulate transcription in the absence of ligand;

(2) a DNA-binding domain (DBD) containing two zinc fingers; (3) a hydrophobic ligand-binding domain (LBD) required for ligand binding and receptor dimerization; and, (4) a carboxy-terminal ligand-dependent transactivation sequence (also referred to as the activation function-2 (AF-2) domain) that stimulates transcription in response to ligand binding (Robinson-Rechavi M et al. 2003; Jakobsson T et al. 2012; Färnegardh M et al. 2003; Lin CY & Gustafsson JA 2015). Although both NR1H3 and NR1H2 are activated by the same ligands and are structurally similar, their tissue expression profiles are very different. NR1H3 is selectively expressed in specific tissues and cell types, such as the liver, intestine, adrenal gland, adipose tissue and macrophages, whereas NR1H2 is ubiquitously expressed (Nishimura M et al. 2004; Bookout AL et al. 2006). Upon activation NR1H2 or NR1H3 heterodimerizes with retinoid X receptors (RXR) and binds to LXR-response elements (LXREs) consisting of a direct repeat of the core sequence 5'-AGGTCA-3' separated by 4 nucleotides (DR4) in the DNA of target genes (Wiebel FF & Gustafsson JA 1997). An inverted repeat of the same consensus sequence with no spacer region (IR-0) and an inverted repeat of the same consensus sequence separated by a 1 bp spacer (IR-1) have also been shown to mediate LXR transactivation (Mak PA et al. 2002, Landrier JF et al. 2003). NR1H3 and NR1H2 have been shown to regulate gene expression via LXREs in the promoter regions of their target genes such as UDP glucuronosyltransferase 1 family, polypeptide A3 (UGT1A3) (Verreault M et al. 2006), fatty acid synthase (FAS) (Joseph SB et al. 2002a), carbohydrate response element binding protein (ChREBP, also known as MLX-interacting protein-like or MLXIPL) (Cha JY & Repa JJ 2007) and phospholipid transfer protein (PLTP) (Mak PA et al. 2002). LXREs have also been reported to be present in introns of target genes such as the ATP-binding cassette transporter G1 (ABCG1) (Sabol SL et al. 2005). NR1H3 has been shown to activate gene expression via the FXR-responsive element found in the proximal promoter of the human ileal bile acid-binding protein (FABP6) (Landrier JF et al. 2003). The NR1H2,3:RXR heterodimers are permissive, in that they can be activated by ligands for either NR1H2,3 (LXR) or RXR (Willy PJ et al. 1995).

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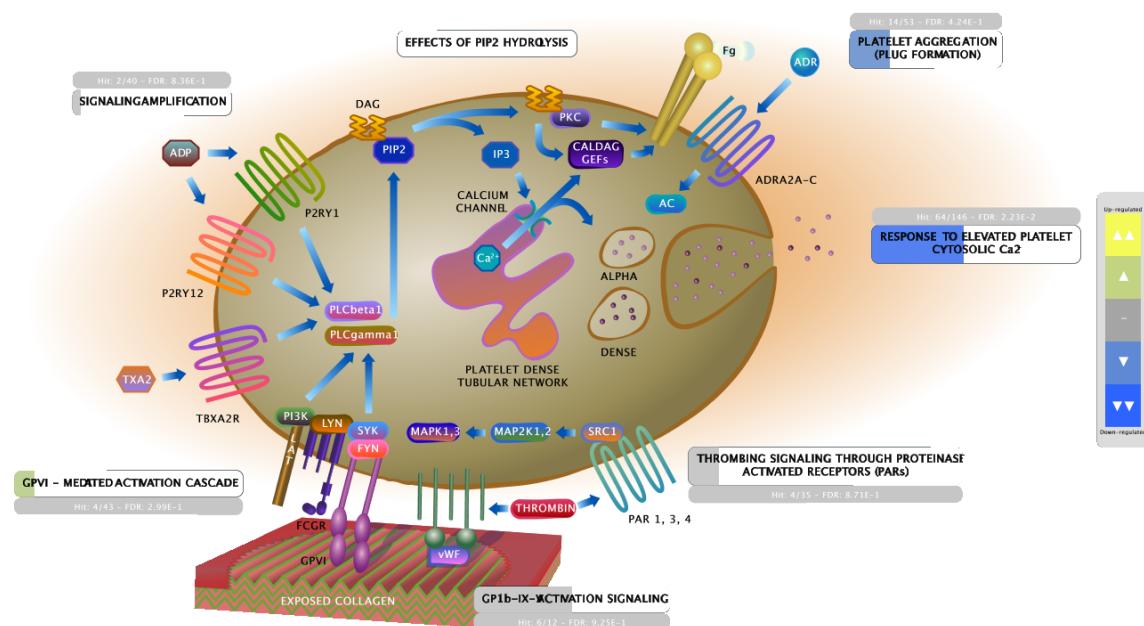
Edit history

Date	Action	Author
2017-10-04	Created	Shamovsky V
2018-01-19	Authored	Shamovsky V
2018-12-29	Reviewed	D'Eustachio P
2019-08-09	Edited	Shamovsky V
2019-08-09	Reviewed	Repa JJ, Cummins CL
2021-05-22	Modified	Shorser S

Entities found in this pathway (6)

Input	UniProt Id	Camera_ms...
P05090	P05090	-1.00e+00
P02655	P02655	-1.00e+00
P02654	P02654	-1.00e+00
P11597	P11597	-1.00e+00
P02649	P02649	-1.00e+00
P55058	P55058-1, P55058-2	-1.00e+00

25. 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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Edit history

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
2021-05-22	Modified	Shorser S

Entities found in this pathway (76)

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6. Identifiers found

Below is a list of the input identifiers that have been found or mapped to an equivalent element in Reactome, classified by resource.

Entities (602)

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Q9UQP3	Q9UQP3	Q9Y251	Q9Y251	Q9Y266	Q9Y266
Q9Y277	Q9Y277	Q9Y336	Q9Y336	Q9Y490	Q9Y490
Q9Y4L1	Q9Y4L1	Q9Y5Y7	Q9Y5Y7	Q9Y624	Q9Y624
Q9Y6N7	Q9Y6N7	Q9Y6Z7	Q9Y6Z7		

7. Identifiers not found

These 49 identifiers were not found neither mapped to any entity in Reactome.

O00151	O14745	O43583	O60812	O75368	O95810	P06703	P0DJI9
P10155	P11684	P13489	P13667	P14317	P17813	P20073	P36955
P40121	P56537	Q00325	Q00688	Q04941	Q09666	Q13228	Q13642
Q14847	Q15828	Q15942	Q5T619	Q5T749	Q6E0U4	Q6EMK4	Q8WWY7
Q8WWZ8	Q96FE7	Q96QA5	Q99784	Q99972	Q9BVC6	Q9BXJ4	Q9GZT8
Q9H299	Q9H361	Q9HCU0	Q9NZD1	Q9NZD4	Q9UGM5	Q9UII2	Q9ULV4
Q9Y6R7							