reactome

Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 88 on 12/04/2024. The web link to these results is:

https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyNDA0MTIwNjU0MDJfMzk2Mg%3D%3D

Please keep in mind that analysis results are temporarily stored on our server. The storage period depends on usage of the service but is at least 7 days. As a result, please note that this URL is only valid for a limited time period and it might have expired.

Table of Contents

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 14 non-human species including mouse, rat, chicken, puffer fish, worm, fly and yeast. 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:

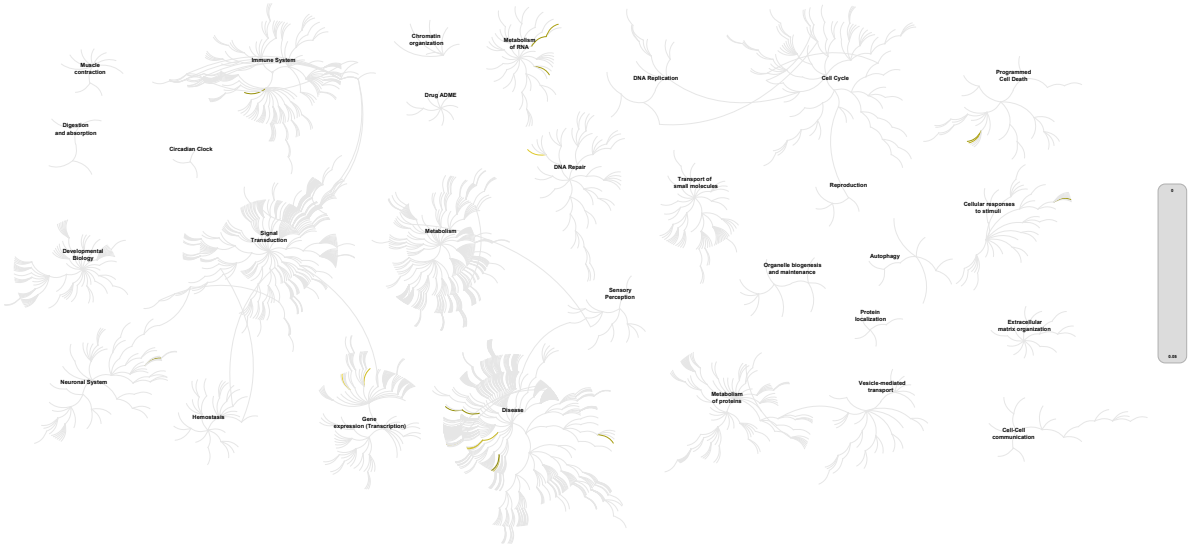
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, … D'Eustachio P (2016). The reactome pathway knowledgebase. Nucleic Acids Research, 44(D1), D481–D487. https://doi.org/10.1093/nar/gkv1351.

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.
- 27 out of 38 identifiers in the sample were found in Reactome, where 726 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 MjAyNDA0MTIwNjU0MDJfMzk2Mg%3D%3D. This ID is valid for at least 7 days in Reactome's server. Use it to access Reactome services with your data.

3. Genome-wide overview



This figure shows a genome-wide overview of the results of your pathway analysis. Reactome pathways are arranged in a hierarchy. The center of each of the circular "bursts" is the root of one top-level pathway, for example "DNA Repair". Each step away from the center represents the next level lower in the pathway hierarchy. The color code denotes over-representation of that pathway in your input dataset. Light grey signifies pathways which are not significantly over-represented.

4. Most significant pathways

The following table shows the 25 most relevant pathways sorted by p-value.

Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
MECP2 regulates transcription factors	2 / 44	0.002	0.007	0.469	2 / 8	5.37e-04
DNA Damage Recognition in GG-NER	2 / 58	0.003	0.012	0.469	5 / 5	3.36e-04
TP53 Regulates Transcription of DNA Repair Genes	5 / 201	0.009	0.02	0.469	11 / 17	0.001
Enhanced binding of GP1BA variant to VWF multimer:collagen	1 / 7	3.04e-04	0.02	0.469	1 / 1	6.72e-05
Defective binding of VWF variant to GPIb:IX:V	1 / 7	3.04e-04	0.02	0.469	1 / 1	6.72e-05
Defective Mismatch Repair Associated With MSH2	1 / 8	3.48e-04	0.022	0.469	1 / 2	1.34e-04
Defects of platelet adhesion to exposed collagen	1 / 8	3.48e-04	0.022	0.469	2 / 5	3.36e-04
Defective CBLIF causes IFD	1 / 9	3.91e-04	0.025	0.469	1 / 1	6.72e-05
Activation of NOXA and translocation to mitochondria	1 / 11	4.78e-04	0.031	0.469	2 / 5	3.36e-04
Formation of editosomes by ADAR proteins	1 / 13	5.65e-04	0.036	0.469	1 / 4	2.69e-04
LTC4-CYSLTR mediated IL4 production	1 / 14	6.09e-04	0.039	0.469	1 / 3	2.02e-04
SLBP Dependent Processing of Replication-Dependent Histone Pre-mRNAs	1 / 14	6.09e-04	0.039	0.469	1 / 3	2.02e-04
Activation of PUMA and translocation to mitochondria	1 / 15	6.52e-04	0.042	0.469	2 / 5	3.36e-04
mRNA Editing: A to I Conversion	1 / 15	6.52e-04	0.042	0.469	1 / 6	4.03e-04
NFE2L2 regulating inflammation associated genes	1 / 16	6.96e-04	0.044	0.469	1 / 3	2.02e-04
Neutrophil degranulation	4 / 478	0.021	0.047	0.469	4 / 10	6.72e-04
Defective binding of RB1 mutants to E2F1,(E2F2, E2F3)	1 / 17	7.39e-04	0.047	0.469	1 / 1	6.72e-05
Aberrant regulation of mitotic G1/S transition in cancer due to RB1 defects	1 / 17	7.39e-04	0.047	0.469	1 / 2	1.34e-04
CREB1 phosphorylation through the activation of Adenylate Cyclase	1 / 17	7.39e-04	0.047	0.469	1 / 6	4.03e-04
Defective Mismatch Repair Associated With MSH6	1 / 18	7.83e-04	0.05	0.469	1 / 1	6.72e-05
Defective Mismatch Repair Associated With MSH3	1 / 19	8.26e-04	0.052	0.469	1 / 1	6.72e-05

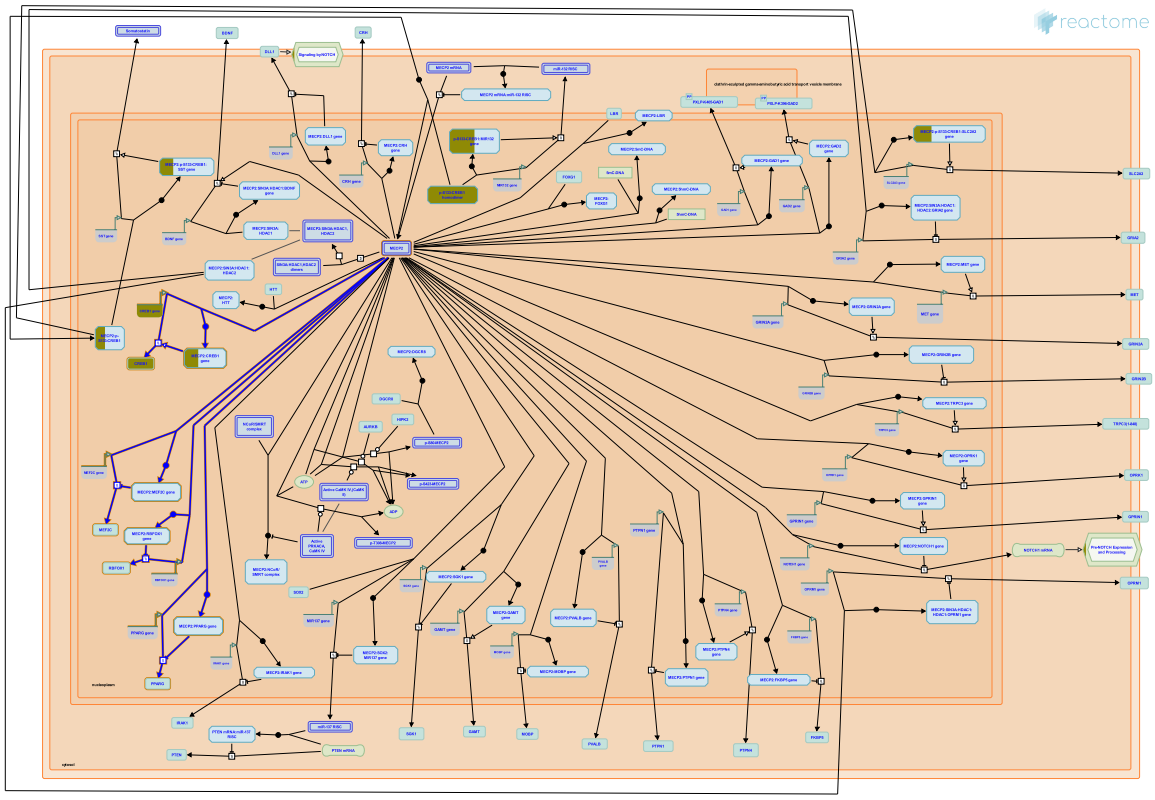
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
PDH complex synthesizes acetyl-CoA from PYR	1 / 19	8.26e-04	0.052	0.469	3 / 3	2.02e-04
Defective F9 activation	1 / 20	8.70e-04	0.055	0.469	1 / 1	6.72e-05
HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand	2 / 134	0.006	0.055	0.469	9 / 22	0.001
Intestinal hexose absorption	1 / 21	9.13e-04	0.058	0.469	1 / 3	2.02e-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. MECP2 regulates transcription factors (R-HSA-9022707)



MECP2 regulates transcription of several transcription factors involved in functioning of the nervous system, such as CREB1, MEF2C, RBFOX1 (Chahrour et al. 2008) and PPARG (Mann et al. 2010, Joss Moore et al. 2011).

References

McKnight RA, Lane RH, Callaway CW, Ogata EM, Albertine KH, Sainz AJ, ... Wang Y (2011). IUGR differentially alters MeCP2 expression and H3K9Me3 of the PPARΒ gene in male and female rat lungs during alveolarization. Birth Defects Res. Part A Clin. Mol. Teratol., 91, 672-81.

Chu DC, Oakley F, Maxwell A, Tsukamoto H, Zhu NL, Mann J & Mann DA (2010). MeCP2 controls an epigenetic pathway that promotes myofibroblast transdifferentiation and fibrosis. Gastroenterology, 138, 705-14, 714.e1-4.

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.

Edit history

Date	Action	Author
2017-09-25	Created	Orlic-Milacic M
2017-10-02	Authored	Orlic-Milacic M

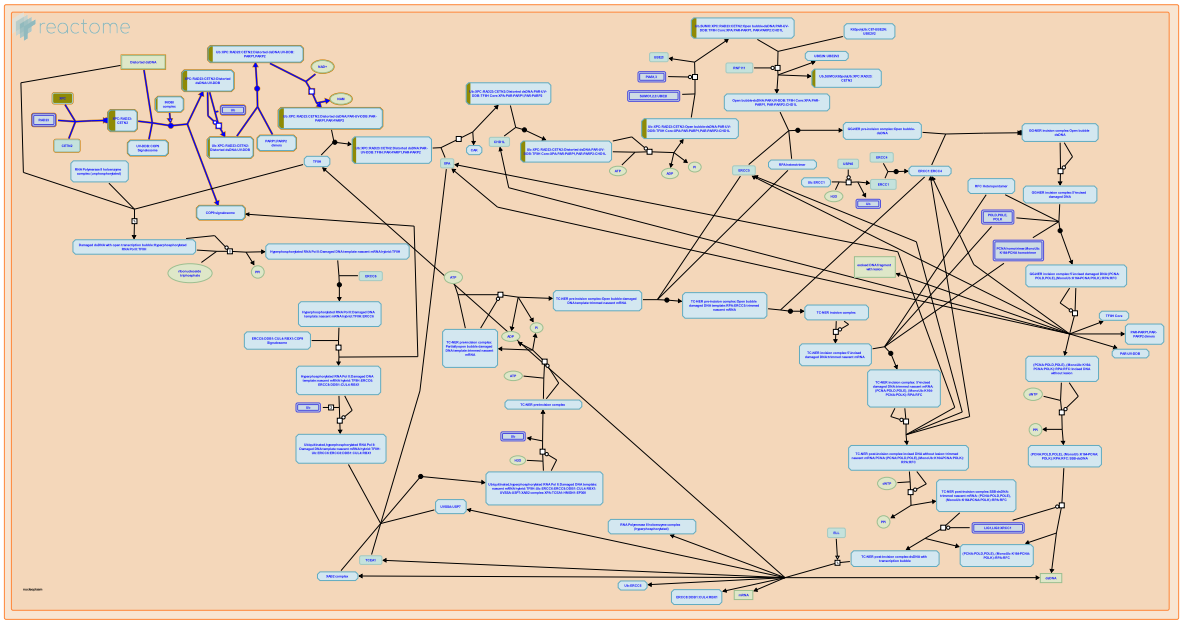
Date	Action	Author
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Edited	Orlic-Milacic M
2023-03-08	Modified	Matthews L

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

Input	UniProt Id
CREB1	P16220-1

Input	Ensembl Id
CREB1	ENSG00000118260

2. DNA Damage Recognition in GG-NER (R-HSA-5696394)



Cellular compartments: nucleoplasm.

In global genome nucleotide excision repair (GG-NER), the DNA damage is recognized by two protein complexes. The first complex consists of XPC, RAD23A or RAD23B, and CETN2. This complex probes the DNA helix and recognizes damage that disrupts normal Watson-Crick base pairing, which results in binding of the XPC:RAD23:CETN2 complex to the undamaged DNA strand. The second complex is a ubiquitin ligase UV-DDB that consists of DDB2, DDB1, CUL4A or CUL4B and RBX1. The UV-DDB complex is necessary for the recognition of UV-induced DNA damage and may contribute to the retention of the XPC:RAD23:CETN2 complex at the DNA damage site. The UV-DDB complex binds the damaged DNA strand (Fitch et al. 2003, Wang et al. 2004, Moser et al. 2005, Camenisch et al. 2009, Oh et al. 2011).

References

Tamura D, Emmert S, Oh KS, DiGiovanna JJ, Kraemer KH & Imoto K (2011). Nucleotide excision repair proteins rapidly accumulate but fail to persist in human XP-E (DDB2 mutant) cells. Photochem. Photobiol., 87, 729-33.

Clement FC, Naegeli H, Ferrando-May E, Fei J, Leitenstorfer A, Träutlein D & Camenisch U (2009). Two-stage dynamic DNA quality check by xeroderma pigmentosum group C protein. EMBO J., 28, 2387-99.

Wang QE, Zhu Q, Wani G, Chen J & Wani AA (2004). UV radiation-induced XPC translocation within chromatin is mediated by damaged-DNA binding protein, DDB2. Carcinogenesis, 25, 1033-43.

Alekseev S, Yasui A, Mullenders LH, Volker M, Moser J, Kool H, ... Vrieling H (2005). The UV-damaged DNA binding protein mediates efficient targeting of the nucleotide excision repair complex to UV-induced photo lesions. DNA Repair (Amst.), 4, 571-82.

Nakajima S, Ford JM, Yasui A & Fitch ME (2003). In vivo recruitment of XPC to UV-induced cyclobutane pyrimidine dimers by the DDB2 gene product. J. Biol. Chem., 278, 46906-10.

Edit history

Date	Action	Author
2003-07-14	Authored	Joshi-Tope G
2004-01-29	Authored	Hoeijmakers JH
2015-05-28	Revised	Orlic-Milacic M
2015-05-28	Edited	Orlic-Milacic M
2015-05-28	Authored	Orlic-Milacic M
2015-05-28	Created	Orlic-Milacic M
2015-08-03	Reviewed	Fousteri M

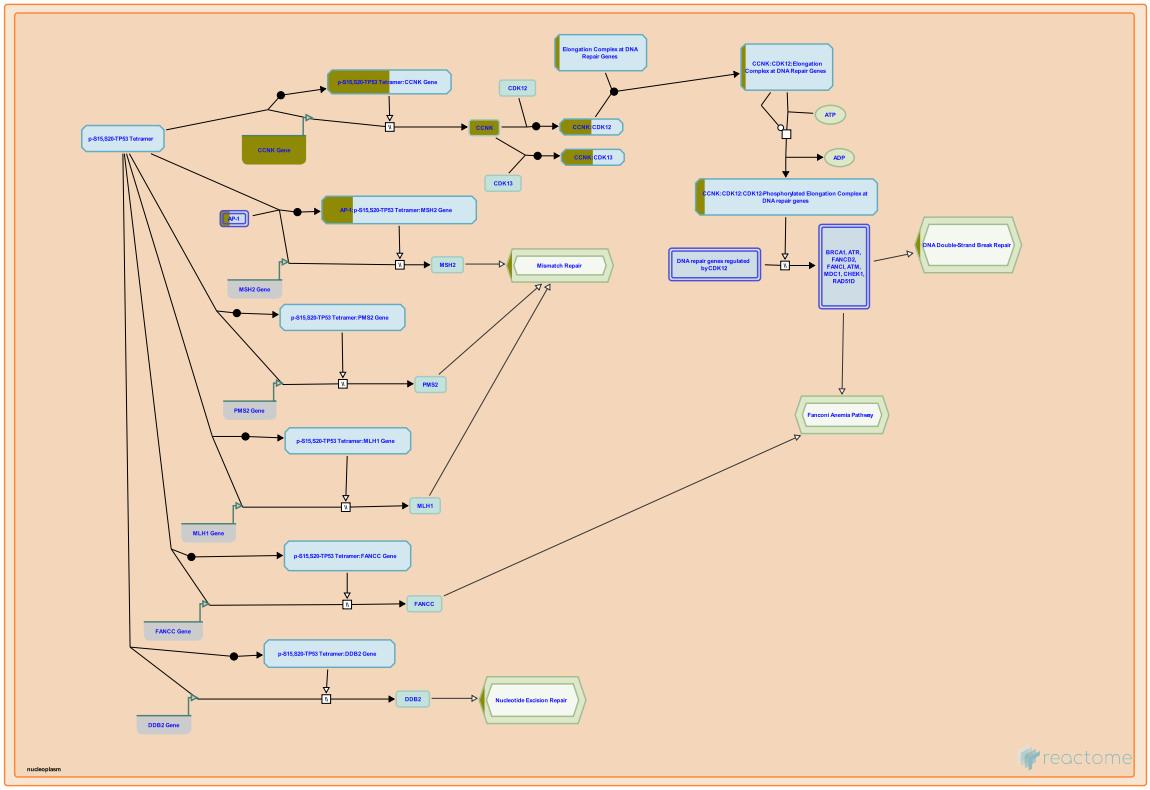
2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
INO80C	Q6PI98	XPC	Q01831

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
XPC	Q01831	P41208			

3. TP53 Regulates Transcription of DNA Repair Genes (R-HSA-6796648)



Several DNA repair genes contain p53 response elements and their transcription is positively regulated by TP53 (p53). TP53-mediated regulation probably ensures increased protein level of DNA repair genes under genotoxic stress.

TP53 directly stimulates transcription of several genes involved in DNA mismatch repair, including MSH2 (Scherer et al. 2000, Warnick et al. 2001), PMS2 and MLH1 (Chen and Sadowski 2005). TP53 also directly stimulates transcription of DDB2, involved in nucleotide excision repair (Tan and Chu 2002), and FANCC, involved in the Fanconi anemia pathway that repairs DNA interstrand crosslinks (Liebetrau et al. 1997). Other p53 targets that can influence DNA repair functions are RRM2B (Kuo et al. 2012), XPC (Fitch et al. 2003), GADD45A (Amundson et al. 2002), CDKN1A (Cazzalini et al. 2010) and PCNA (Xu and Morris 1999). Interestingly, the responsiveness of some of these DNA repair genes to p53 activation has been shown in human cells but not for orthologous mouse genes (Jegga et al. 2008, Tan and Chu 2002). Contrary to the positive modulation of nucleotide excision repair (NER) and mismatch repair (MMR), p53 can negatively modulate base excision repair (BER), by down-regulating the endonuclease APEX1 (APE1), acting in concert with SP1 (Poletto et al. 2016).

Expression of several DNA repair genes is under indirect TP53 control, through TP53-mediated stimulation of cyclin K (CCNK) expression (Mori et al. 2002). CCNK is the activating cyclin for CDK12 and CDK13 (Blazek et al. 2013). The complex of CCNK and CDK12 binds and phosphorylates the C-terminal domain of the RNA polymerase II subunit POLR2A, which is necessary for efficient transcription of long DNA repair genes, including BRCA1, ATR, FANCD2, FANCI, ATM, MDC1, CHEK1 and RAD51D. Genes whose transcription is regulated by the complex of CCNK and CDK12 are mainly involved in the repair of DNA double strand breaks and/or the Fanconi anemia pathway (Blazek et al. 2011, Cheng et al. 2012, Bosken et al. 2014, Bartkowiak and Greenleaf 2015, Ekumi et al. 2015).

References

Sadowski I & Chen J (2005). Identification of the mismatch repair genes PMS2 and MLH1 as p53 target genes by using serial analysis of binding elements. Proc. Natl. Acad. Sci. U.S.A., 102, 4813-8.

Morris GF & Xu J (1999). p53-mediated regulation of proliferating cell nuclear antigen expression in cells exposed to ionizing radiation. Mol. Cell. Biol., 19, 12-20.

Cimermancic P, Johansen E, Ule J, Peterlin BM, Hulinkova P, Luo Z, ... Bartholomeeusen K (2011). The Cyclin K/Cdk12 complex maintains genomic stability via regulation of expression of DNA damage response genes. Genes Dev., 25, 2158-72.

Fletcher SC, Legrand AJ, Dianov GL & Poletto M (2016). p53 coordinates base excision repair to prevent genomic instability. Nucleic Acids Res..

Dabbas B, Strait KA, Ford CD & Warnick CT (2001). Identification of a p53 response element in the promoter region of the hMSH2 gene required for expression in A2780 ovarian cancer cells. J. Biol. Chem., 276, 27363-70.

Edit history

Date	Action	Author
2015-09-05	Created	Orlic-Milacic M
2015-10-14	Edited	Orlic-Milacic M
2015-10-14	Authored	Orlic-Milacic M
2016-02-04	Reviewed	Zaccara S, Inga A

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

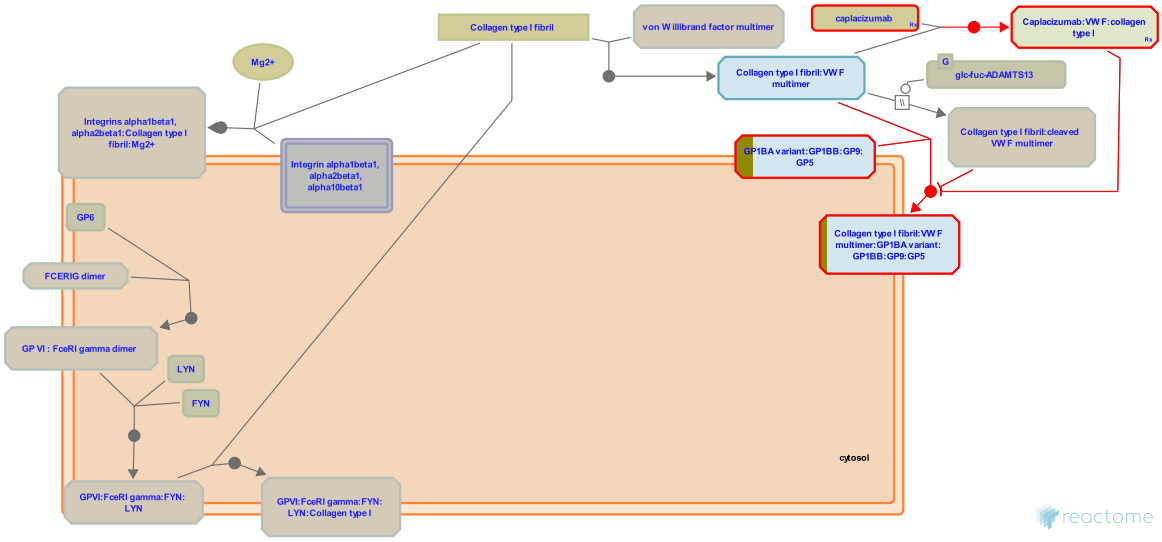
Input	UniProt Id	Input	UniProt Id
CCNK	O75909	JUN	P05412

Input	Ensembl Id
CCNK	ENSG00000090061

Interactors found in this pathway (3)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
CCNK	O75909	Q9NYV4, Q14004	MSH3	P20585	P40692, P43246
XPC	Q01831-1	Q92466			

4. Enhanced binding of GP1BA variant to VWF multimer:collagen (R-HSA-9845620)



Diseases: blood platelet disease.

The Reactome event describes gain-of-function variants of glycoprotein Ib (GPIb, encoded by GP1BA) that cause macrothrombocytopenia and mucocutaneous bleeding in patients with platelet-type von Willebrand disease (PT-VWD) due to enhanced affinity for von Willebrand factor (VWF).

References

Bermejo E, Alberto MF, Woods AI, Kempfer AC, Sanchez-Luceros A, Grosso SH, ... Lazzari MA (2014). Identification of p.W246L as a novel mutation in the GP1BA gene responsible for platelet-type von Willebrand disease. Semin Thromb Hemost, 40, 151-60.

Cunningham D, Miller JL, Lyle VA & Finch CN (1991). Mutation in the gene encoding the alpha chain of platelet glycoprotein Ib in platelet-type von Willebrand disease. Proc Natl Acad Sci U S A, 88, 4761-5.

Othman M, Jazebi M, Ravanbod S, Rassoulzadegan M, Emsley J, Ala F, ... Enayat S (2012). A novel D235Y mutation in the GP1BA gene enhances platelet interaction with von Willebrand factor in an Iranian family with platelet-type von Willebrand disease. Thromb Haemost, 108, 946-54.

Sugita K, Matsubara Y, Murata M & Ikeda Y (2003). Identification of a novel point mutation in platelet glycoprotein Ibalpha, Gly to Ser at residue 233, in a Japanese family with platelet-type von Willebrand disease. J Thromb Haemost, 1, 2198-205.

Roth GJ & Russell SD (1993). Pseudo-von Willebrand disease: a mutation in the platelet glycoprotein Ib alpha gene associated with a hyperactive surface receptor. Blood, 81, 1787-91.

Edit history

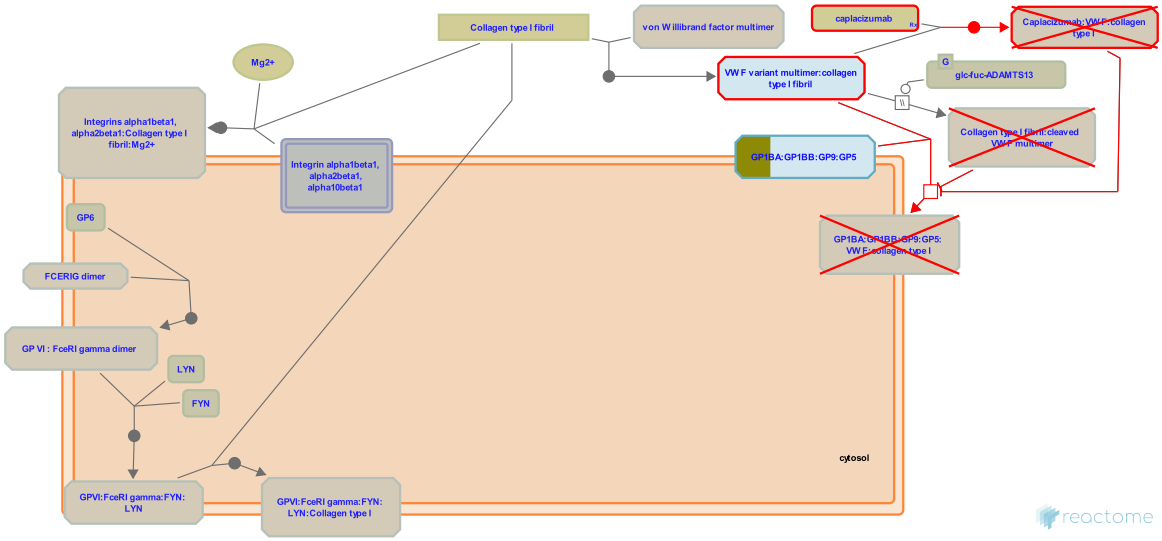
Date	Action	Author
2023-01-07	Authored	Shamovsky V
2023-10-06	Created	Shamovsky V
2023-11-06	Reviewed	Gao R
2023-11-07	Modified	Shamovsky V

Date	Action	Author
2023-11-07	Edited	Shamovsky V

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

Input	UniProt Id
GP1BB	P13224

5. Defective binding of VWF variant to GPIb:IX:V (R-HSA-9846298)



Diseases: blood platelet disease.

This Reactome event describes von Willebrand disease (VWD)-associated missense mutations in the A1 domain of VWF, namely VWF S1358N, S1387I, S1394F and Q1402P, that compromise the clot formation due to reduced binding to GPIb (Larsen DM et al., 2013).

References

Shapiro AD, Larsen DM, Flood VH, Gill JC & Haberichter SL (2013). Variability in platelet- and collagen-binding defects in type 2M von Willebrand disease. Haemophilia, 19, 590-4.

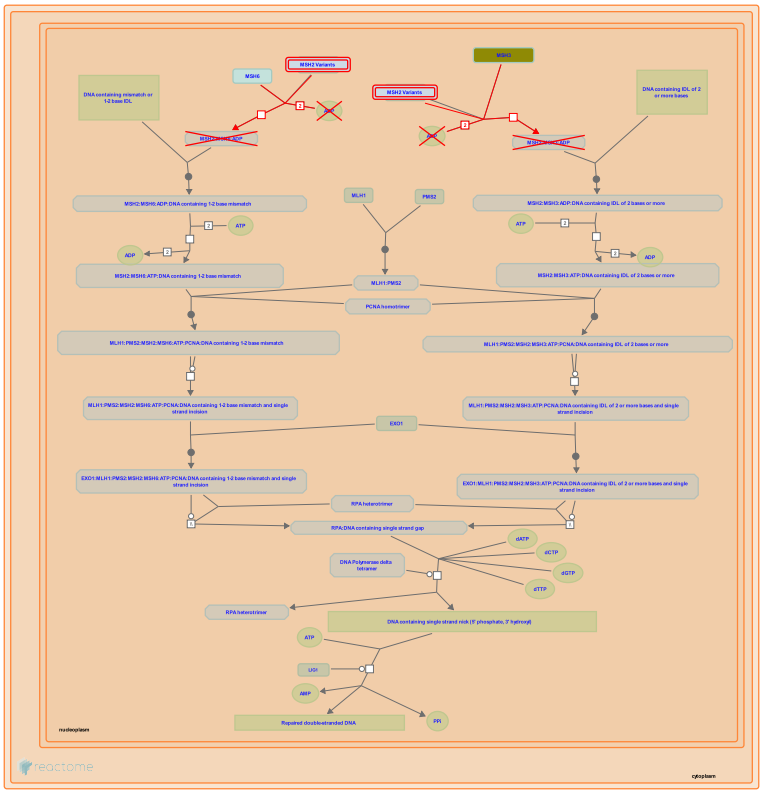
Edit history

Date	Action	Author
2023-01-07	Authored	Shamovsky V
2023-10-10	Created	Shamovsky V
2023-11-06	Reviewed	Gao R
2023-11-07	Modified	Shamovsky V
2023-11-07	Edited	Shamovsky V

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

Input	UniProt Id
GP1BB	P13224

6. Defective Mismatch Repair Associated With MSH2 (R-HSA-5632928)



Cellular compartments: nucleoplasm.

Diseases: cancer.

MSH2 is homologous to the E. coli MutS gene and is involved in DNA mismatch repair (MMR) (Fishel et al., 1994). Heterozygous mutations in the MSH2 gene result in hereditary nonpolyposis colorectal cancer-1. Variants of MSH2 are associated with hereditary nonpolyposis colorectal cancer. Alteration of MSH2 is also involved in Muir-Torre syndrome and mismatch repair cancer syndrome.

References

Dunlop MG, Farrington SM, Mitchell RJ & Campbell H (2002). Mismatch repair genes hMLH1 and hMSH2 and colorectal cancer: a HuGE review. Am. J. Epidemiol., 156, 885-902.

Copeland NG, Kane M, Rao MR, Jenkins NA, Lescoe MK, Kolodner R, ... Fishel R (1993). The human mutator gene homolog MSH2 and its association with hereditary nonpolyposis colon cancer. Cell, 75, 1027-38.

Edit history

Date	Action	Author
2011-11-10	Authored	Gillespie ME
2014-10-29	Created	Gillespie ME
2016-11-01	Reviewed	Arora S
2017-02-27	Edited	Gillespie ME
2023-03-08	Modified	Matthews L

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

Input	UniProt Id
MSH3	P20585

7. Defects of platelet adhesion to exposed collagen (R-HSA-9823587)

Diseases: blood platelet disease, autoimmune thrombocytopenic purpura.

This Reactome module describes dysfunctions in platelet adhesion caused by mutations in different genes, including VWF, ADAMTS13 and GP1BA.

References

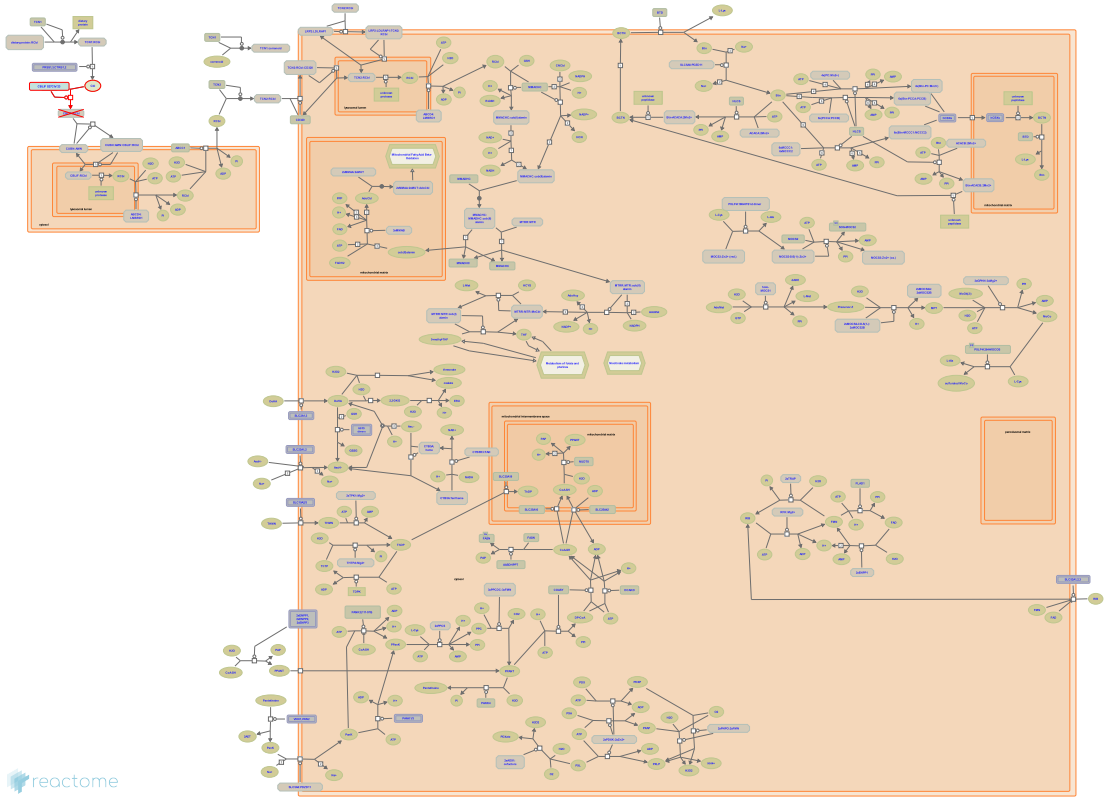
Edit history

Date	Action	Author
2023-01-07	Authored	Shamovsky V
2023-01-07	Created	Shamovsky V
2023-11-06	Reviewed	Gao R
2023-11-07	Edited	Shamovsky V
2023-11-16	Modified	Wright A

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

Input	UniProt Id
GP1BB	P13224

8. Defective CBLIF causes IFD (R-HSA-3359457)



Diseases: megaloblastic anemia.

Defects in cobalamin binding intrinsic factor CBLIF, aka gastric intrinsic factor GIF) cause hereditary intrinsic factor deficiency (IFD, aka congenital pernicious anemia; MIM:261000). IFD is an autosomal recessive disorder characterized by megaloblastic anemia (Tanner et al. 2005).

References

Oner C, Tanner SM, Li Z, de la Chapelle A, Altay C, Perko JD, ... Faivre L (2005). Hereditary juvenile cobalamin deficiency caused by mutations in the intrinsic factor gene. Proc. Natl. Acad. Sci. U.S.A., 102, 4130-3.

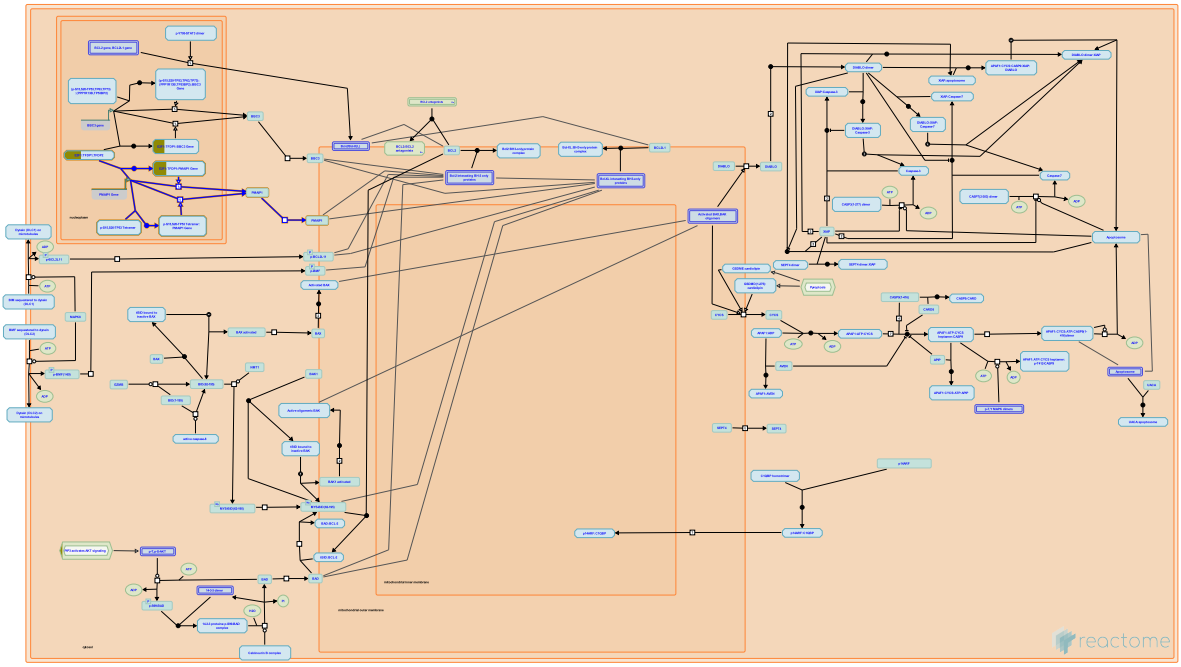
Edit history

Date	Action	Author
2013-05-13	Edited	Jassal B
2013-05-13	Authored	Jassal B
2013-05-13	Created	Jassal B
2013-08-14	Reviewed	Watkins D
2023-10-12	Modified	Weiser JD

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
TMEM237	Q96Q45-2	P27352			

9. Activation of NOXA and translocation to mitochondria (R-HSA-111448)



Cellular compartments: cytosol.

NOXA is transactivated in a p53-dependent manner and by E2F1. Activated NOXA is translocated to mitochondria.

References

Hershko T & Ginsberg D (2004). Up-regulation of Bcl-2 homology 3 (BH3)-only proteins by E2F1 mediates apoptosis. J Biol Chem, 279, 8627-34.

Hanigan CL, Robles AI, Trudel LJ, Hofseth LJ, Li CQ, Wogan GN & Harris CC (2004). Apoptotic signaling pathways induced by nitric oxide in human lymphoblastoid cells expressing wild-type or mutant p53. Cancer Res, 64, 3022-9.

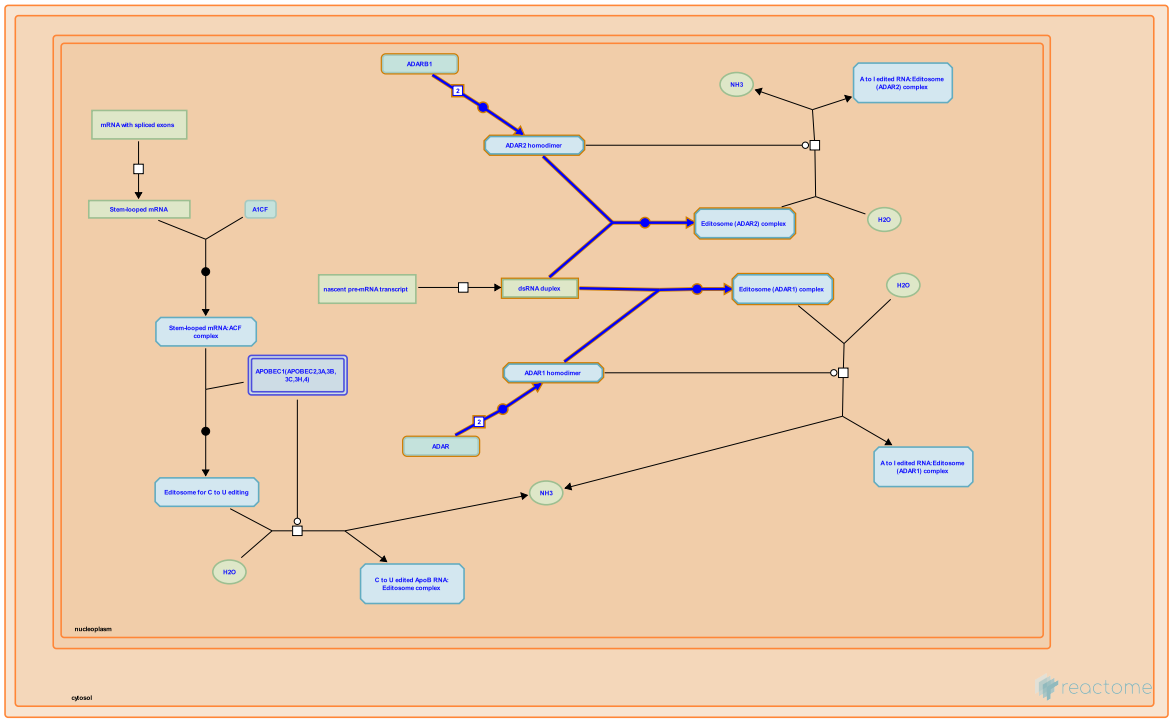
Edit history

Date	Action	Author
2004-08-09	Created	Tsujimoto Y, Hardwick JM

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

Input	UniProt Id
TFDP1	Q14186

10. Formation of editosomes by ADAR proteins (R-HSA-77042)



Cellular compartments: nucleoplasm.

It is still unclear how ADAR 1 and ADAR 2 proteins form the editosomes with the target RNA. Other components of these editosomes for A to I editing are unknown.

References

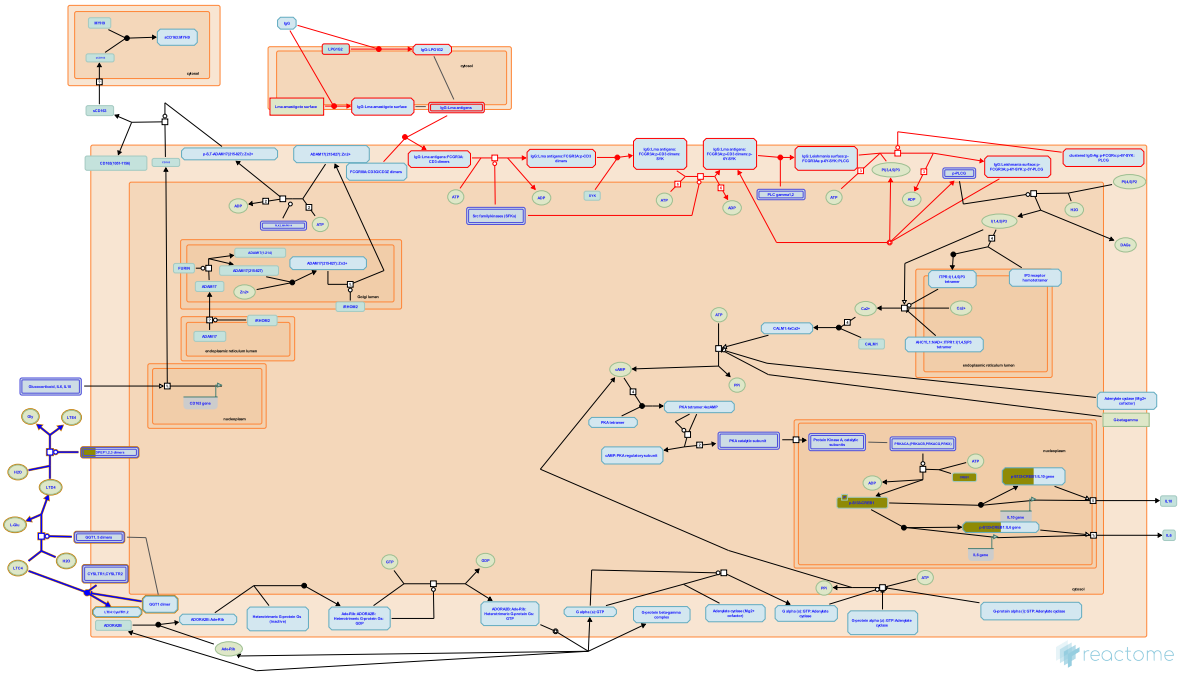
Edit history

Date	Action	Author
2003-12-05	Authored	Gopinathrao G
2003-12-05	Created	Carmichael GG
2024-03-08	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
JUN	P05412	P78563			

11. LTC4-CYSLTR mediated IL4 production (R-HSA-9664535)



Diseases: cutaneous leishmaniasis.

The Leukotriene C4 (LTC4) is a metabolite of arachidonic acid that can be produced intracellularly or extracellularly. LTC4 binds an unidentified, intracellular cysLTR. Signalling downstream LTC4 cysLTR binding has been associated with the production of IL4, independent of the GPCR associated heterotrimeric protein Gq (Bandeira Melo et al. 2002).

References

Weller PF, Phoofolo M, Bandeira-Melo C & Woods LJ (2002). Intracrine cysteinyl leukotriene receptor-mediated signaling of eosinophil vesicular transport-mediated interleukin-4 secretion. J. Exp. Med., 196, 841-50.

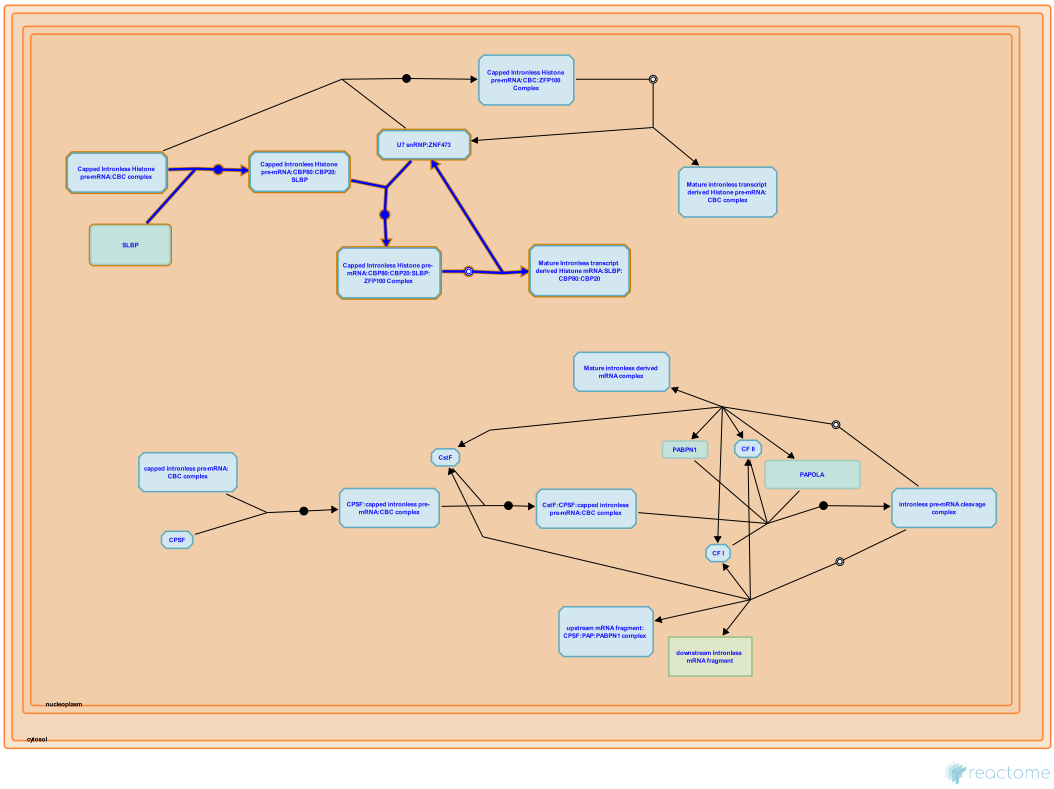
Edit history

Date	Action	Author
2019-10-25	Created	Murillo JI
2020-01-07	Edited	Jassal B, Murillo JI
2020-01-07	Authored	Jassal B, Murillo JI
2020-02-04	Reviewed	Gregory DJ
2023-03-08	Modified	Matthews L

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

Input	UniProt Id
DPEP1	P16444

12. SLBP Dependent Processing of Replication-Dependent Histone Pre-mRNAs (R-HSA-77588)



Cellular compartments: nucleoplasm.

There are two well-documented trans-acting factors required for histone pre-mRNA processing. These are:

1 Stem-loop binding protein (SLBP), also termed hairpin binding protein (HBP). This 32 kDa protein is likely the first protein that binds to the histone pre-mRNA as it is being transcribed.

The U7 snRNP. This particle contains the U7 snRNA, the smallest of the snRNAs which varies from 57-70 nts long depending on the species. The 5' end of U7 snRNA binds to a sequence 3' of the stem-loop, termed the histone downstream element (HDE). There are a number of proteins found in the U7 snRNP. There are 7 Sm proteins, as are present in the spliceosomal snRNP. Five of these proteins are the same as ones found in the spliceosomal snRNPs and there are 2, Lsm10 and Lsm11 that are unique to U7 snRNP.

A third protein joins the U7 snRNP, ZFP100, a large zinc finger protein. ZFP100 interacts with SLBP bound to the histone pre-mRNA and with Lsm11 and likely plays a critical role in recruiting U7 snRNP to the histone pre-mRNA.

It should be noted that there must be other trans-acting factors, including the factor that catalyzes the cleavage reaction. The cleavage occurs in the presence of EDTA as does the cleavage reaction in polyadenylation, it is likely that this reaction is catalyzed by a protein. There may well be additional proteins associated with U7 snRNP, and since under some conditions in vitro processing occurs in the absence of SLBP, it is possible that all of the other factors required for processing are associated with the active form of U7 snRNP.

References

Marzluff WF, Schumperli D, Schneiderman MH, Ramamurthy L, Harris ME & Bohni R (1991). Regulation of histone mRNA in the unperturbed cell cycle: evidence suggesting control at two posttranscriptional steps. Mol Cell Biol, 11, 2416-24.

Schumperli D, Soldati D, Melin L, Streit A & Koning TW (1993). Variable effects of the conserved RNA hairpin element upon 3' end processing of histone pre-mRNA in vitro. Nucleic Acids Res, 21, 1569-75.

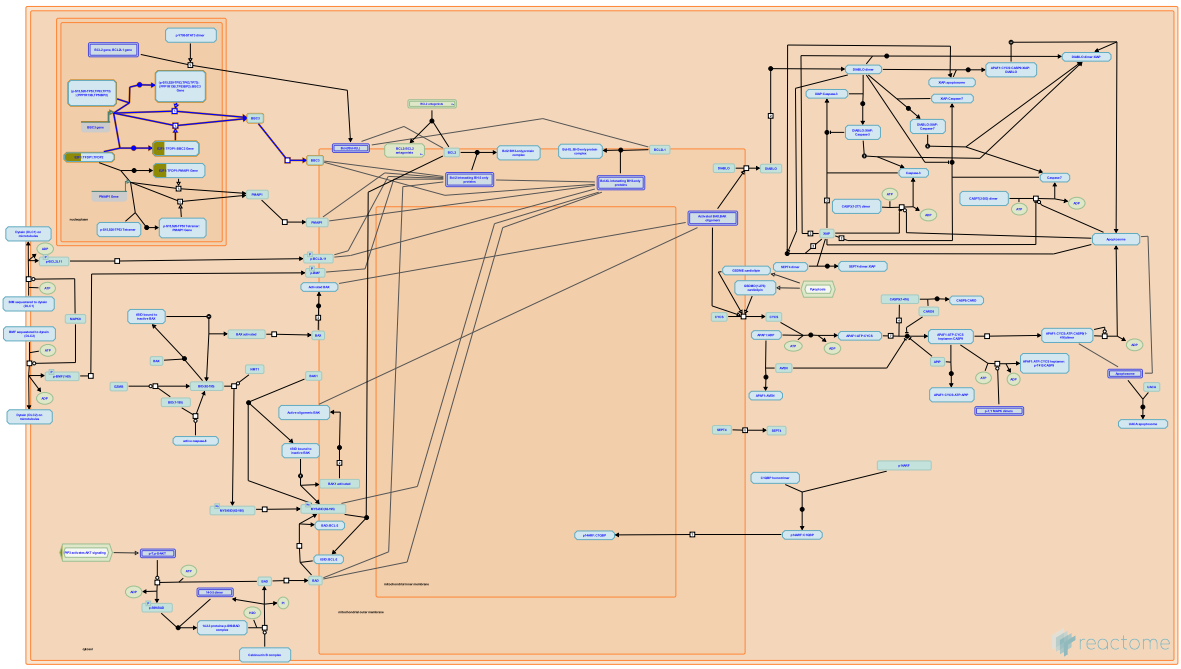
Edit history

Date	Action	Author
2003-08-22	Authored	Marzluff WF
2003-08-22	Created	Marzluff WF
2024-03-06	Edited	Gillespie ME
2024-03-08	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
MIF4GD	A9UHW6	Q14493			

13. Activation of PUMA and translocation to mitochondria (R-HSA-139915)



Cellular compartments: cytosol.

Puma is transactivated in a p53-dependent manner and by E2F1. Activated Puma is translocated to mitochondria.

References

Hershko T & Ginsberg D (2004). Up-regulation of Bcl-2 homology 3 (BH3)-only proteins by E2F1 mediates apoptosis. J Biol Chem, 279, 8627-34.

Nakano K & Vousden KH (2001). PUMA, a novel proapoptotic gene, is induced by p53. Mol Cell, 7, 683-94.

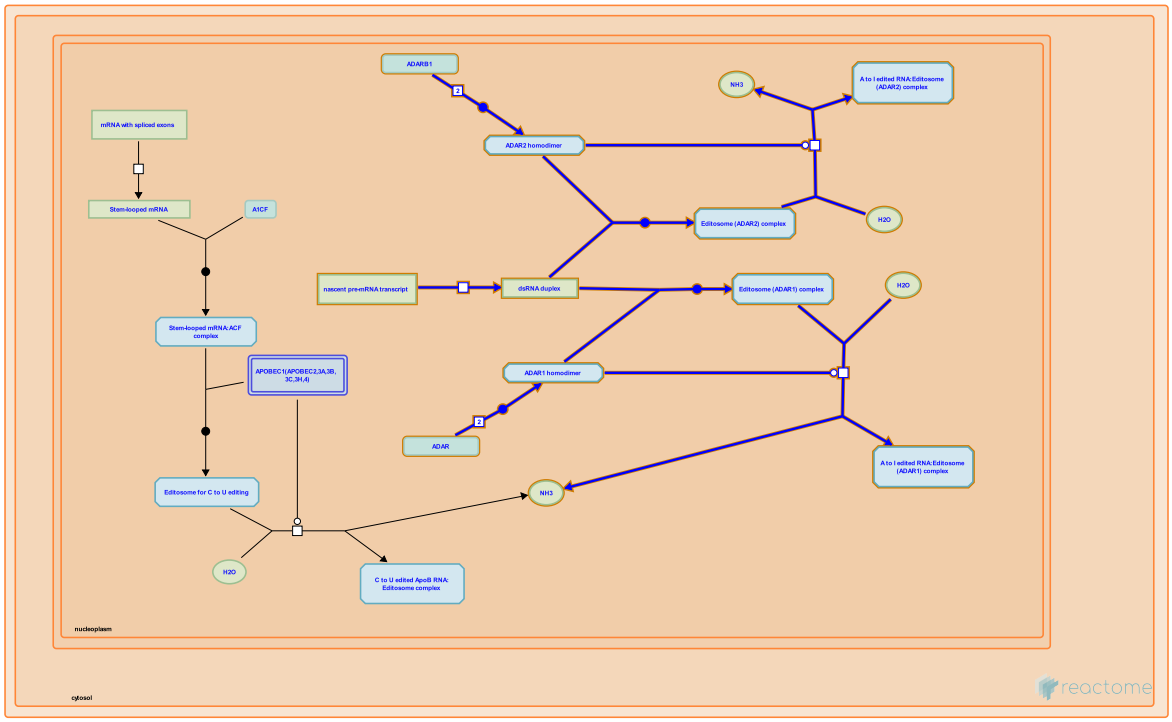
Edit history

Date	Action	Author
2004-08-09	Created	Tsujimoto Y, Hardwick JM

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

Input	UniProt Id
TFDP1	Q14186

14. mRNA Editing: A to I Conversion (R-HSA-75064)



Cellular compartments: nucleoplasm.

In humans the deamination of adenosines to inosines is the most common editing event. It is particularly prevalent in the brain, where it leads to amino acid changes that affect the conductance of several ion channels. Inosines are recognized by the translation machinery as if they were guanosines.

ADARs (Adenosine Deaminases Acting on RNA) modify pre-mRNA, acting as single peptides and recognize structural determinants in the RNA. To date 3 members of this deaminase family are known: ADAR 1, ADAR 2, and ADAR 3 that share a common modular domain structure. ADAR 1 and 2 contain a catalytic deaminase domain, a double-stranded RNA binding domain and exhibit RNA editing activity. ADAR1 activity is found in various mammalian tissues with the highest concentration in brain.

An increasing number of mammalian genes have been found to undergo deamination by ADARs. Deamination by editing in pre-mRNAs encoding subunits of ionotropic glutamate receptors (GluRs) is another well studied example. An editing event at the Q/R site of the GluR2 (GluRB) subunit of AMPA receptors converts a Gln codon CAG to an Arg codon CIG rendering the heteromeric receptor impermeable to Ca 2+ ions. Another example is the editing of 5-HT2C subtype serotonin receptor mRNA resulting in receptor isoforms with reduced G-protein coupling efficiency (reviewed by Gerber and Keller, 2001).

In mice, the editosomes with ADAR proteins require some cis-acting elements like an intronic 'editing-site complementary sequence (ECS)'. Although evolutionarily conserved, the actual role of ECS is not yet elucidated in humans. The editing complex can be generally represented as:

References

Keller W & Gerber AP (2001). RNA editing by base deamination: more enzymes, more targets, new mysteries. Trends Biochem Sci, 26, 376-84.

Pomerantz SC, McCloskey JA, Crain PF, Polson AG & Bass BL (1992). The mechanism of adenosine to inosine conversion by the double-stranded RNA unwinding/modifying activity: a high-performance liquid chromatography-mass spectrometry analysis. Biochemistry, 30, 11507-14.

Bass BL (2002). RNA editing by adenosine deaminases that act on RNA. Annu Rev Biochem, 71, 817-46.

Davidson NO & Blanc V (2003). C-to-U RNA editing: mechanisms leading to genetic diversity. J Biol Chem, 278, 1395-8.

Higuchi M, Herb A, Sprengel R, Maas S, Seeburg PH & Melcher T (1997). RED2, a brain-specific member of the RNA-specific adenosine deaminase family. J Biol Chem, 271, 31795-8.

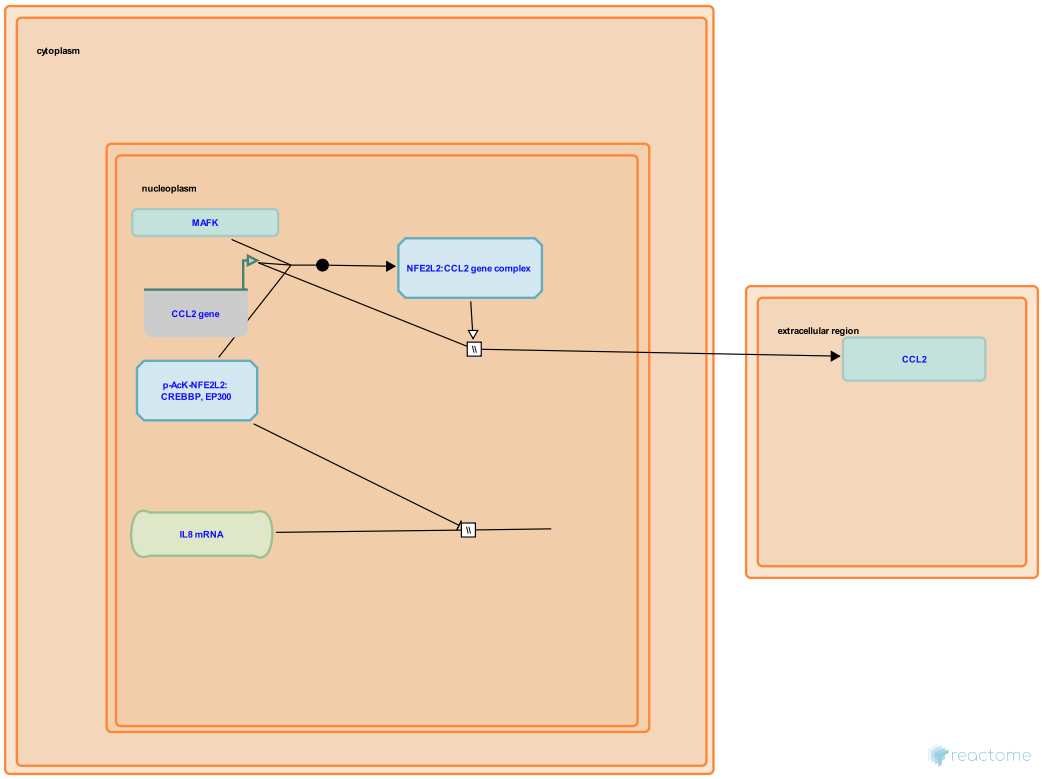
Edit history

Date	Action	Author
2003-08-22	Authored	Carmichael GG
2003-08-22	Created	Carmichael GG
2024-03-08	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
JUN	P05412	P78563			

15. NFE2L2 regulating inflammation associated genes (R-HSA-9818026)



Cellular compartments: nucleoplasm.

Subpathway representing inflammatory genes regulated by NFE2L2. NFE2L2 plays a pivotal role in regulating inflammation directly (by regulating inflammation-related genes like CCL2, IL8) and indirectly (through the HO-1-NFKB axis). This role of NFE2L2 plays a role in inflammatory diseases and expands NFE2L2 role beyond the antioxidant system. (Ahmed et al, 2017; Saha et al, 2020)

References

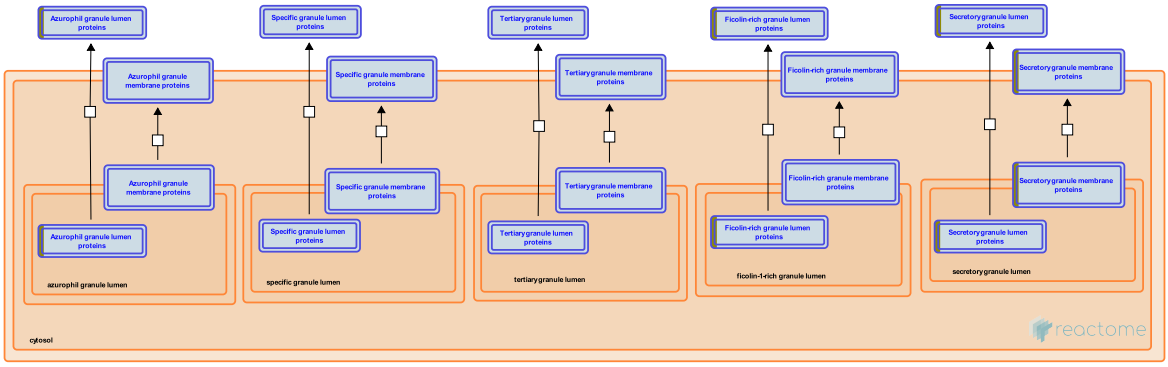
Edit history

Date	Action	Author
2022-10-10	Created	Tiwari K
2023-08-08	Edited	Tiwari K
2023-08-08	Authored	Tiwari K
2023-08-21	Modified	Matthews L

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
RNF4	P78317	P13500			

16. Neutrophil degranulation (R-HSA-6798695)



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

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

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

References

Heegaard NH, Rørvig S, Borregaard N & Østergaard O (2013). Proteome profiling of human neutrophil granule subsets, secretory vesicles, and cell membrane: correlation with transcriptome profiling of neutrophil precursors. J. Leukoc. Biol., 94, 711-21.

Sørensen OE, Borregaard N & Theilgaard-Mönch K (2007). Neutrophil granules: a library of innate immunity proteins. Trends Immunol., 28, 340-5.

Nielsen MH, Johnsen AH, Bjerrum OW, Borregaard N, Kjeldsen L, Rygaard K, ... Bastholm L (1992). Stimulus-dependent secretion of plasma proteins from human neutrophils. J. Clin. Invest., 90, 86-96.

Bucknall RC, Wright HL, Edwards SW & Moots RJ (2010). Neutrophil function in inflammation and inflammatory diseases. Rheumatology (Oxford), 49, 1618-31.

Le Cabec V, Borregaard N, Calafat J & Cowland JB (1996). Targeting of proteins to granule subsets is determined by timing and not by sorting: The specific granule protein NGAL is localized to azurophil granules when expressed in HL-60 cells. Proc. Natl. Acad. Sci. U.S.A., 93, 6454-7.

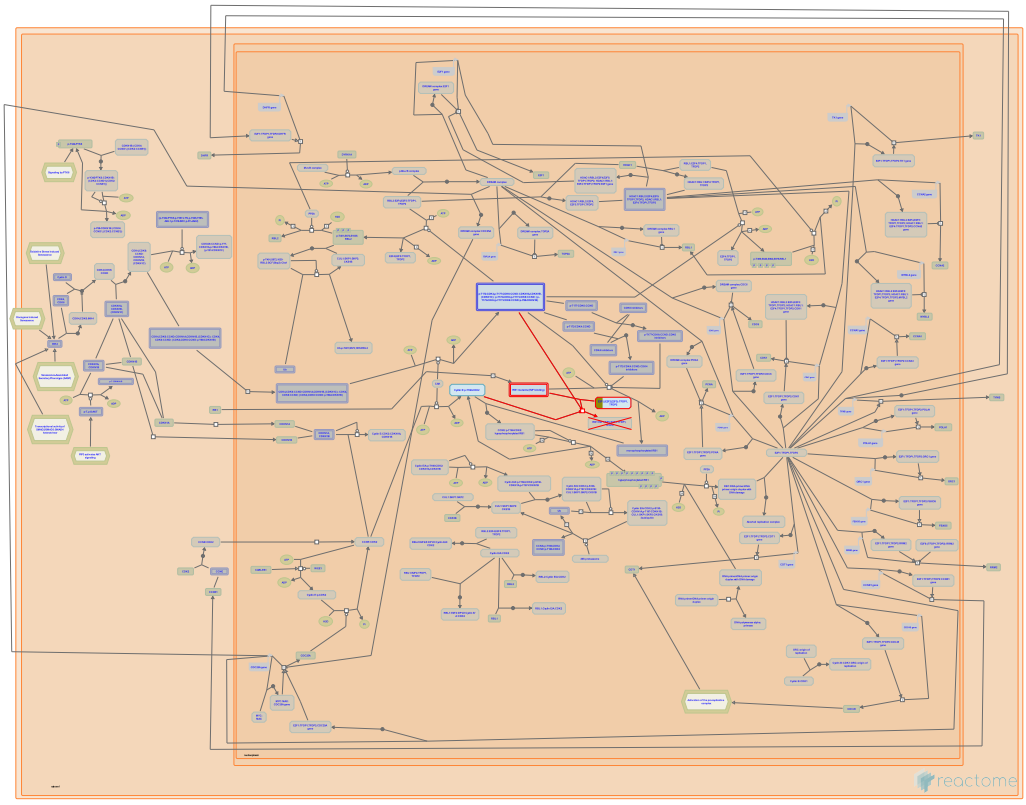
Edit history

Date	Action	Author
2015-09-21	Authored	Jupe S
2015-09-21	Created	Jupe S
2016-06-13	Edited	Jupe S
2016-06-13	Reviewed	Heegaard N
2024-03-08	Modified	Wright A

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

Input	UniProt Id	Input	UniProt Id
DDX3X	O00571	Hsc70-4	P11142
TUBB4B	P68371	sell	P14151

17. Defective binding of RB1 mutants to E2F1,(E2F2, E2F3) (R-HSA-9661069)



Cellular compartments: nucleoplasm.

Diseases: cancer.

This pathway describes impaired binding of RB1 pocket domain mutants to activating E2Fs, E2F1, E2F2 and E2F3 (Templeton et al. 1991, Helin et al. 1993, Otterson et al. 1997, Ji et al. 2004).

References

Kaye FJ, Otterson GA, Chen Wd, Coxon AB & Khleif SN (1997). Incomplete penetrance of familial retinoblastoma linked to germ-line mutations that result in partial loss of RB function. Proc. Natl. Acad. Sci. U.S.A., 94, 12036-40.

Ji P, Rekhtman K, Pagano M, Bloom J, Jiang H, Zhu L & Ichetovkin M (2004). An Rb-Skp2-p27 pathway mediates acute cell cycle inhibition by Rb and is retained in a partial-penetrance Rb mutant . Mol. Cell, 16, 47-58.

Fattaey A, Harlow E & Helin K (1993). Inhibition of E2F-1 transactivation by direct binding of the retinoblastoma protein. Mol. Cell. Biol., 13, 6501-8.

Park SH, Weinberg RA, Lanier L & Templeton DJ (1991). Nonfunctional mutants of the retinoblastoma protein are characterized by defects in phosphorylation, viral oncoprotein association, and nuclear tethering. Proc. Natl. Acad. Sci. U.S.A., 88, 3033-7.

Edit history

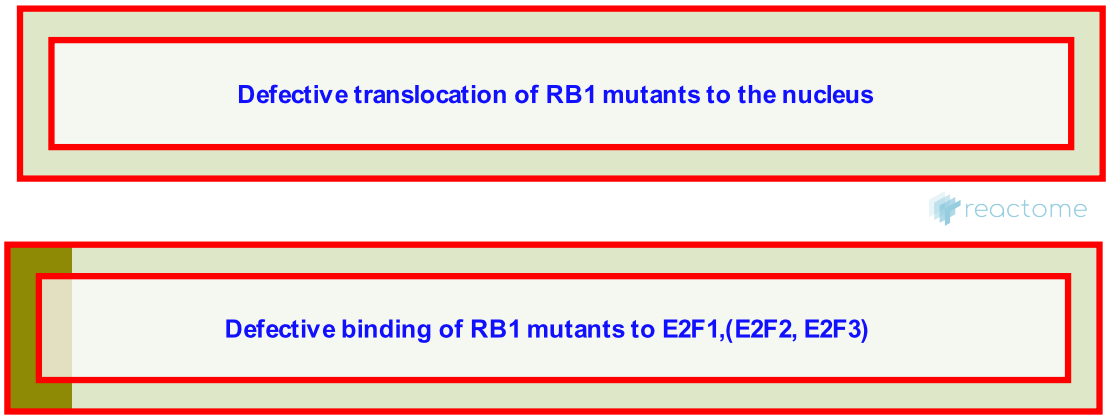
Date	Action	Author
2019-09-13	Created	Orlic-Milacic M
2020-05-07	Authored	Orlic-Milacic M

Date	Action	Author
2020-05-17	Reviewed	Dick FA
2020-05-18	Edited	Orlic-Milacic M

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

Input	UniProt Id
TFDP1	Q14186

18. Aberrant regulation of mitotic G1/S transition in cancer due to RB1 defects (R-HSA-9659787)



Diseases: cancer.

RB1 protein, also known as pRB or retinoblastoma protein, is a nuclear protein that plays a major role in the regulation of the G1/S transition during mitotic cell cycle in multicellular eukaryotes. RB1 performs this function by binding to activating E2Fs (E2F1, E2F2 and E2F3), and preventing transcriptional activation of E2F1/2/3 target genes, which include a number of genes involved in DNA synthesis. RB1 binds E2F1/2/3 through the so-called pocket region, which is formed by two parts, pocket domain A (amino acid residues 373-579) and pocket domain B (amino acid residues 640-771). Besides intact pocket domains, RB1 requires an intact nuclear localization signal (NLS) at its C-terminus (amino acid residues 860-876) to be fully functional (reviewed by Classon and Harlow 2002, Dick 2007). Functionally characterized RB1 mutations mostly affect pocket domains A and B and the NLS. RB1 mutations reported in cancer are, however, scattered over the entire RB1 coding sequence and the molecular consequences of the vast majority of these mutations have not been studied (reviewed by Dick 2007).

Many viral oncoproteins inactivate RB1 by competing with E2F1/2/3 for binding to the pocket region of RB1. RB1 protein is targeted by the large T antigen of the Simian virus 40 (SV40), the adenoviral E1A protein, and the E7 protein of oncogenic human papilloma viruses (HPVs) (reviewed by Classon and Harlow 2002).

References

Classon M & Harlow E (2002). The retinoblastoma tumour suppressor in development and cancer. Nat. Rev. Cancer, 2, 910-7.

Dick FA (2007). Structure-function analysis of the retinoblastoma tumor suppressor protein - is the whole a sum of its parts?. Cell Div, 2, 26.

Edit history

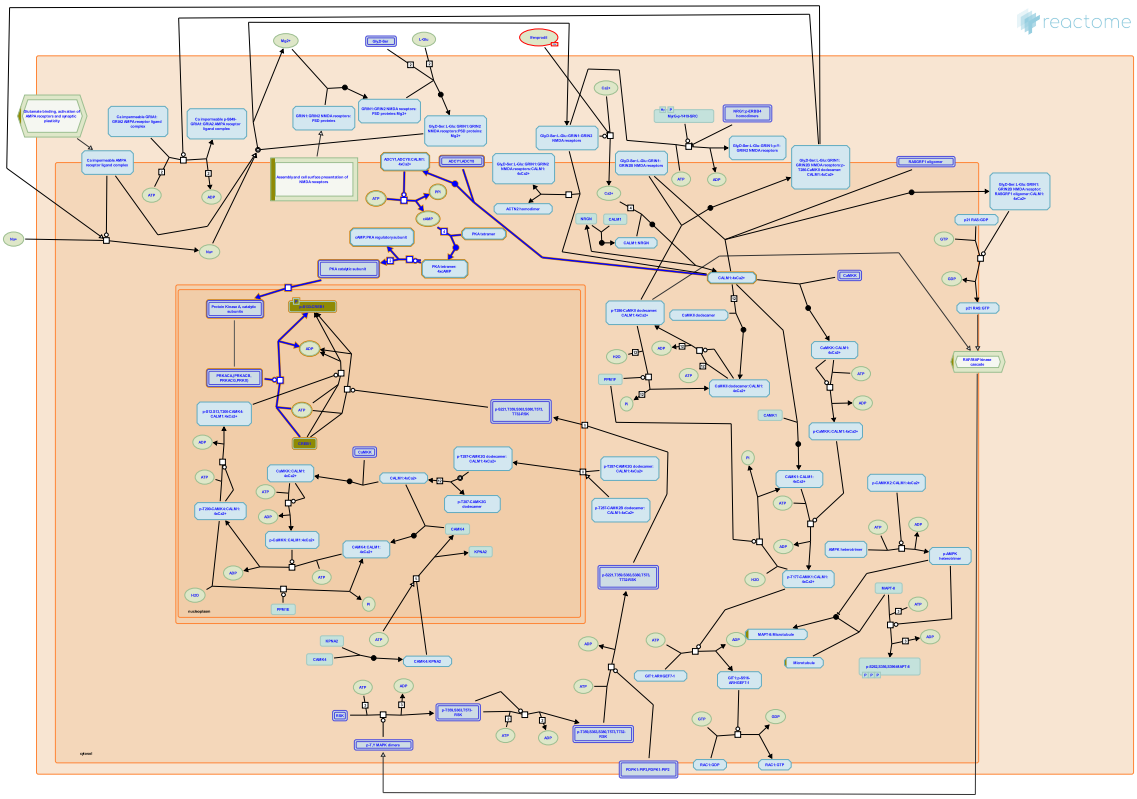
Date	Action	Author
2019-09-05	Created	Orlic-Milacic M
2020-05-07	Authored	Orlic-Milacic M
2020-05-17	Reviewed	Dick FA

Date	Action	Author
2020-05-18	Edited	Orlic-Milacic M
2023-03-08	Modified	Matthews L

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

Input	UniProt Id
TFDP1	Q14186

19. 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.

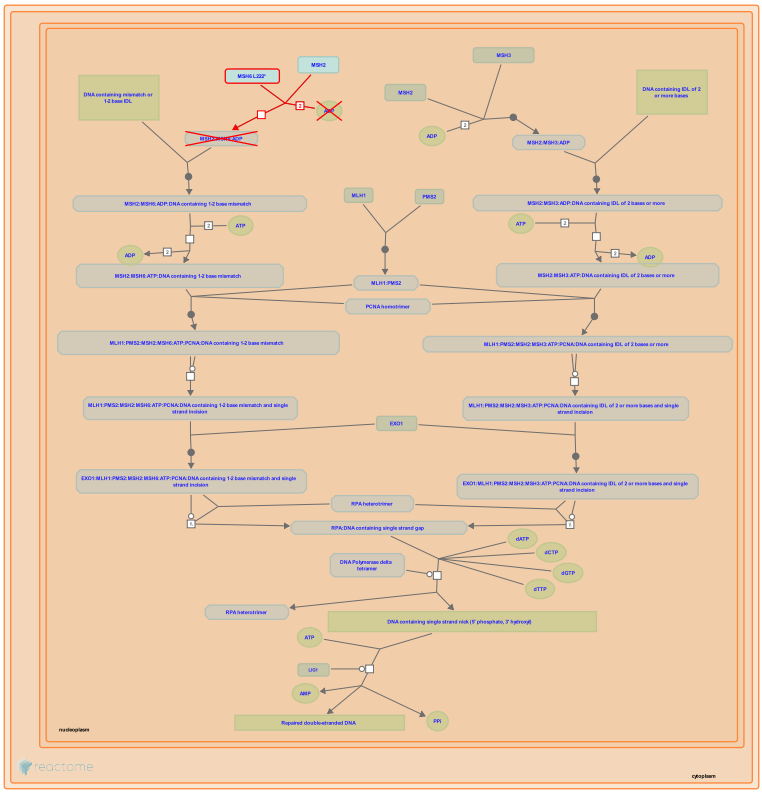
Edit history

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
2018-10-10	Revised	Orlic-Milacic M
2018-11-02	Reviewed	Hansen KB, Yi F
2018-11-07	Edited	Orlic-Milacic M
2024-03-08	Modified	Wright A

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

Input	UniProt Id
CREB1	P16220-1

20. Defective Mismatch Repair Associated With MSH6 (R-HSA-5632968)



Cellular compartments: nucleoplasm.

Diseases: cancer.

MSH6 encodes a G/T mismatch-binding protein encoded by a gene localized to within 1 megabase of the related hMSH2 gene on chromosome 2. Unlike other mismatch repair genes, the MSH6 deficient cells showed alterations primarily in mononucleotide tracts, indicating the role MSH6 plays in maintaining the integrity of the human genome. Cells deficient in MSH6, accrue mutations in tracts of repeated nucleotides. MSH6 defects seem to be less common than MLH1 and MSH2 defects. They have been mostly observed in atypical HNPCC families and are characterized by a weaker family history of tumor development, higher age at disease onset, and low degrees of microsatellite instability (MSI) that predominantly involving mononucleotide runs.

References

Dunlop MG, Farrington SM, Mitchell RJ & Campbell H (2002). Mismatch repair genes hMLH1 and hMSH2 and colorectal cancer: a HuGE review. Am. J. Epidemiol., 156, 885-902.

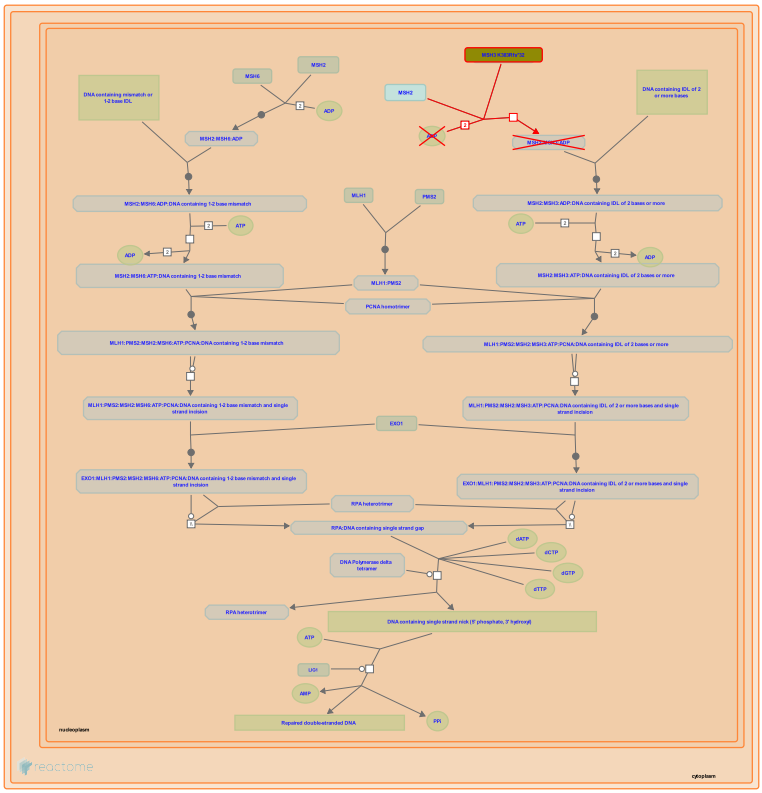
Edit history

Date	Action	Author
2011-11-10	Authored	Gillespie ME
2014-10-29	Created	Gillespie ME
2016-11-01	Reviewed	Arora S
2017-02-27	Edited	Gillespie ME

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
MSH3	P20585	P43246			

21. Defective Mismatch Repair Associated With MSH3 (R-HSA-5632927)



Cellular compartments: nucleoplasm.

Diseases: cancer.

MSH3 forms a heterodimer with MSH2 to form the MSH3:MSH2 complex, part of the post-replicative DNA mismatch repair system. This complex initiates mismatch repair by binding to a mismatch and then forming a complex with MutL alpha heterodimer. This gene contains a polymorphic 9 bp tandem repeat sequence in the first exon. Defects in this gene are a cause of susceptibility to endometrial cancer.

References

Umar A, Risinger JI, Kunkel TA, Berchuck A, Barrett JC & Boyd J (1996). Mutation of MSH3 in endometrial cancer and evidence for its functional role in heteroduplex repair. Nat. Genet., 14, 102-5.

Edit history

Date	Action	Author
2011-11-10	Authored	Gillespie ME
2014-10-29	Created	Gillespie ME
2016-11-01	Reviewed	Arora S
2017-02-27	Edited	Gillespie ME
2023-03-08	Modified	Matthews L

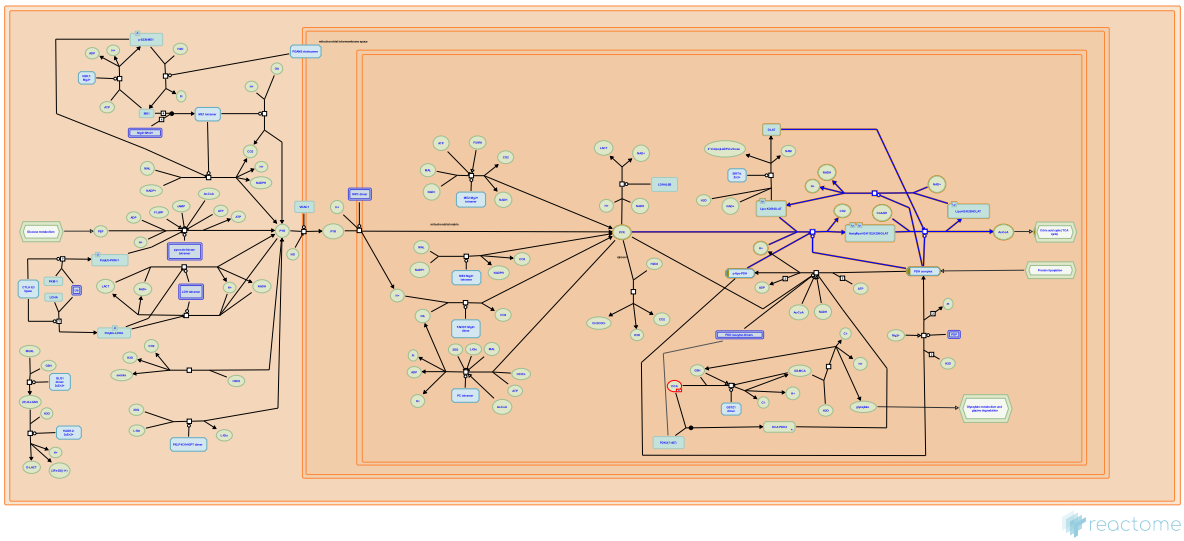
1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
MSH3	P20585

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
MSH3	P20585	P43246			

22. PDH complex synthesizes acetyl-CoA from PYR (R-HSA-9861559)



Cellular compartments: mitochondrial inner membrane, mitochondrial matrix.

The mitochondrial pyruvate dehydrogenase complex catalyzes the reaction of pyruvate, CoASH, and NAD+ to form acetylCoA, CO2, and NADH. The enzyme complex contains multiple copies of E1 alpha, E1 beta, E2, and E3, each with distinct catalytic activities (Reed and Hackert 1990; Zhou et al 2001), and the X-component (PDHX) which is required for anchoring E3 to E2 (Hiromasa et al., 2004; Vijayakrishnan et al., 2010). The reaction starts with the oxidative decarboxylation of pyruvate catalyzed by E1 alpha and beta (pyruvate dehydrogenase). Lipoamide cofactor associated with E2 is reduced at the same time. Next, the acetyl group derived from pyruvate is transferred to coenzyme A in two steps catalyzed by E2 (DLAT, dihydrolipolyl transacetylase). Finally, the oxidized form of lipoamide is regenerated and electrons are transferred to NAD+ in two steps catalyzed by E3 (DLD, dihydrolipoyl dehydrogenase). The biochemical details of this reaction have been worked out with pyruvate dehydrogenase complex and subunits purified from bovine tissue and other non-human sources. Direct evidence for the roles of the corresponding human proteins comes from studies of patients expressing mutant forms of E1 alpha (Lissens et al. 2000), E1 beta (Brown et al. 2004), E2 (Head et al. 2005), and E3 (Brautigam et al. 2005). The most common PDH complex deficiencies are caused by defects in PDHA and PDHX but can be caused by defects in any component of the complex (e.g. Pavlu-Pereira et al., 2020; reviewed in Prasad et al., 2011).

References

Zolkipli Z, Shahdadpuri R, Head RA, Brown GK, Clayton PT, King MD & Brown RM (2005). Clinical and genetic spectrum of pyruvate dehydrogenase deficiency: dihydrolipoamide acetyltransferase (E2) deficiency. Ann Neurol, 58, 234-41.

Reed LJ & Hackert ML (1990). Structure-function relationships in dihydrolipoamide acyltransferases. J Biol Chem, 265, 8971-4.

Boubriak II, Leonard JV, Thomas NH, Head RA, Brown GK & Brown RM (2004). Mutations in the gene for the E1beta subunit: a novel cause of pyruvate dehydrogenase deficiency. Hum Genet, 115, 123-7.

Fujisawa T, Aso Y, Roche TE & Hiromasa Y (2004). Organization of the cores of the mammalian pyruvate dehydrogenase complex formed by E2 and E2 plus the E3-binding protein and their capacities to bind the E1 and E3 components. J Biol Chem, 279, 6921-33.

Rivera I, Ferreira AC, Tavares de Almeida I, Bandeira A, Gomes R, Sequeira S, ... Pavlu-Pereira H (2020). Pyruvate dehydrogenase complex deficiency: updating the clinical, metabolic and mutational landscapes in a cohort of Portuguese patients. Orphanet J Rare Dis, 15, 298.

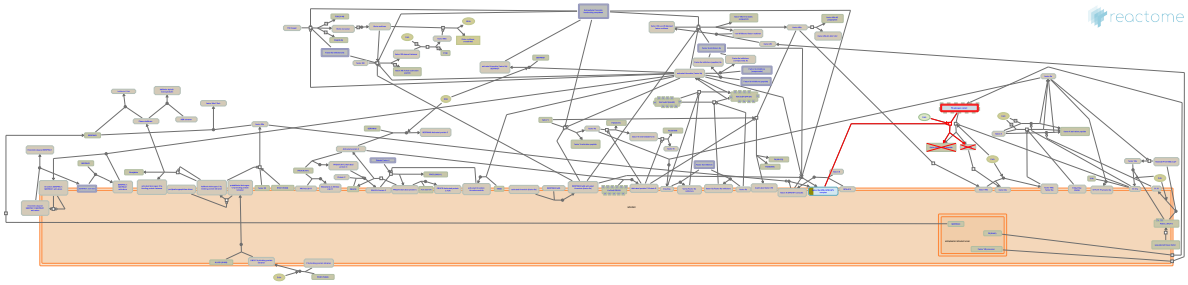
Edit history

Date	Action	Author
2024-01-25	Authored	Stephan R
2024-02-21	Created	Stephan R
2024-02-23	Edited	Stephan R
2024-02-23	Reviewed	Hill DP

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

Input	UniProt Id
PDHX	O00330

23. Defective F9 activation (R-HSA-9673221)



Diseases: hemophilia B.

Deficiency or dysfunction of FIX leads to hemophilia B (HB), an X-linked, recessive, bleeding disorder. On a molecular basis, HB is due to a heterogeneous spectrum of mutations spread throughout the F9 gene (Rallapalli PM et al. 2013).

The Reactome event describes the defective proteolytic activation of FIX by factor XIa due to the presence of HB-associated point mutations R191C, R191H, R226Q and R226W in the cleavage sites of FIX (Liddell MB et al. 1989; Monroe DM et al. 1989; Suehiro K et al. 1989; Diuguid DL et al. 1989; Bertina RM et al.1990). In addition, naturally occurring point mutations in the FIX propeptide sequence such as N43Q, N43L or N46S are also annotated here. These FIX variants are secreted into the circulation with a mutant 18-amino acid propeptide still attached (Bentley AK et al. 1986; Galeffi P & Brownlee GG 1987). The unprocessed FIX variants were found to affect the function of the protein by destabilizing the calcium-induced conformation of FIX (Wojcik EG et al. 1997) and showed delayed activation by FXIa (Liddell MB et al. 1989; Ware J et al. 1989; de la Salle C et al. 1993; Wojcik EG et al. 1997; Bristol JA et al. 1993).

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Edit history

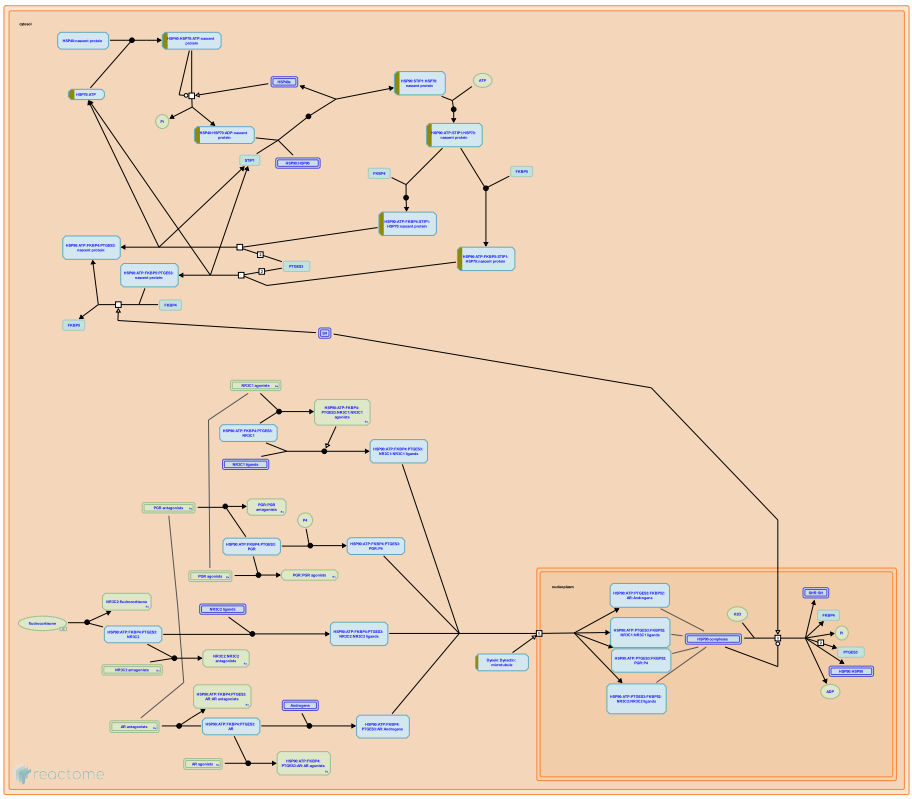
Date	Action	Author
2019-09-09	Authored	Shamovsky V
2020-01-07	Created	Shamovsky V

Date	Action	Author
2020-01-09	Reviewed	D'Eustachio P
2020-04-02	Reviewed	Zhang B
2020-05-26	Edited	Shamovsky V

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

Input	UniProt Id
GP1BB	P13224

24. HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand (R-HSA-3371497)



Cellular compartments: cytosol.

Steroid hormone receptors (SHR) are transcription factors that become activated upon sensing steroid hormones such as glucocorticoids, mineralocorticoids, progesterone, androgens, or estrogen (Escriva et al 2000; Griekspoor A et al. 2007; Eick GN & Thornton JW. 2011). Depending on SHR type and the presence of ligand, they show different subcellular localizations. Whereas both unliganded and liganded estrogen receptors (ERalpha and ERbeta) are predominantly nuclear, unliganded glucocorticoid (GR) and androgen receptors (AR) are mostly located in the cytoplasm and completely translocate to the nucleus only after binding hormone (Htun H et al. 1999; Stenoien D et al. 2000; Tyagi RK et al. 2000; Cadepond F et al. 1992; Jewell CM et al. 1995; Kumar S et al. 2006). The unliganded mineralocorticoid receptor (MR) is partially cytoplasmic but can be found in nucleus in the ligand-bound or ligand-free form (Nishi M & Kawata M 2007). The progesterone receptor (PR) exists in two forms (PRA and PRB) with different ratios of nuclear versus cytoplasmic localization of the unliganded receptor. In most cell contexts, the PRA isoform is a repressor of the shorter PRB isoform, and without hormone induction it is mostly located in the nucleus, whereas PRB distributes both in the nucleus and in the cytoplasm (Lim CS et al. 1999; Griekspoor A et al. 2007). In the absence of ligand, members of the steroid receptor family remain sequestered in the cytoplasm and/or nucleus in the complex with proteins of HSP70/HSP90 chaperone machinery (Pratt WB & Dittmar KD1998). The highly dynamic ATP-dependent interactions of SHRs with HSP90 complexes regulate SHR cellular location, protein stability, competency to bind steroid hormones and transcriptional activity (Echeverria PC & Picard D 2010). Understanding the mechanism of ATPase activity of HSP90 is mostly based on structural and functional studies of the Saccharomyces cerevisiae Hsp90 complexes (Meyer P et al. 2003, 2004; Ali MM et al. 2006; Prodromou C et al. 2000; Prodromou C 2012). The ATPase cycle of human HSP90 is less well understood, however several studies suggest that the underlying enzymatic mechanisms and a set of conformational changes that accompany the ATPase cycle are highly similar in both species (Richter K et al. 2008; Vaughan CK et al. 2009). Nascent SHR proteins are chaperoned by HSP70 and HSP40 to HSP90 cycle via STIP1 (HOP) (and its TPR domains) (Hernández MP et al. 2002a,b; EcheverriaPC & Picard D 2010; Li J et al. 2011). The ATP-bound form of HSP90 leads to the displacement of STIP1 by immunophilins FKBP5 or FKBP4 resulting in conformational changes that allow efficient hormone binding (Li J et al. 2011). PTGES3 (p23) binds to HSP90 complex finally stabilizing it in the conformation with a high hormone binding affinity. After hydrolysis of ATP the hormone bound SHR is released from HSP90 complex. The cytosolic hormone-bound SHR can be transported to the nucleus by several import pathways such as the dynein-based nuclear transport along microtubules involving the transport of the entire HSP90 complex or nuclear localization signals (NLS)-mediated nuclear targeting by importins (Tyagi RK et al. 2000; Cadepond F et al. 1992; Jewell CM et al. 1995; Kumar S et al. 2006). It is worth noting that GR-importin interactions can be ligand-dependent or independent (Freedman & Yamamoto 2004; Picard & Yamamoto 1987). In the nucleus ligand-activated SHR dimerizes, binds specific sequences in the DNA, called Hormone Responsive Elements (HRE), and recruits a number of coregulators that facilitate gene transcription. Nuclear localization is essential for SHRs to transactivate their target genes, but the same receptors also possess non-genomic functions in the cytoplasm.

The Reactome module describes the ATPase-driven conformational cycle of HSP90 that regulates ligand-dependent activation of SHRs.

References

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Buchner J & Li J (2013). Structure, function and regulation of the hsp90 machinery. Biomed J, 36, 106-17.

Jackson SE (2013). Hsp90: structure and function. Top Curr Chem, 328, 155-240.

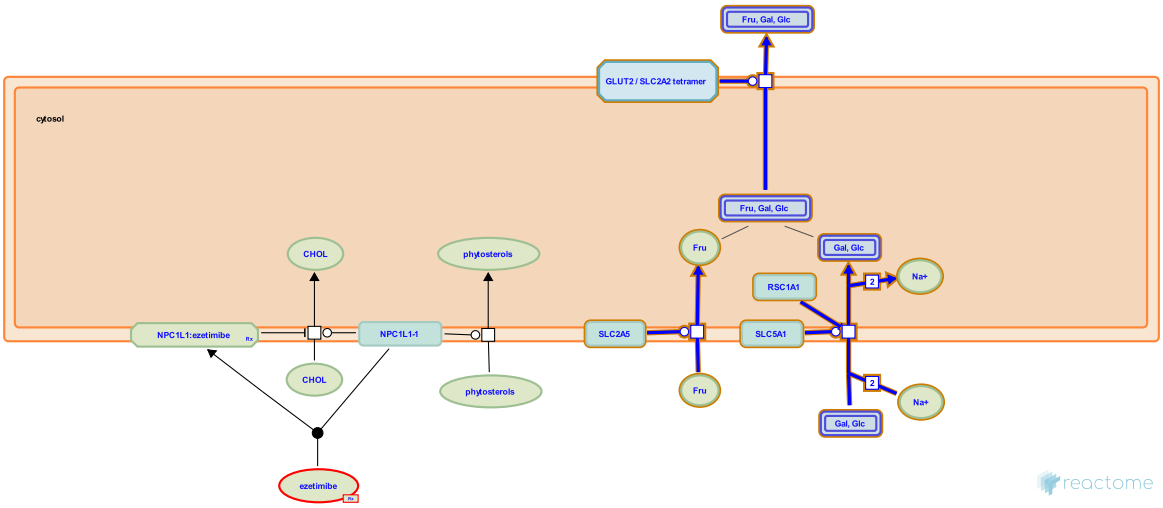
Edit history

Date	Action	Author
2013-05-13	Created	Shamovsky V
2016-09-17	Reviewed	Rothfels K
2016-11-19	Authored	Shamovsky V
2017-02-22	Reviewed	Picard D, Echeverria PC
2017-02-25	Edited	Shamovsky V
2024-03-08	Modified	Wright A

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

Input	UniProt Id	Input	UniProt Id
Hsc70-4	P11142	TUBB4B	P68371

25. Intestinal hexose absorption (R-HSA-8981373)



Hexoses, notably fructose, glucose, and galactose generated in the lumen of the small intestine by breakdown of dietary carbohydrate, are taken up by enterocytes lining the microvilli of the small intestine and released from them into the blood. Uptake into enterocytes is mediated by two transporters localized on the luminal surfaces of the cells. SLC5A1, also known as SGLT1, mediates the co-transport of sodium ions and glucose and galactose, and SLC2A5, also known as GLUT5, mediates fructose uptake (Wright 1998). Tetrameric SLC2A2, also known as GLUT2, localized on the basolateral surfaces of enterocytes, mediates the release of these hexoses into the blood (Kellett & Brot-Laroche 2005; Wright et al. 2004).

References

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Loo DD, Hirayama BA, Turk E & Wright EM (2004). Surprising versatility of Na+-glucose cotransporters: SLC5. Physiology (Bethesda), 19, 370-6.

Kellett GL & Brot-Laroche E (2005). Apical GLUT2: a major pathway of intestinal sugar absorption. Diabetes, 54, 3056-62.

Edit history

Date	Action	Author
2006-11-03	Edited	D'Eustachio P
2006-11-03	Authored	D'Eustachio P
2007-01-16	Reviewed	Wright EM
2017-03-06	Created	D'Eustachio P
2024-03-08	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
TMEM237	Q96Q45-2	P22732			

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.

27 of the submitted entities were found, mapping to 32 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CASC3	O15234	CCNK	O75909	CCRN4L	Q9UK39
CEP89	Q96ST8	CREB1	P16220-1	DDX3X	O00571
DPEP1	P16444	FBXW10	Q5XX13	GEMIN5	Q8TEQ6
GP1BB	P13224	Hsc70-4	P11142	IDH3G	P51553
INO80C	Q6PI98	JUN	P05412	MEAF6	Q9HAF1
MSH3	P20585	PAN3	Q58A45	PDHX	O00330
PNPLA2	Q96AD5	RNF4	P78317	RNF8	O76064
TDRD12	Q587J7	TFDP1	Q14186	TP53INP1	Q96A56
TUBB4B	P68371	XPC	Q01831	sell	P14151

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
CCNK	ENSG00000090061	CCRN4L	ENSG00000151014	CREB1	ENSG00000118260
TP53INP1	ENSG00000164938	TUBB4B	ENST00000340384		

Interactors (28)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
CALML3	P27482	Q9HD67	CASC3	O15234	Q92900
CCNK	O75909	Q9NYV4, Q14004	CEP89	Q96ST8-3	Q9NRD5
CREB1	P16220	P18846	DDX3X	O00571	P04608
FAM154B	Q658L1	Q14192	GEMIN5	Q8TEQ6	P06730
GP1BB	P13224	P07359	INO80C	Q6PI98	P50454
JUN	P05412	P78563	KIAA0586	Q9BVV6	Q8IW35, O43303
KLHL6	Q8WZ60	Q49AN0	LIN28B	Q6ZN17	P67809
MEAF6	Q9HAF1	P40937	MIF4GD	A9UHW6	Q14493
MSH3	P20585	P40692, P43246	PAN3	Q58A45	Q8NDV7
PDHX	O00330	Q8IWL3	PNPLA2	Q96AD5	P00533
RNF4	P78317	P13500	RNF8	O76064	P50570, O00401
TFDP1	Q14186	P06400	TMEM237	Q96Q45-2	P27352
TUBB4B	P68371	P10636-8	XPC	Q01831	P41208
ZMYND8	Q9ULU4	P41182	sell	P14151-2	Q9BRI3

7. Identifiers not found

These 11 identifiers were not found neither mapped to any entity in Reactome.

C17orf75	IAH1	KIAA1257	LENG9	LMNTD1	NWD1	NWD2	PMFBP1
TMEM135	VWDE	Iron-7					