reactome

Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 88 on 11/04/2024. The web link to these results is:

https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyNDA0MTExNTQwMTRfMzYyNQ%3D%3D

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

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1. Introduction

Reactome is a curated database of pathways and reactions in human biology. Reactions can be considered as pathway 'steps'. Reactome defines a 'reaction' as any event in biology that changes the state of a biological molecule. Binding, activation, translocation, degradation and classical biochemical events involving a catalyst are all reactions. Information in the database is authored by expert biologists, entered and maintained by Reactome's team of curators and editorial staff. Reactome content frequently cross-references other resources e.g. NCBI, Ensembl, UniProt, KEGG (Gene and Compound), ChEBI, PubMed and GO. Orthologous reactions inferred from annotation for Homo sapiens are available for 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:

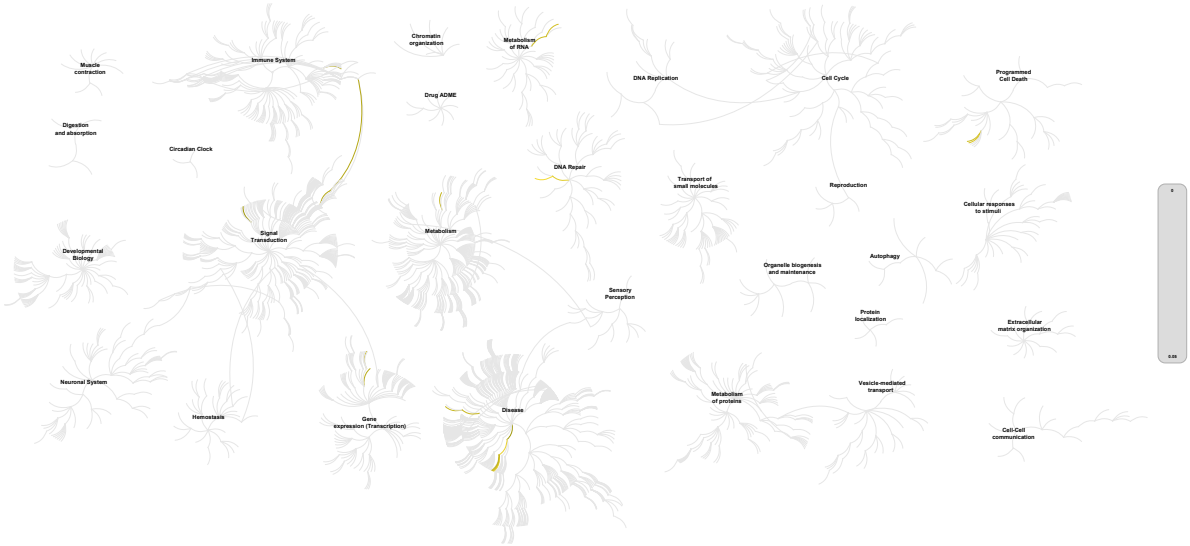
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, … D'Eustachio P (2016). The reactome pathway knowledgebase. Nucleic Acids Research, 44(D1), D481–D487. https://doi.org/10.1093/nar/gkv1351.

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.
- 14 out of 17 identifiers in the sample were found in Reactome, where 438 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 MjAyNDA0MTExNTQwMTRfMzYyNQ%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
Mismatch repair (MMR) directed by MSH2:MSH3 (MutSbeta)	3 / 42	0.002	0.001	0.338	7 / 9	6.05e-04
Defective Mismatch Repair Associated With MLH1	1 / 4	1.74e-04	0.005	0.338	1 / 1	6.72e-05
Diseases of Mismatch Repair (MMR)	4 / 93	0.004	0.007	0.338	5 / 6	4.03e-04
Mismatch Repair	4 / 115	0.005	0.011	0.338	13 / 17	0.001
Defective Mismatch Repair Associated With MSH2	1 / 8	3.48e-04	0.011	0.338	1 / 2	1.34e-04
Activation of NOXA and translocation to mitochondria	1 / 11	4.78e-04	0.015	0.338	2 / 5	3.36e-04
Formation of editosomes by ADAR proteins	1 / 13	5.65e-04	0.017	0.338	1 / 4	2.69e-04
Activation of PUMA and translocation to mitochondria	1 / 15	6.52e-04	0.02	0.338	2 / 5	3.36e-04
mRNA Editing: A to I Conversion	1 / 15	6.52e-04	0.02	0.338	1 / 6	4.03e-04
TP53 Regulates Transcription of Genes Involved in Cytochrome C Release	2 / 169	0.007	0.022	0.338	2 / 25	0.002
Defective binding of RB1 mutants to E2F1,(E2F2, E2F3)	1 / 17	7.39e-04	0.023	0.338	1 / 1	6.72e-05
Aberrant regulation of mitotic G1/S transition in cancer due to RB1 defects	1 / 17	7.39e-04	0.023	0.338	1 / 2	1.34e-04
Defective Mismatch Repair Associated With MSH6	2 / 18	7.83e-04	0.024	0.338	1 / 1	6.72e-05
Defective Mismatch Repair Associated With MSH3	2 / 19	8.26e-04	0.025	0.338	1 / 1	6.72e-05
PDH complex synthesizes acetyl-CoA from PYR	1 / 19	8.26e-04	0.025	0.338	3 / 3	2.02e-04
TP53 Regulates Transcription of DNA Repair Genes	5 / 201	0.009	0.03	0.338	4 / 17	0.001
CREB phosphorylation	1 / 24	0.001	0.032	0.338	1 / 4	2.69e-04
Interleukin-38 signaling	1 / 24	0.001	0.032	0.338	1 / 5	3.36e-04
Pre-NOTCH Transcription and Translation	2 / 239	0.01	0.041	0.338	3 / 28	0.002
Diseases of DNA repair	4 / 242	0.011	0.042	0.338	5 / 34	0.002
Activation of BIM and translocation to mitochondria	1 / 42	0.002	0.055	0.338	1 / 2	1.34e-04

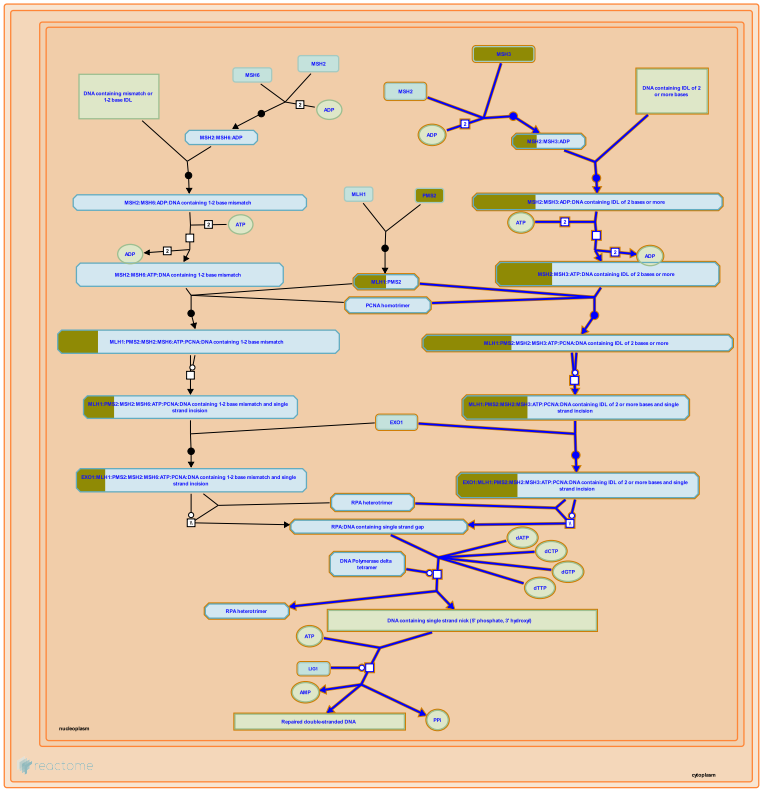
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
PIWI-interacting RNA (piRNA) biogenesis	1 / 42	0.002	0.055	0.338	7 / 15	0.001
mRNA Editing	1 / 42	0.002	0.055	0.338	1 / 9	6.05e-04
Regulation of pyruvate dehydrogenase (PDH) complex	1 / 43	0.002	0.056	0.338	2 / 6	4.03e-04
Association of TriC/CCT with target proteins during biosynthesis	1 / 44	0.002	0.058	0.338	1 / 2	1.34e-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. Mismatch repair (MMR) directed by MSH2:MSH3 (MutSbeta) (R-HSA-5358606)



MSH2:MSH3 (MutSbeta) binds unpaired loops of 2 or more nucleotides (Palombo et al. 1996, Genschel et al. 1998). Human cells contain about 6-fold more MSH2:MSH6 than MSH2:MSH3 (MutSbeta) and an imbalance in the ratio can cause a mutator phenotype (Drummond et al. 1997, Marra et al. 1998). Binding of the mismatch activates MSH2:MSH3 to exchange ADP for ATP, adopt the conformation to allow movement along the DNA, and interact with downstream effectors PCNA, MLH1:PMS2 and EXO1. The interaction with PCNA initiates excision of the recently replicated strand. MLH1:PMS2 makes a nick that is enlarged to a gap of hundreds of nucleotides by EXO1. DNA is polymerized across the gap by DNA polymerase delta and the remaining nick is sealed by DNA ligase I.

References

Marti TM, Fleck O & Kunz C (2002). DNA mismatch repair and mutation avoidance pathways. J. Cell. Physiol., 191, 28-41.

Jiricny J, Iaccarino I, Palombo F, Shimada T, Nakajima E & Ikejima M (1996). hMutSbeta, a heterodimer of hMSH2 and hMSH3, binds to insertion/deletion loops in DNA. Curr. Biol., 6, 1181-4.

Drummond JT, Littman SJ, Genschel J & Modrich P (1998). Isolation of MutSbeta from human cells and comparison of the mismatch repair specificities of MutSbeta and MutSalpha. J. Biol. Chem., 273, 19895-901.

Jiricny J, Roscilli G, Iaccarino I, Marra G, Lettieri T & Delmastro P (1998). Mismatch repair deficiency associated with overexpression of the MSH3 gene. Proc. Natl. Acad. Sci. U.S.A., 95, 8568-73.

Drummond JT, Genschel J, Wolf E & Modrich P (1997). DHFR/MSH3 amplification in methotrexate-resistant cells alters the hMutSalpha/hMutSbeta ratio and reduces the efficiency of base-base mismatch repair. Proc. Natl. Acad. Sci. U.S.A., 94, 10144-9.

Edit history

Date	Action	Author
2014-03-28	Edited	May B
2014-03-28	Authored	May B
2014-03-30	Created	May B
2014-05-23	Reviewed	Edelbrock MA
2024-03-08	Modified	Wright A

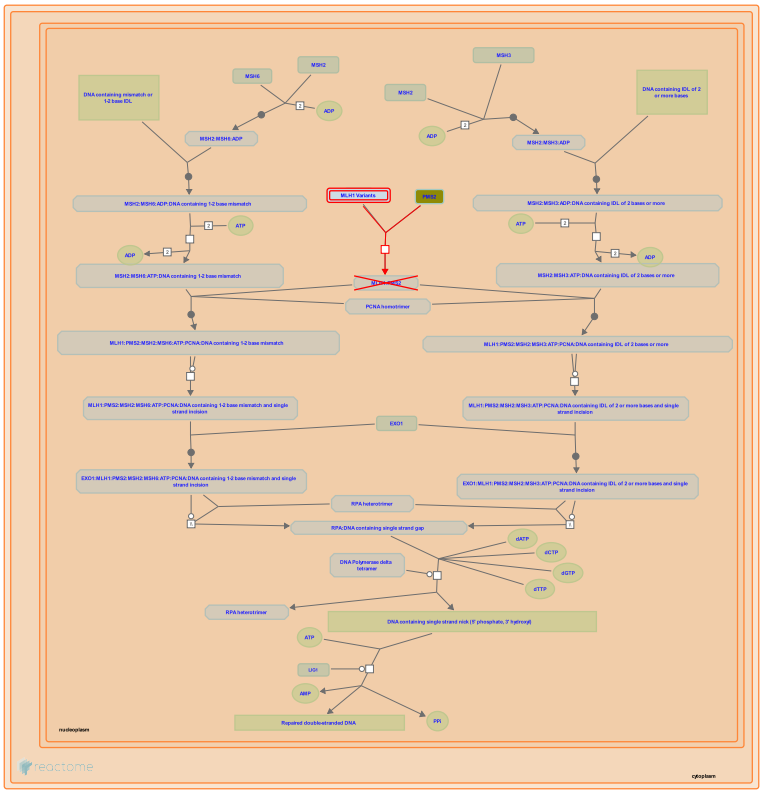
2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
MSH3	P20585	PMS1	P54278

Interactors found in this pathway (2)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
MSH3	P20585	P43246	SLX4	Q8IY92	P43246

2. Defective Mismatch Repair Associated With MLH1 (R-HSA-5545483)



Cellular compartments: nucleoplasm.

Diseases: cancer.

The MLH1:PMS2 complex is homologous to the E. coli MutL gene and is involved in DNA mismatch repair. Heterozygous mutations in the MLH1 gene result in hereditary nonpolyposis colorectal cancer-2 (Papadopoulos et al., 1994).

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.

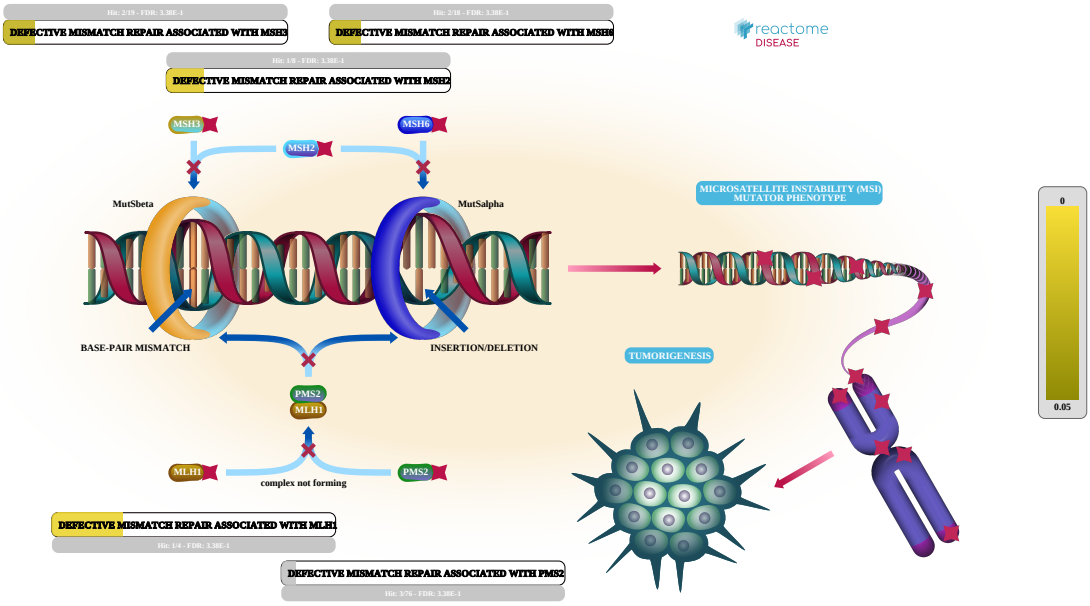
Edit history

Date	Action	Author
2011-11-10	Authored	Gillespie ME
2014-05-21	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
PMS1	P54278

3. Diseases of Mismatch Repair (MMR) (R-HSA-5423599)



Diseases: cancer.

Defects in mammalian DNA mismatch repair (MMR) genes (MLH1, PMS2, MSH2, and MSH6) are characterized by microsatellite instability and reduced fidelity during replication and repair steps. The MMR proteins interact with each other to execute steps within the mismatch repair pathway. Defective variants of these proteins are associated with nonpolyposis colorectal cancer. The MutS proteins are thought to directly contact double-stranded DNA, scanning along the genomic DNA for mismatches analogous to a "sliding clamp" until they encounter a base pair containing a mismatch. The MutS proteins interact with multiple proteins including other MLH and MutL, the later have significant amino acid identify and structural similarity to the MLH proteins, as well as RPA, EXO1, RFC, possibly HMGB1, and other less well-characterized proteins.

With respect to the mutator function, the MSH2/MutSaplha heterodimer is thought primarily to repair single-base substitutions and 1 bp insertiondeletion mutations, while MSH2/MutSbeta is thought primarily to repair 1-4 bp insertiondeletion mutations. The MLH and MutL heterodimer proteins interact with heterodimers of MutS proteins to help catalyze different functions. MLH1:MutLalpha is the primary complex that interacts with both MutS alpha and beta complex in mechanisms thought to be relevant to cancer prevention. Recent studies suggest that MLH1:MLH3 may also contributes to some of these processes as well, but in all mechanisms tested to a lesser degree than MLH1:PMS2.

Heterozygous mutations in the MLH1 gene result in hereditary nonpolyposis colorectal cancer-2 (Papadopoulos et al., 1994).

Variants of the MSH2 gene are associated with hereditary nonpolyposis colorectal cancer. Alteration of MSH2 is also involved in Muir-Torre syndrome and mismatch repair cancer syndrome (Fishel et al. 1993).

Defects in the MSH3 gene are a cause of susceptibility to endometrial cancer (Risinger et al. 1996).

Defects in the MSH6 gene are 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) (Lucci-Cordisco et al. 2001).

Mutations in the PMS2 gene are associated with hereditary nonpolyposis colorectal cancer, Turcot syndrome, and are a cause of supratentorial primitive neuroectodermal tumors. Heterozygous truncating mutations in PMS2 play a role in a small subset of hereditary nonpolyposis colorectal carcinoma (Lynch syndrome, HNPCC-like) families. PMS2 mutations lead to microsatellite instability with carriers showing a microsatellite instability high phenotype and loss of PMS2 protein expression in all tumors (Hamilton et al. 1995, Hendriks et al. 2006).

References

Lipkin SM & Chao EC (2006). Molecular models for the tissue specificity of DNA mismatch repair-deficient carcinogenesis. Nucleic Acids Res., 34, 840-52.

Edit history

Date	Action	Author
2014-03-03	Authored	Gillespie ME
2014-05-09	Created	Gillespie ME
2016-11-01	Reviewed	Arora S
2017-02-27	Edited	Gillespie ME
2023-10-12	Modified	Weiser JD

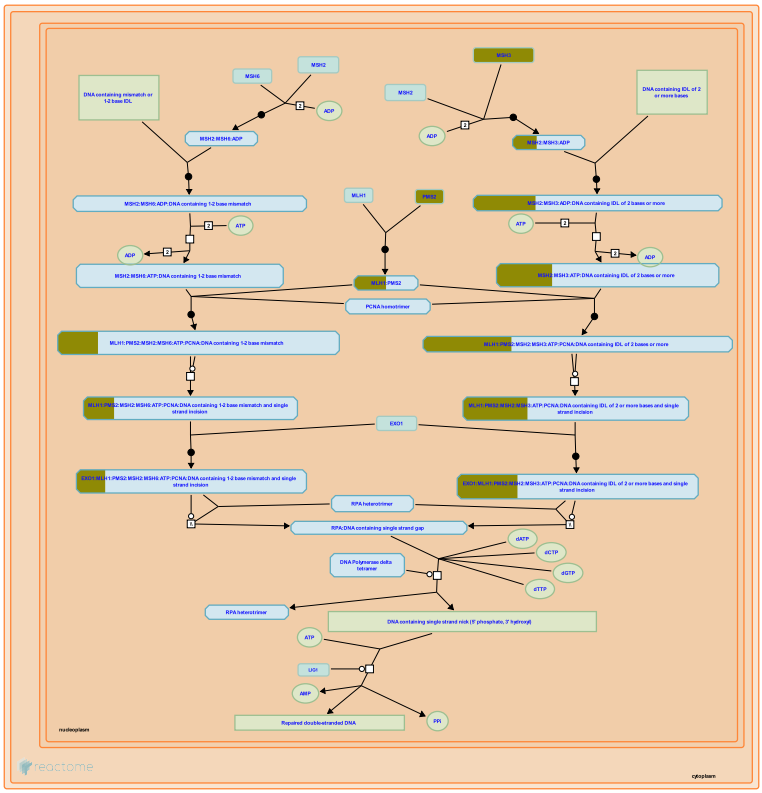
2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
MSH3	P20585	PMS1	P54278

Interactors found in this pathway (3)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
MSH3	P20585	P40692, P43246	PMS1	P54277	P40692
SLX4	Q8IY92	P43246			

4. Mismatch Repair (R-HSA-5358508)



The mismatch repair (MMR) system corrects single base mismatches and small insertion and deletion loops (IDLs) of unpaired bases. MMR is primarily associated with DNA replication and is highly conserved across prokaryotes and eukaryotes. MMR consists of the following basic steps: a sensor (MutS homologue) detects a mismatch or IDL, the sensor activates a set of proteins (a MutL homologue and an exonuclease) that select the nascent DNA strand to be repaired, nick the strand, exonucleolytically remove a region of nucleotides containing the mismatch, and finally a DNA polymerase resynthesizes the strand and a ligase seals the remaining nick (reviewed in Kolodner and Marsischkny 1999, Iyer et al. 2006, Li 2008, Fukui 2010, Jiricny 2013).

Humans have 2 different MutS complexes. The MSH2:MSH6 heterodimer (MutSalpha) recognizes single base mismatches and small loops of one or two unpaired bases. The MSH2:MSH3 heterodimer (MutSbeta) recognizes loops of two or more unpaired bases. Upon binding a mismatch, the MutS complex becomes activated in an ATP-dependent manner allowing for subsequent downstream interactions and movement on the DNA substrate. (There are two mechanisms proposed: a sliding clamp and a switch diffusion model.) Though the order of steps and structural details are not fully known, the activated MutS complex interacts with MLH1:PMS2 (MutLalpha) and PCNA, the sliding clamp present at replication foci. The role of PCNA is multifaceted as it may act as a processivity factor in recruiting MMR proteins to replicating DNA, interact with MLH1:PMS2 and Exonuclease 1 (EXO1) to initiate excision of the recently replicated strand and direct DNA polymerase delta to initiate replacement of bases. MLH1:PMS2 makes an incision in the strand to be repaired and EXO1 extends the incision to make a single-stranded gap of up to 1 kb that removes the mismatched base(s). (Based on assays of purified human proteins, there is also a variant of the mismatch repair pathway that does not require EXO1, however the mechanism is not clear. EXO1 is almost always required, it is possible that the exonuclease activity of DNA polymerase delta may compensate in some situations and it has been proposed that other endonucleases may perform redundant functions in the absence of EXO1.) RPA binds the single-stranded region and a new strand is synthesized across the gap by DNA polymerase delta. The remaining nick is sealed by DNA ligase I (LIG1).

Concentrations of MMR proteins MSH2:MSH6 and MLH1:PMS2 increase in human cells during S phase and are at their highest level and activity during this phase of the cell cycle (Edelbrock et al. 2009). Defects in MSH2, MSH6, MLH1, and PMS2 cause hereditary nonpolyposis colorectal cancer (HNPCC, also known as Lynch syndrome) (reviewed in Martin-Lopez and Fishel 2013).

References

Fishel R & Martín-López JV (2013). The mechanism of mismatch repair and the functional analysis of mismatch repair defects in Lynch syndrome. Fam. Cancer, 12, 159-68.

Fukui K (2010). DNA mismatch repair in eukaryotes and bacteria. J Nucleic Acids, 2010.

Kaliyaperumal S, Williams KJ & Edelbrock MA (2009). DNA mismatch repair efficiency and fidelity are elevated during DNA synthesis in human cells. Mutat. Res., 662, 59-66.

Kolodner RD & Marsischky GT (1999). Eukaryotic DNA mismatch repair. Curr. Opin. Genet. Dev., 9, 89-96.

Jiricny J (2013). Postreplicative mismatch repair. Cold Spring Harb Perspect Biol, 5, a012633.

Edit history

Date	Action	Author
2014-03-28	Edited	May B
2014-03-28	Authored	May B
2014-03-29	Created	May B
2014-05-23	Reviewed	Edelbrock MA
2024-03-08	Modified	Wright A

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

Input	UniProt Id
MSH3	P20585

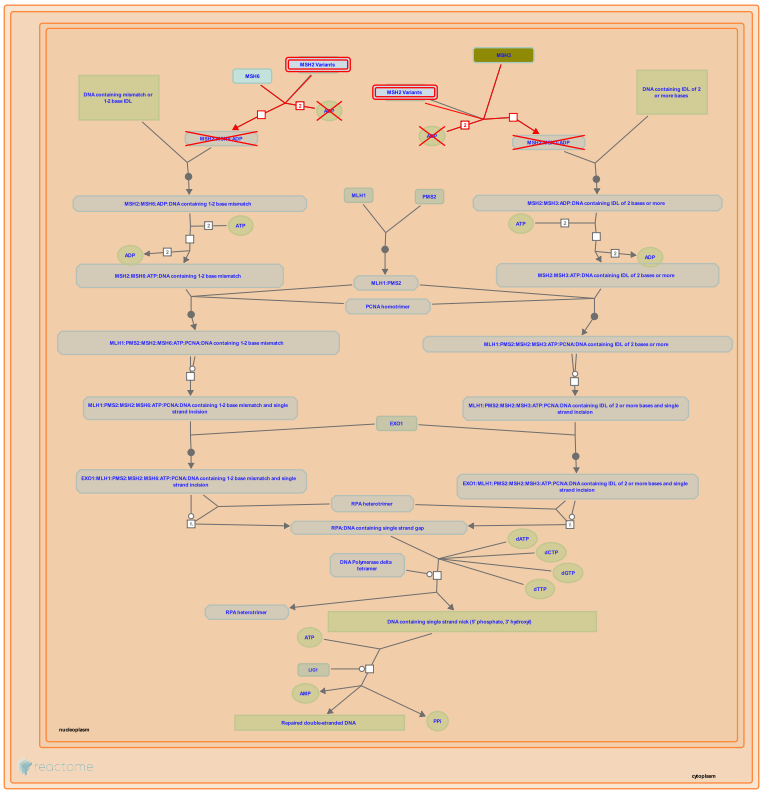
Input	UniProt Id
PMS1	P54278

Interactors found in this pathway (3)

Input	UniProt Id	Interacts with
MSH3	P20585	P40692, P43246
SLX4	Q8IY92	P43246

Input	UniProt Id	Interacts with
PMS1	P54277	P40692

5. 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.

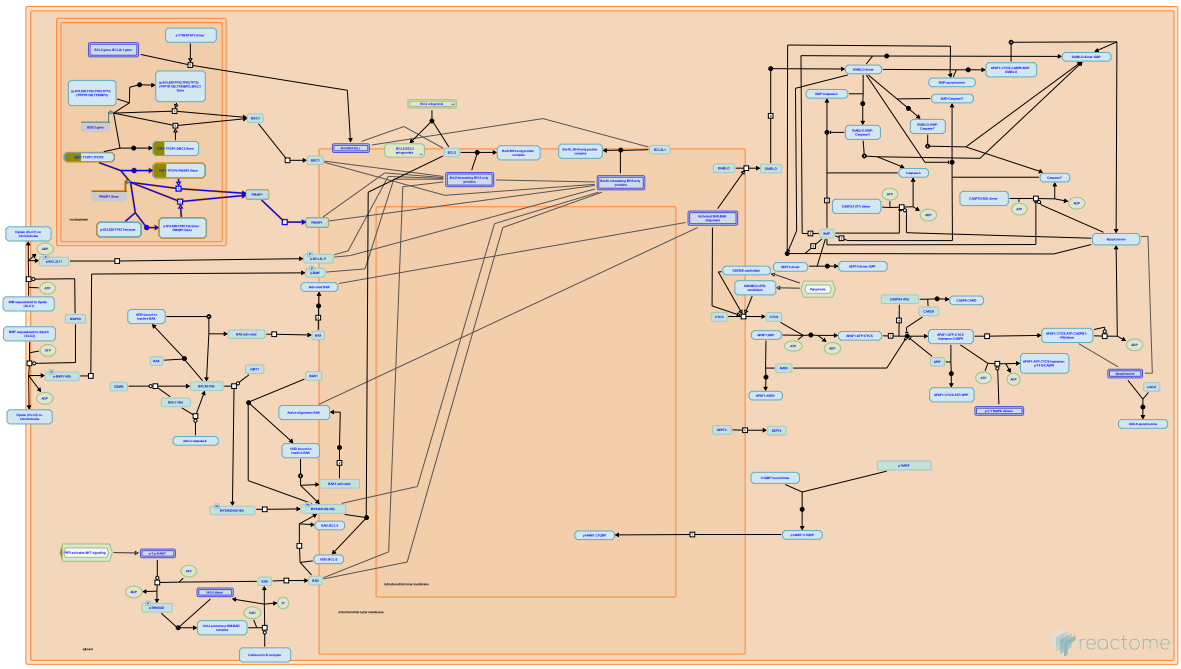
Edit history

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

6. 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.

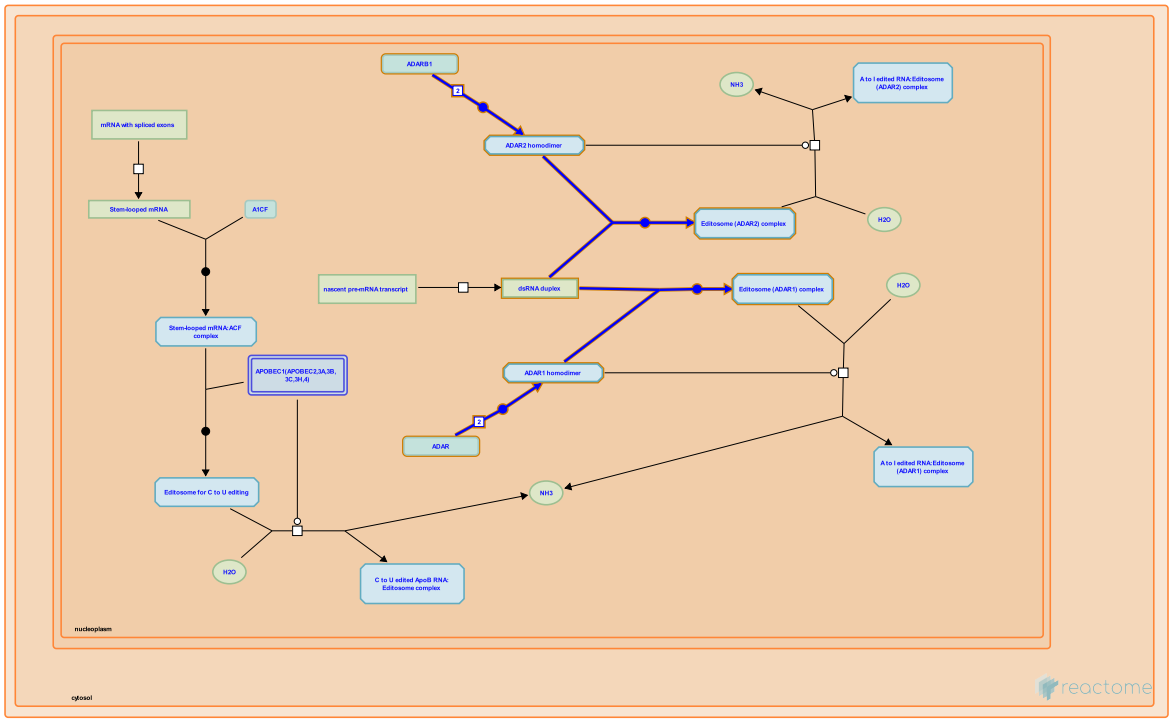
Edit history

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

7. 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

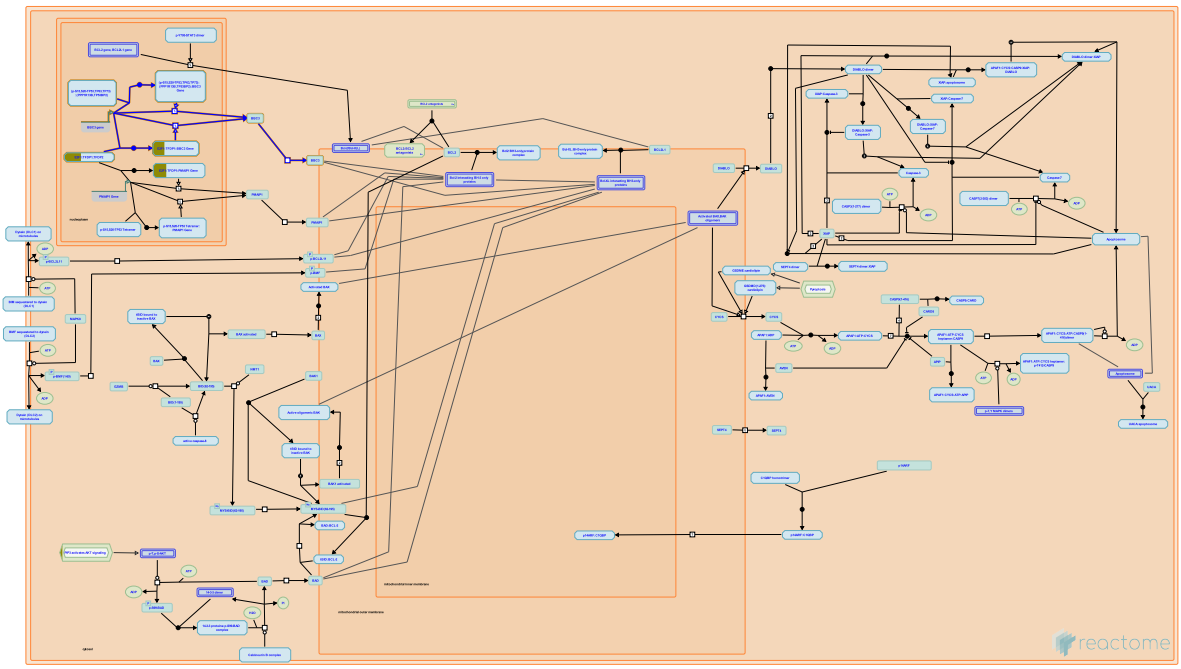
Edit history

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			

8. 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.

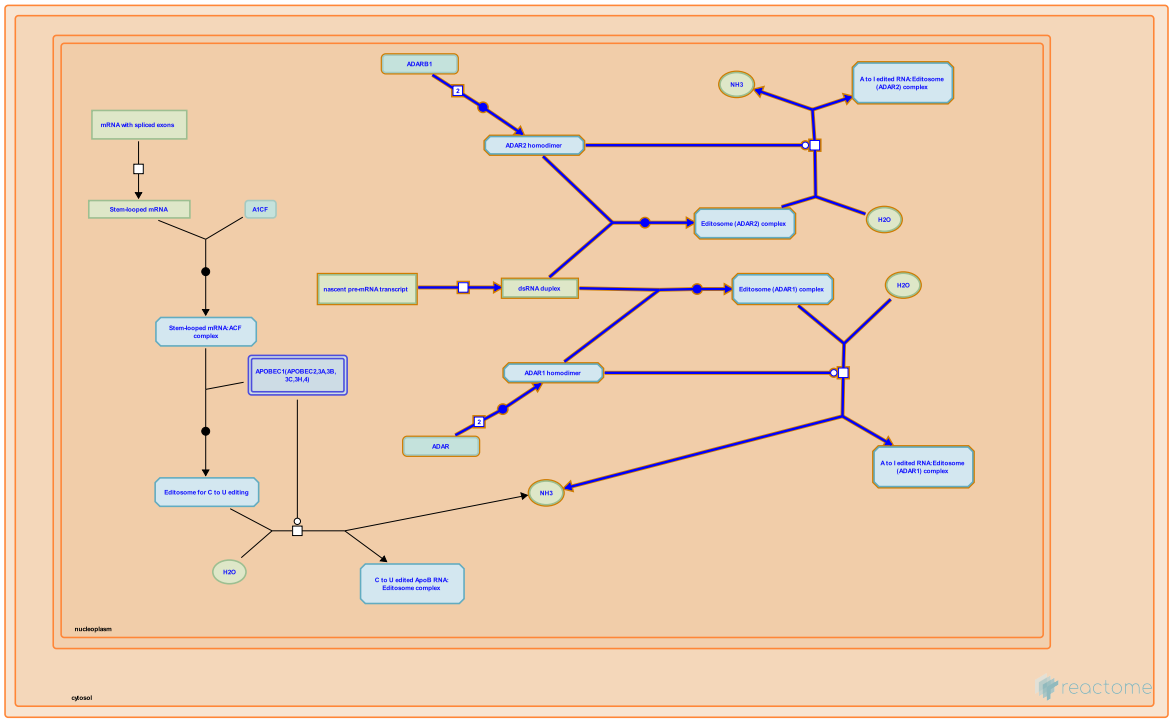
Edit history

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

9. 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.

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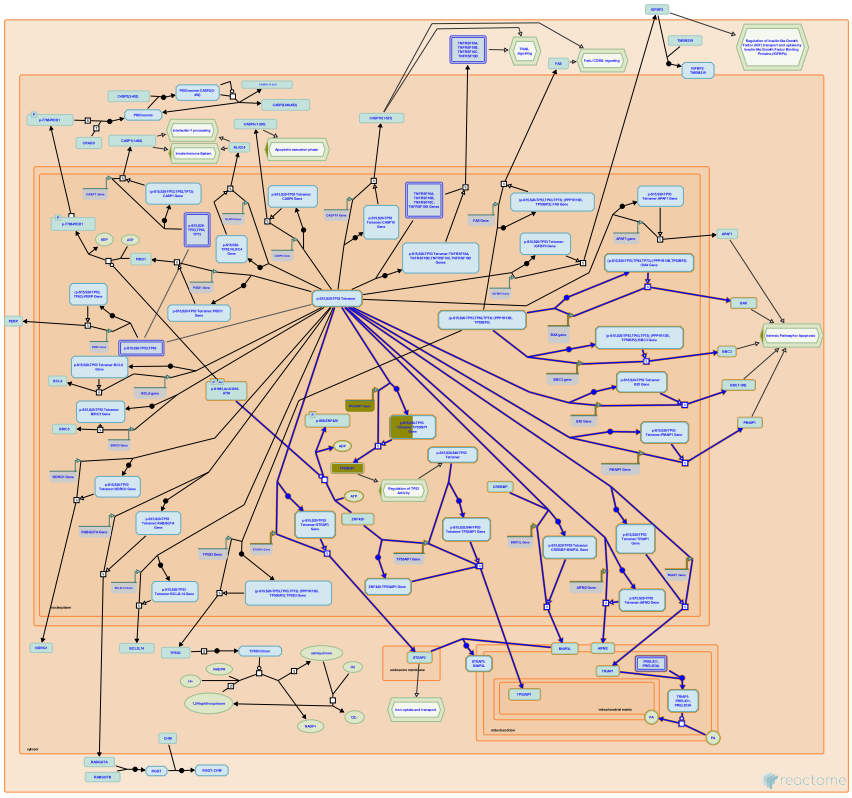
Edit history

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			

10. TP53 Regulates Transcription of Genes Involved in Cytochrome C Release (R-HSA-6803204)



Apoptotic transcriptional targets of TP53 include genes that regulate the permeability of the mitochondrial membrane and/or cytochrome C release, such as BAX, BID, PMAIP1 (NOXA), BBC3 (PUMA) and probably BNIP3L, AIFM2, STEAP3, TRIAP1 and TP53AIP1 (Miyashita and Reed 1995, Oda et al. 2000, Samuels-Lev et al. 2001, Nakano and Vousden 2001, Sax et al. 2002, Passer et al. 2003, Bergamaschi et al. 2004, Li et al. 2004, Fei et al. 2004, Wu et al. 2004, Park and Nakamura 2005, Patel et al. 2008, Wang et al. 2012, Wilson et al. 2013), thus promoting the activation of the apoptotic pathway.

Transcriptional activation of TP53AIP1 requires phosphorylation of TP53 at serine residue S46 (Oda et al. 2000, Taira et al. 2007). Phosphorylation of TP53 at S46 is regulated by another TP53 pro-apoptotic target, TP53INP1 (Okamura et al. 2001, Tomasini et al. 2003).

References

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Edit history

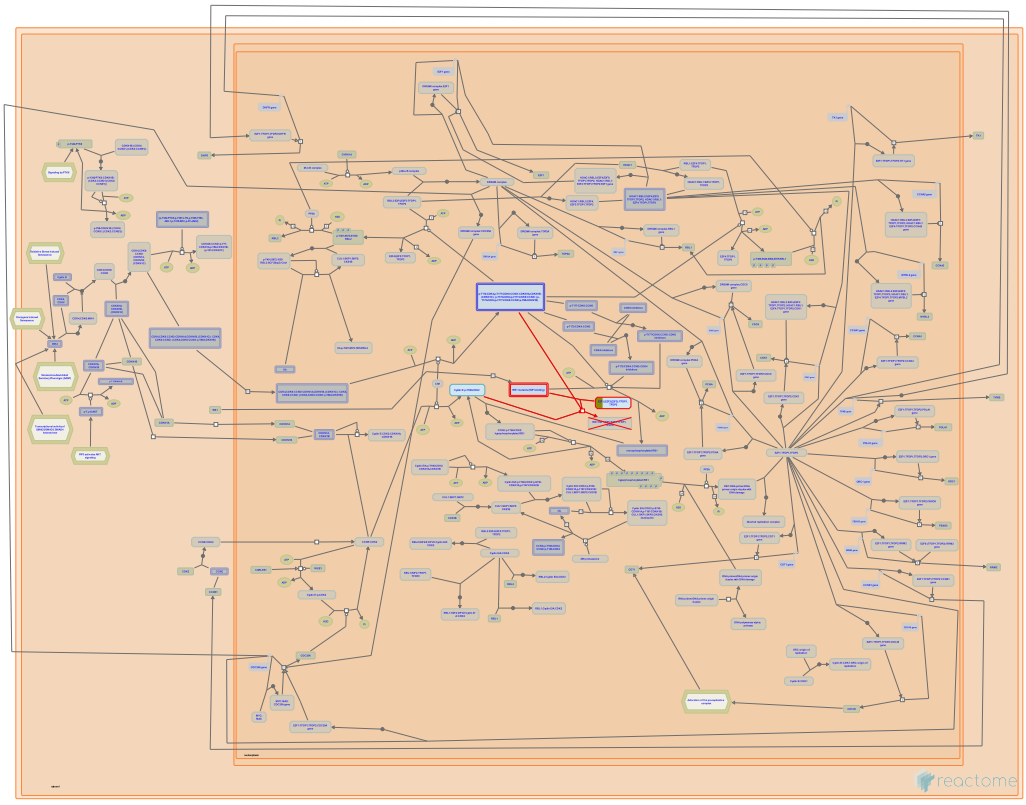
Date	Action	Author
2015-10-05	Created	Orlic-Milacic M
2015-10-14	Edited	Orlic-Milacic M
2015-10-14	Authored	Orlic-Milacic M
2016-02-04	Reviewed	Zaccara S, Inga A

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

Input	UniProt Id
TP53INP1	Q96A56

Input	Ensembl Id
TP53INP1	ENSG00000164938

11. 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

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Edit history

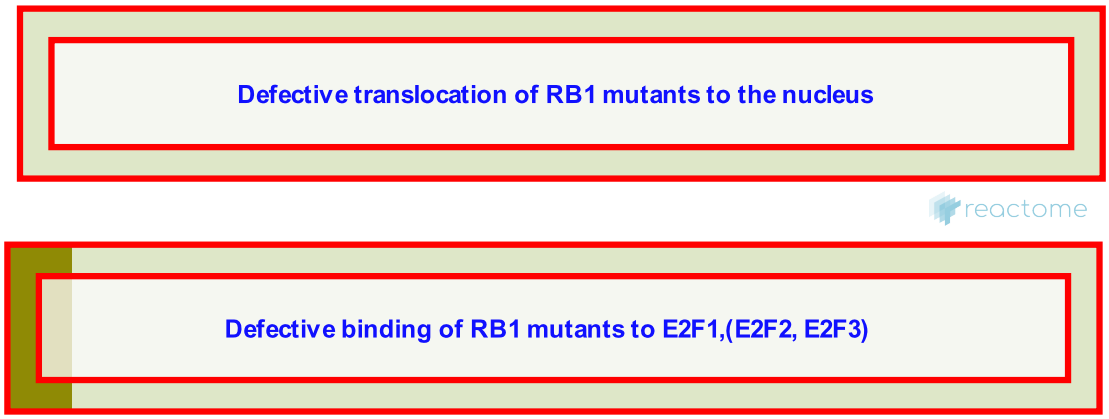
Date	Action	Author
2019-09-13	Created	Orlic-Milacic M
2020-05-07	Authored	Orlic-Milacic M

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

12. 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.

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Edit history

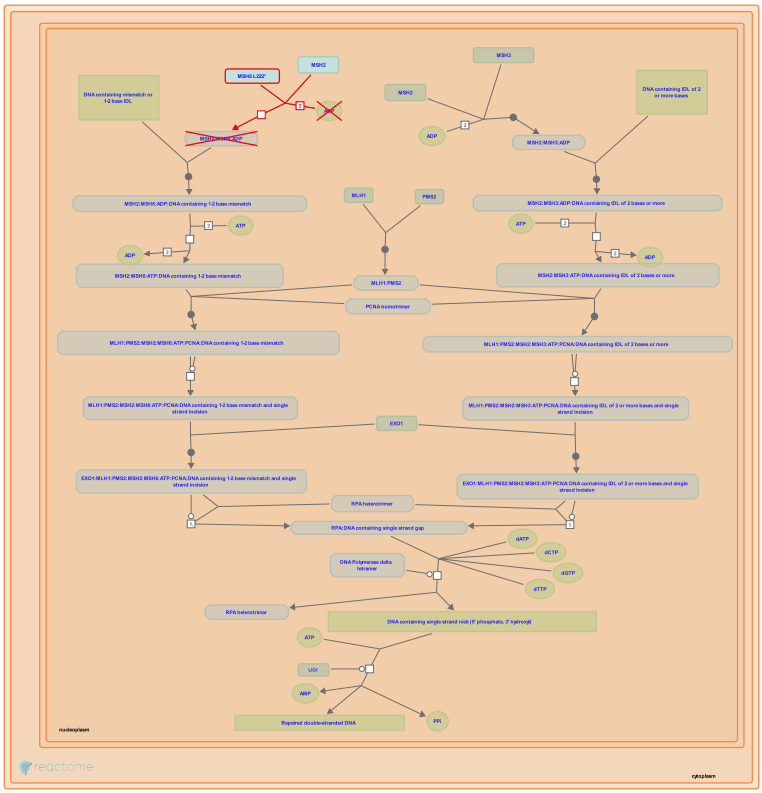
Date	Action	Author
2019-09-05	Created	Orlic-Milacic M
2020-05-07	Authored	Orlic-Milacic M
2020-05-17	Reviewed	Dick FA

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

13. 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

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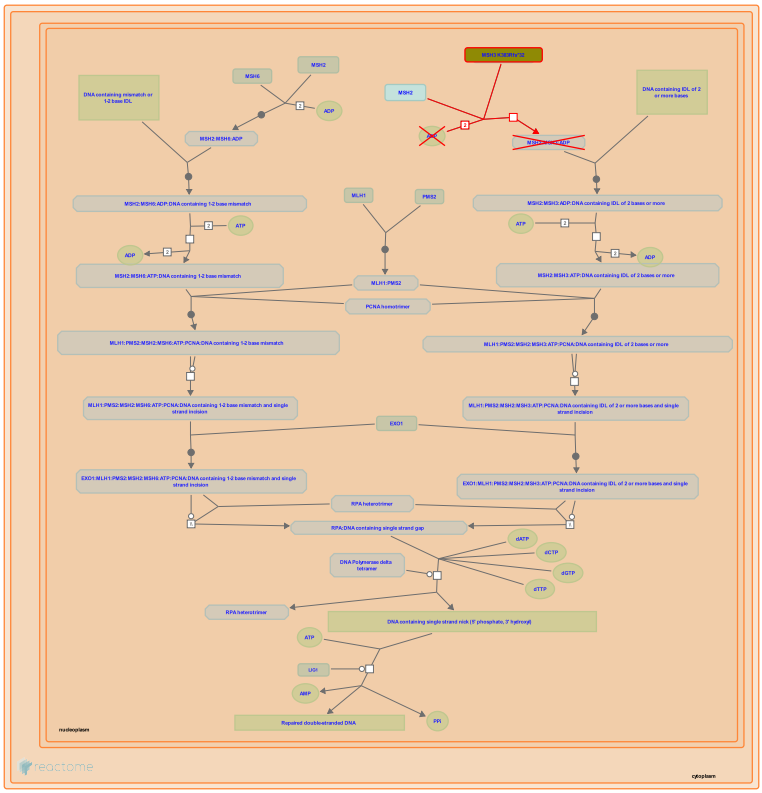
Edit history

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 (2)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
MSH3	P20585	P43246	SLX4	Q8IY92	P43246

14. 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

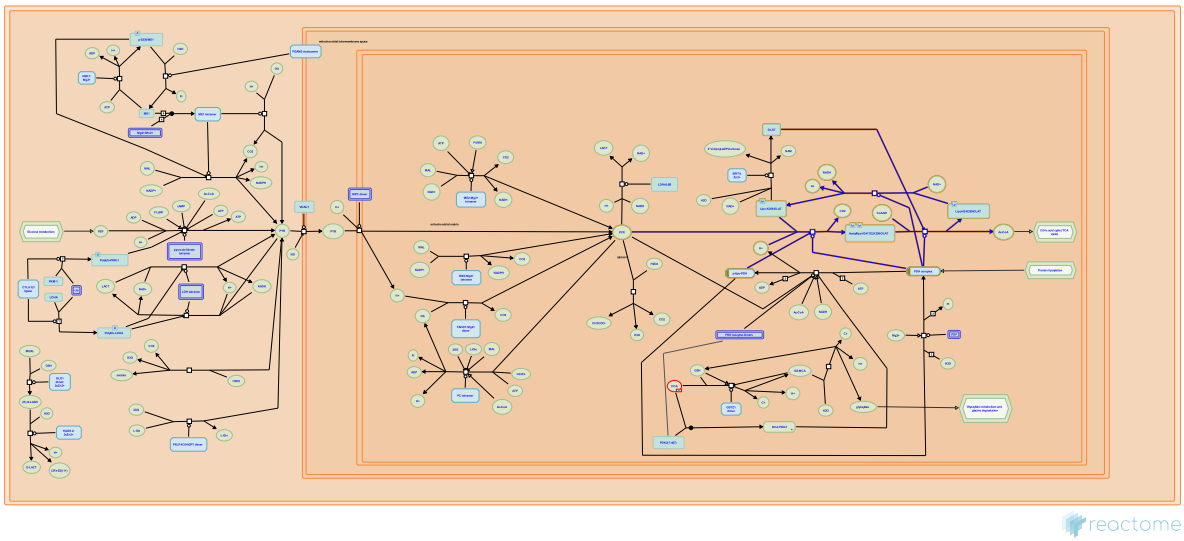
1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
MSH3	P20585

Interactors found in this pathway (2)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
MSH3	P20585	P43246	SLX4	Q8IY92	P43246

15. 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

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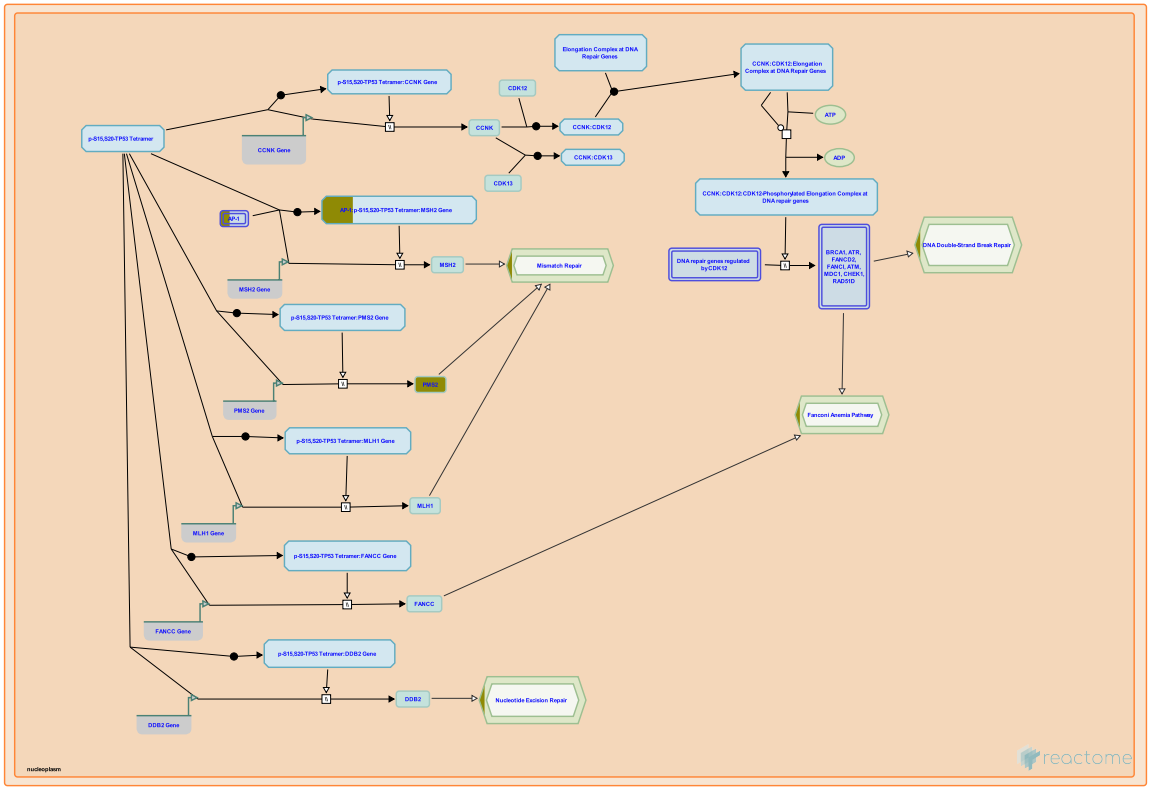
Edit history

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

16. 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

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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

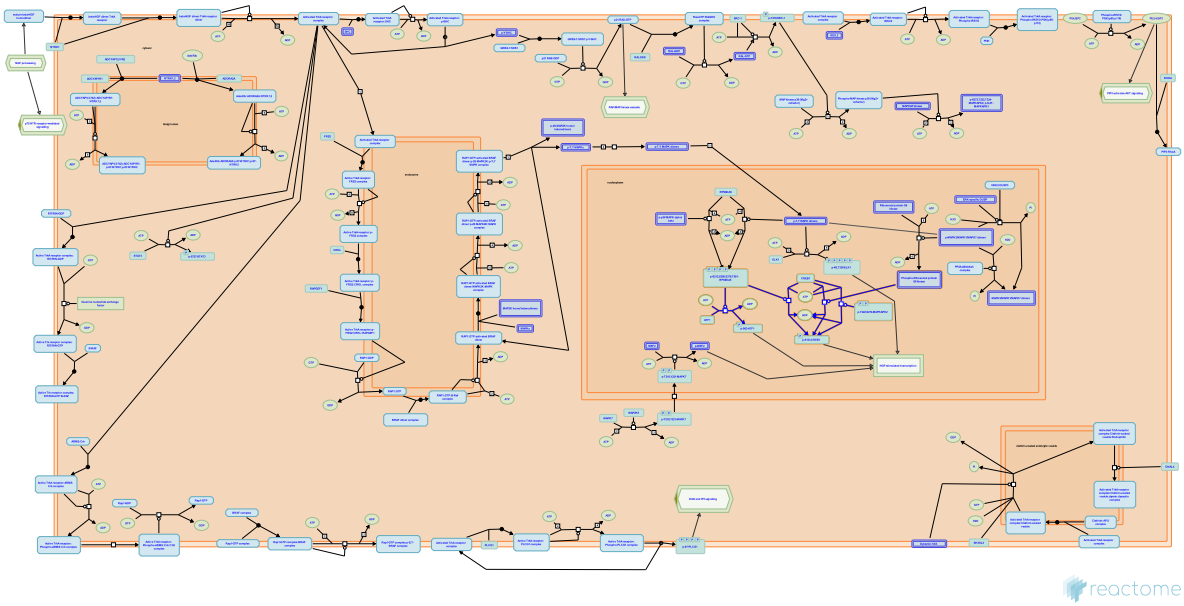
2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
JUN	P05412	PMS1	P54278

Interactors found in this pathway (3)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
MSH3	P20585	P40692, P43246	PMS1	P54277	P40692
SLX4	Q8IY92	P43246			

17. CREB phosphorylation (R-HSA-199920)



Nerve growth factor (NGF) activates multiple signalling pathways that mediate the phosphorylation of CREB at the critical regulatory site, serine 133. CREB phosphorylation at serine 133 is a crucial event in neurotrophin signalling, being mediated by ERK/RSK, ERK/MSK1 and p38/MAPKAPK2 pathways. Several kinases, such as MSK1, RSK1/2/3 (MAPKAPK1A/B/C), and MAPKAPK2, are able to directly phosphorylate CREB at S133. MSK1 is also able to activate ATF (Cyclic-AMP-dependent transcription factor). However, the NGF-induced CREB phosphorylation appears to correlate better with activation of MSK1 rather than RSK1/2/3, or MAPKAPK2. In retrograde signalling, activation of CREB occurs within 20 minutes after neurotrophin stimulation of distal axons.

References

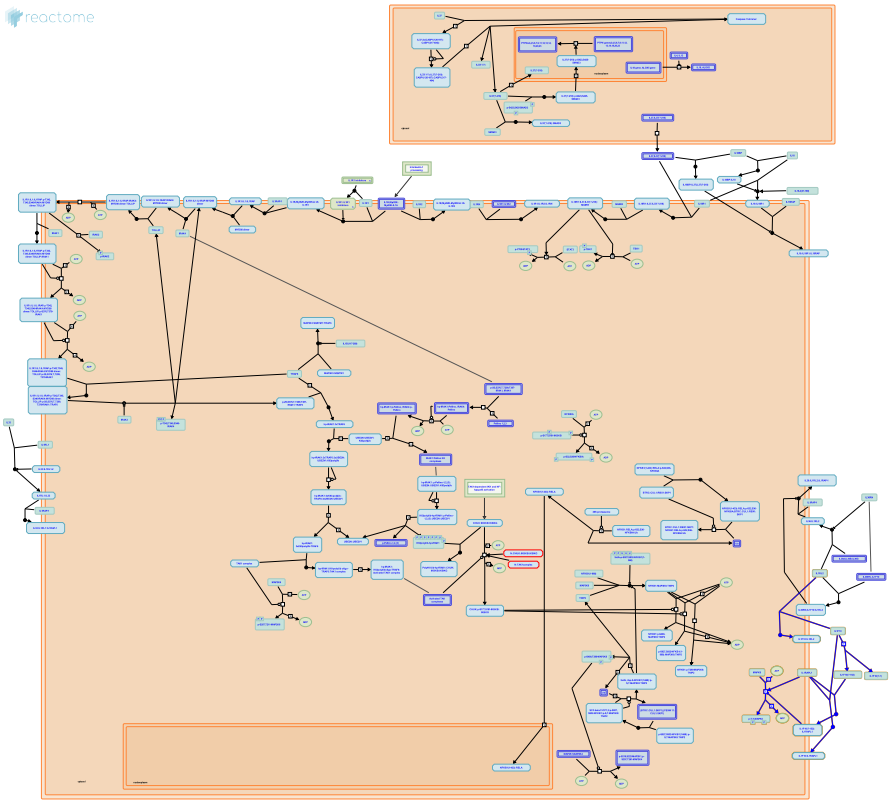
Edit history

Date	Action	Author
2006-10-10	Authored	Annibali D, Nasi S
2007-07-13	Created	Jassal B
2007-11-08	Reviewed	Greene LA
2024-03-08	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
JUN	P05412	P18846			

18. Interleukin-38 signaling (R-HSA-9007892)



Cellular compartments: nucleoplasm, extracellular region, cytosol.

Interleukins are immunomodulatory proteins that elicit a wide array of responses in cells and tissues. Interleukin 1 family member 10 (IL1F10, IL 38) is a member of the IL1 family (Lin et al. 2001, Bensen et al. 2001). IL1F10 is selectively produced by human apoptotic cells (Mora et al. 2016) and human epidermal keratinocytes (based on mRNA studies) (Boutet M A et al. 2016). IL1F10 can bind to interleukin 1 receptor like 2 (IL1RL2) and may result in the suppression of IL 17 and IL 22 and induction of IL 6 production (van de Veerdonk et al. 2012, Mora et al. 2016). IL1F10 is synthesized as precursors that require N terminal processing to attain full receptor agonist or antagonist function (Mora et al. 2016). Both full length (1 – 152 amino acids) and N terminal truncated (20 – 152 amino acids) IL1F10 can bind Interleukin 1 receptor accessory protein like 1 (IL1RAPL1) (Mora et al. 2016). The binding affinity of truncated IL1F10 is much higher than that of the full length. However, binding of the full length or truncated forms has distinct outcomes; the former induces IL6 and the latter suppresses IL6 via JNK and AP1 signaling (Mora et al. 2016).

References

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Yuan X, Li Y, Peng X & Li M (2015). Role of IL-38 and its related cytokines in inflammation. Mediators Inflamm., 2015, 807976.

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Weigert A, Putyrski M, Frank AC, Wittig I, Brüne B, Schlemmer A, ... Mora J (2016). Interleukin-38 is released from apoptotic cells to limit inflammatory macrophage responses. J Mol Cell Biol.

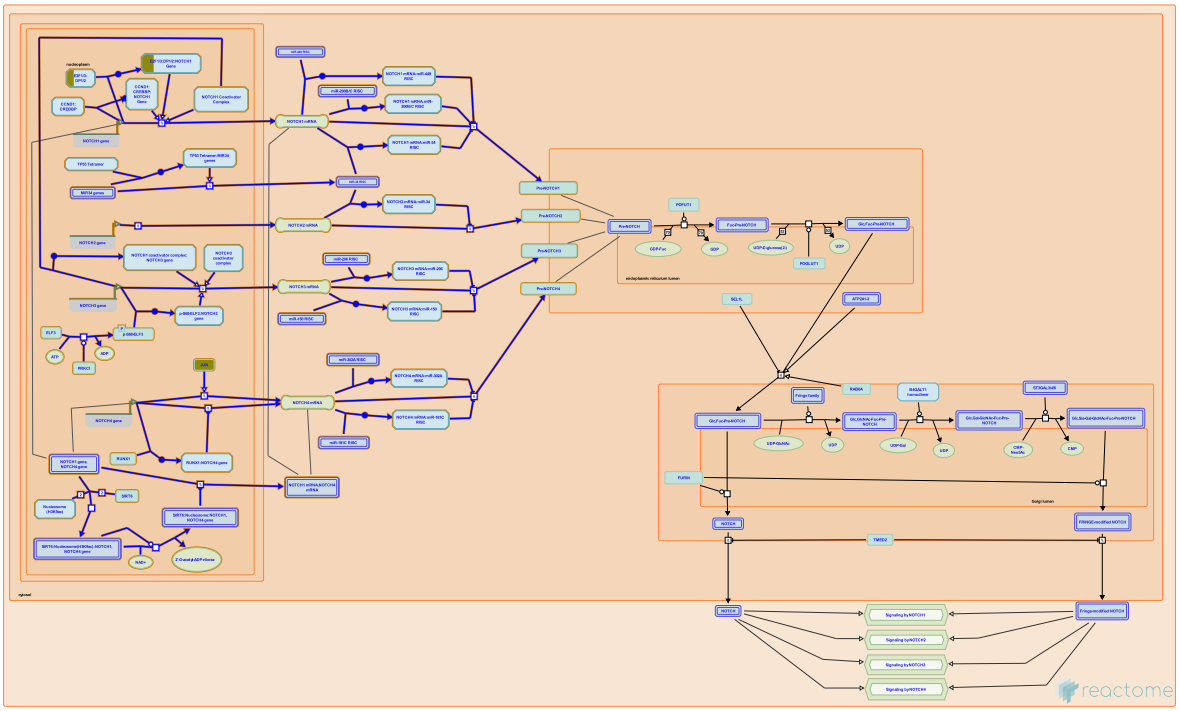
Edit history

Date	Action	Author
2017-06-06	Created	Varusai TM
2017-07-28	Reviewed	Mora J
2017-08-08	Edited	Varusai TM
2017-08-08	Authored	Varusai TM
2024-03-08	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
JUN	P05412	P45983			

19. Pre-NOTCH Transcription and Translation (R-HSA-1912408)



Cellular compartments: cytosol, nucleoplasm, endoplasmic reticulum membrane.

In humans, the NOTCH protein family has four members: NOTCH1, NOTCH2, NOTCH3 and NOTCH4. NOTCH1 protein was identified first, as the product of a chromosome 9 gene translocated in T-cell acute lymphoblastic leukemia that was homologous to Drosophila Notch (Ellisen et al. 1991). At the same time, rat Notch1 was cloned (Weinmaster et al. 1991), followed by cloning of mouse Notch1, named Motch (Del Amo et al. 1992). NOTCH2 protein is the product of a gene on chromosome 1 (Larsson et al. 1994). NOTCH2 expression is differentially regulated during B-cell development (Bertrand et al. 2000). NOTCH2 mutations are a rare cause of Alagille syndrome (McDaniell et al. 2006). NOTCH3 is the product of a gene on chromosome 19. NOTCH3 mutations are the underlying cause of CADASIL, cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (Joutel et al. 1996). NOTCH4, the last NOTCH protein discovered, is the product of a gene on chromosome 6 (Li et al. 1998).

MicroRNAs play an important negative role in translation and/or stability of NOTCH mRNAs. MicroRNAs miR-34 (miR-34A, miR-34B and mi-R34C), whose transcription is directly induced by the tumor suppressor protein p53 (Chang et al. 2007, Raver-Shapira et al. 2007, He et al. 2007, Corney et al. 2007) bind and negatively regulate translation of NOTCH1 mRNA (Li et al. 2009, Pang et al. 2010, Ji et al. 2009) and NOTCH2 mRNA (Li et al. 2009). NOTCH1 mRNA translation is also negatively regulated by microRNAs miR-200B and miR-200C (Kong et al. 2010), as well as miR-449A, miR-449B and miR-449C (Marcet et al. 2011). Translation of NOTCH3 mRNA is negatively regulated by microRNAs miR-150 (Ghisi et al. 2011) and miR-206 (Song et al. 2009). Translation of NOTCH4 mRNA is negatively regulated by microRNAs miR-181C (Hashimoto et al. 2010) and miR-302A (Costa et al. 2009).

Nascent NOTCH peptides are co-translationally targeted to the endoplasmic reticulum for further processing, followed by modification in the Golgi apparatus, before trafficking to the plasma membrane. Endoplasmic reticulum calcium ATPases, positively regulate NOTCH trafficking, possibly by contributing to accurate folding of NOTCH precursors (Periz et al. 1999).

References

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Yeung WS, Lee KF, Pang RT, Chiu PCN, Leung CON, Liu W, ... Ye TM (2010). MicroRNA-34a suppresses invasion through downregulation of Notch1 and Jagged1 in cervical carcinoma and choriocarcinoma cells. Carcinogenesis, 31, 1037-44.

Arndt K, Costa FF, Bischof JM, Seftor EA, Soares MB, Hendrix MJC, ... Strizzi L (2009). Epigenetically reprogramming metastatic tumor cells with an embryonic microenvironment. Epigenomics , 1, 387-398.

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Edit history

Date	Action	Author
2011-09-27	Edited	Jupe S
2011-11-02	Created	Orlic-Milacic M
2011-11-14	Authored	Egan SE, Orlic-Milacic M
2012-02-06	Reviewed	Haw R
2012-02-07	Edited	D'Eustachio P
2012-02-09	Edited	May B, Gillespie ME
2012-02-11	Edited	Orlic-Milacic M
2012-05-14	Revised	Egan SE, Orlic-Milacic M
2012-05-16	Edited	D'Eustachio P
2012-05-17	Reviewed	Haw R
2017-09-20	Revised	Orlic-Milacic M
2017-10-30	Reviewed	Haw R
2017-11-02	Edited	Orlic-Milacic M
2018-04-05	Revised	Orlic-Milacic M
2018-05-01	Reviewed	Haw R
2024-03-08	Modified	Wright A

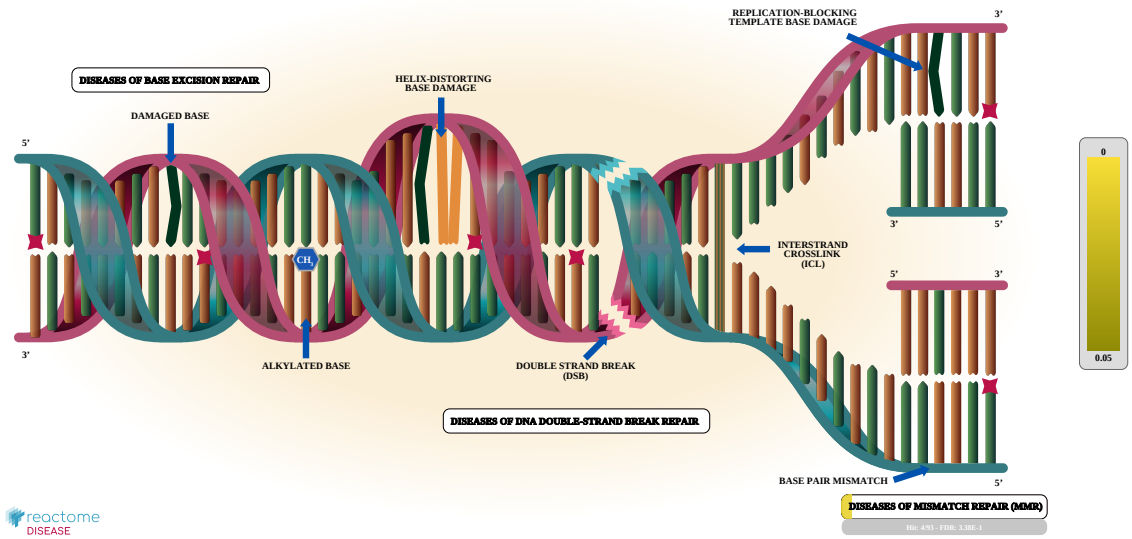
2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
JUN	P05412	TFDP1	Q14186

Interactors found in this pathway (1)

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

20. Diseases of DNA repair (R-HSA-9675135)



Diseases: genetic disease.

Germline and somatic defects in genes that encode proteins that participate in DNA repair give rise to genetic instability that can lead to malignant transformation or trigger cellular senescence or apoptosis. Germline defects in DNA repair genes are an underlying cause of familial cancer syndromes and premature ageing syndromes. Somatic defects in DNA repair genes are frequently found in tumors. For review, please refer to Tiwari and Wilson 2019.

We have so far annotated diseases of mismatch repair, diseases of base excision repair and diseases of DNA double-strand break repair.

Defects in mammalian DNA mismatch repair (MMR) genes (MLH1, PMS2, MSH2, and MSH6) result in microsatellite instability (MSI) and reduced fidelity during replication and repair steps. Defective variants of MMR genes are associated with sporadic cancers with hypermutation phenotypes as well as hereditary cancer syndromes such as Lynch syndrome (hereditary non-polyposis colorectal cancer) and constitutional mismatch repair deficiency syndrome (CMMRD). MSI is an important predictor of sensitivity to cancer immunotherapy as the high mutational burden renders MSI tumors immunogenic and sensitive to programmed cell death-1 (PD-1) immune checkpoint inhibitors (Mandal et al. 2019). For review, please refer to Pena-Diaz and Rasmussen 2016, Sijmons and Hofstra 2016, Tabori et al. 2017, Baretti and Le 2018.

Germline mutations, single nucleotide polymorphisms (SNPs) and somatic mutations in several genes involved in base excision repair (BER), a DNA repair pathway where a damaged DNA base is excised and replaced with a correct base, are involved in the development of cancer and several oxidative stress-related diseases. For review, please refer to Fu et al. 2012, Fletcher and Houlston 2010, Brenerman et al. 2014, Patrono et al. 2014, and D'Errico et al. 2017.

Germline mutations in genes involved in repair of DNA double-strand breaks (DSBs) are the underlying cause of several cancer predisposition syndromes, some of which also encompass developmental disorders associated with immune dysfunction, radiosensitivity and neurodegeneration. Somatic mutations in genes involved in DSB repair also occur in sporadic cancers. For review, please refer to McKinnon and Caldecott 2007, Keijzers et al. 2017, and Jachimowicz et al. 2019.

References

Houlston RS & Fletcher O (2010). Architecture of inherited susceptibility to common cancer. Nat. Rev. Cancer, 10, 353-61.

Wilson DM & Tiwari V (2019). DNA Damage and Associated DNA Repair Defects in Disease and Premature Aging. Am. J. Hum. Genet., 105, 237-257.

Fu D, Samson LD & Calvo JA (2012). Balancing repair and tolerance of DNA damage caused by alkylating agents. Nat. Rev. Cancer, 12, 104-20.

Wilson DM, Brenerman BM & Illuzzi JL (2014). Base excision repair capacity in informing healthspan. Carcinogenesis, 35, 2643-52.

Peña-Diaz J & Rasmussen LJ (2016). Approaches to diagnose DNA mismatch repair gene defects in cancer. DNA Repair (Amst.), 38, 147-154.

Edit history

Date	Action	Author
2020-01-31	Created	Orlic-Milacic M
2020-02-21	Authored	Orlic-Milacic M
2020-02-24	Edited	Orlic-Milacic M
2020-02-24	Reviewed	D'Eustachio P
2020-11-11	Reviewed	D'Eustachio P
2020-11-12	Edited	Orlic-Milacic M
2023-10-12	Modified	Weiser JD

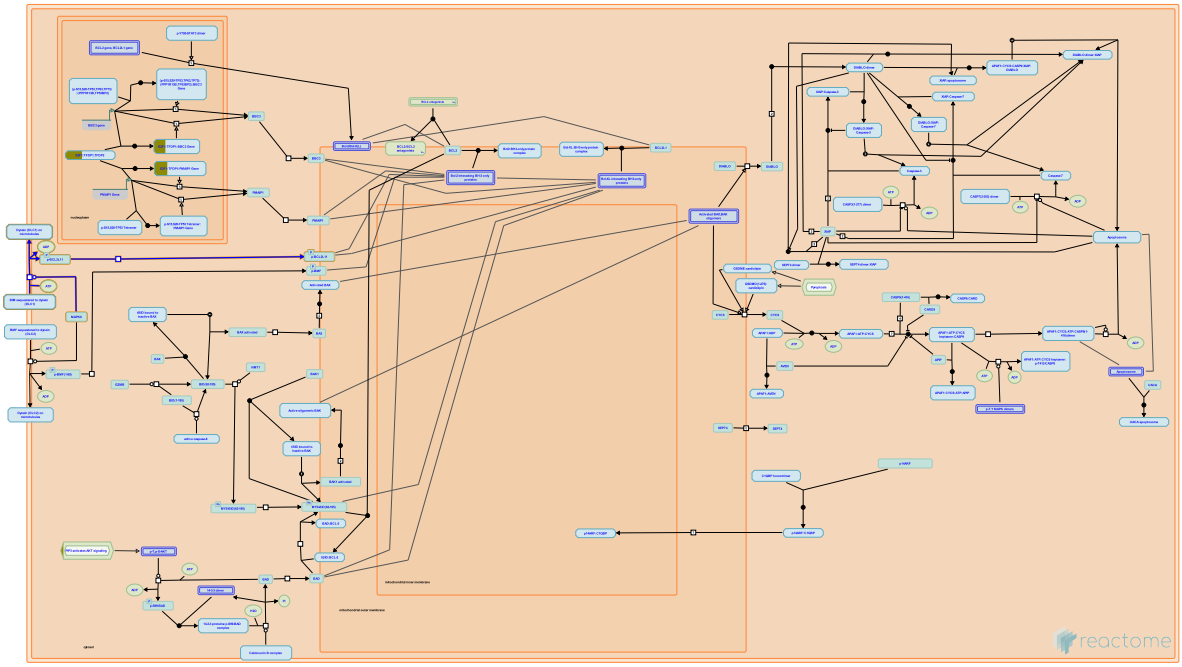
2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
MSH3	P20585	PMS1	P54278

Interactors found in this pathway (3)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
MSH3	P20585	P40692, P43246	PMS1	P54277	P40692
SLX4	Q8IY92	P43246			

21. Activation of BIM and translocation to mitochondria (R-HSA-111446)



Cellular compartments: cytosol.

BIM acts as a sentinel to check the integrity of the cytoskeleton. It exists as two variant proteins: BIM-EL and BIM-L. In healthy cells, these two isoforms are sequestered to the dynein motor complex on microtubules via the dynein light chain DLC1. JNK or MAPK8 releases BIM in response to UV irradiation by phosphorylation.

References

Vazquez A, Leprince C, Auffredou MT, Leca G, Bourgeade MF, Besnault L & Mouhamad S (2004). B cell receptor-mediated apoptosis of human lymphocytes is associated with a new regulatory pathway of Bim isoform expression. J Immunol, 172, 2084-91.

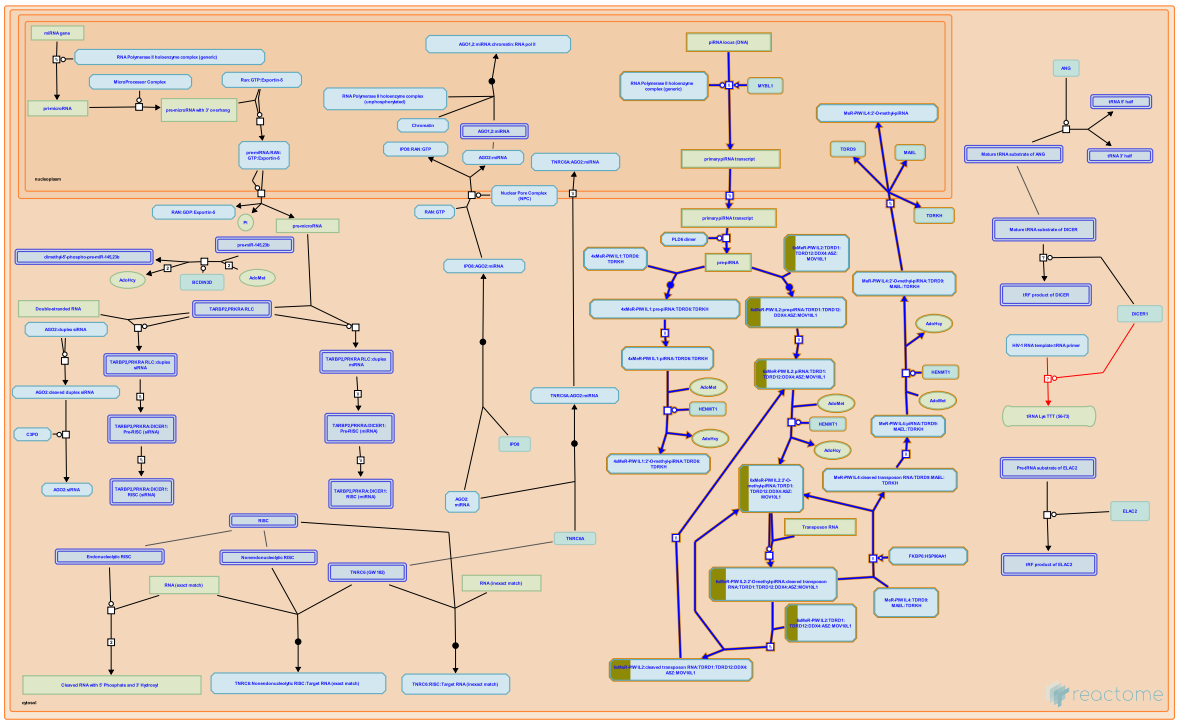
Edit history

Date	Action	Author
2004-08-09	Created	Tsujimoto Y, Hardwick JM
2004-08-20	Authored	Gopinathrao G
2024-03-06	Reviewed	Vaux DL
2024-03-07	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
JUN	P05412	P45983			

22. PIWI-interacting RNA (piRNA) biogenesis (R-HSA-5601884)



In germ cells of humans and mice, precursors of PIWI-interacting RNAs (piRNAs) are transcribed from a few hundred sequence clusters, as well as individual transposons, intergenic regions, and genes in the genome. These longer transcripts are processed to yield piRNAs of 26-30 nucleotides independently of DICER, the enzyme responsible for microRNAs (miRNAs) and small interfering RNAs (siRNAs) (reviewed in Girard and Hannon 2008, Siomi et al. 2011, Ishizu et al. 2012, Pillai and Chuma 2012, Bortvin 2013, Chuma and Nakano 2013, Sato and Siomi 2013). The initial step in processing long transcripts to piRNAs is cleavage by PLD6 (MitoPLD), which generates the mature 5' end. The cleavage products of PLD6 are bound by either PIWIL1 (HIWI, MIWI) or PIWIL2 (HILI, MILI) in complexes with several other proteins. The 3' end is trimmed by an unknown exonuclease to generate the mature piRNA. PIWIL1:piRNA complexes appear to be involved in post-transcriptional silencing in the cytosol while PIWIL2:piRNA complexes generate further piRNAs from transposon transcripts and other transcripts in the cytosol. Cleavage products from PIWIL2:piRNA may be loaded into either PIWIL2 or PIWIL4 (HIWI2, MIWI2). Loading into PIWIL2 forms a step in a cytosolic amplification loop called the "ping-pong cycle" which yields further PIWIL2:piRNA complexes from cleaved precursor RNAs. Loading into PIWIL4 yields a complex also containing TDRD9 that translocates to the nucleus and directs DNA methylation of cognate loci, causing transcriptional silencing during spermatogenesis. Transcriptional silencing by piRNAs is necessary to limit transposition of endogenous transposons such as L1 elements in the genome.

References

Pillai RS & Chuma S (2012). piRNAs and their involvement in male germline development in mice. Dev. Growth Differ., 54, 78-92.

Siomi MC, Pezic D, Aravin AA & Sato K (2011). PIWI-interacting small RNAs: the vanguard of genome defence. Nat. Rev. Mol. Cell Biol., 12, 246-58.

Siomi H, Siomi MC & Ishizu H (2012). Biology of PIWI-interacting RNAs: new insights into biogenesis and function inside and outside of germlines. Genes Dev., 26, 2361-73.

Hannon GJ & Girard A (2008). Conserved themes in small-RNA-mediated transposon control. Trends Cell Biol., 18, 136-48.

Siomi MC & Sato K (2013). Piwi-interacting RNAs: biological functions and biogenesis. Essays Biochem., 54, 39-52.

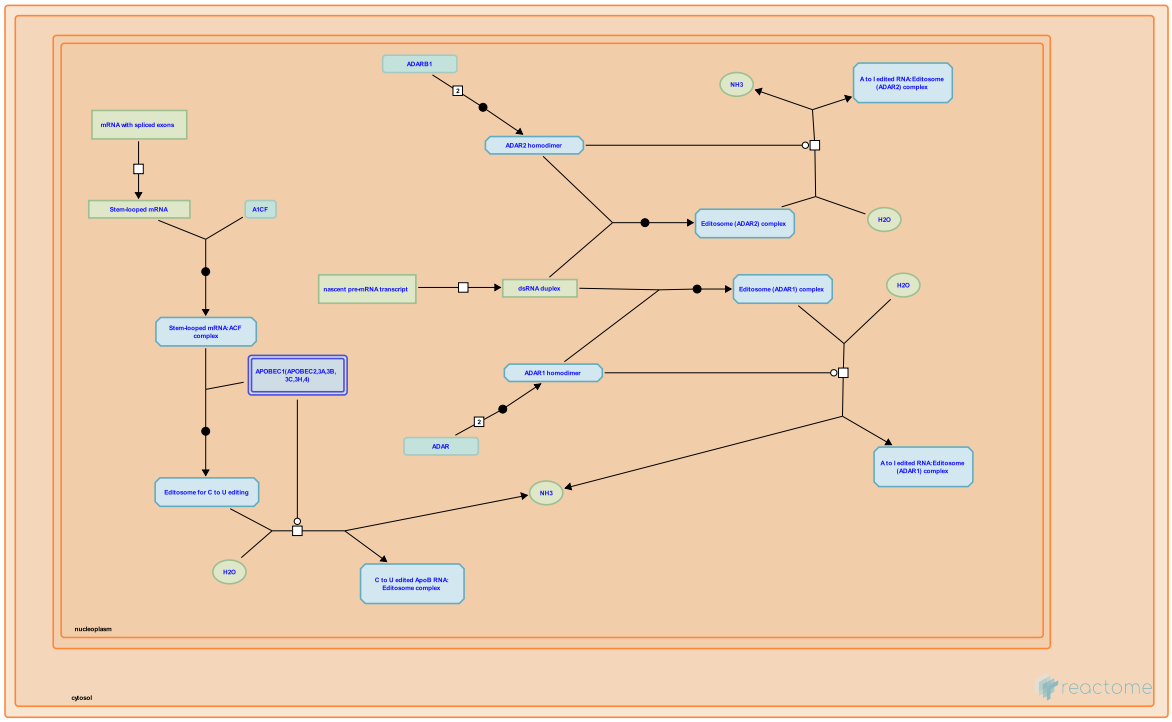
Edit history

Date	Action	Author
2014-06-14	Edited	May B
2014-06-14	Authored	May B
2014-06-15	Created	May B
2014-10-25	Reviewed	Saito K
2023-10-12	Modified	Weiser JD

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

Input	UniProt Id
TDRD12	Q587J7

23. mRNA Editing (R-HSA-75072)



Cellular compartments: nucleoplasm.

After transcription, some RNA molecules are altered to contain bases not encoded in the genome. Most often this involves the editing or modification of one base to another, but in some organisms can involve the insertion or deletion of a base. Such editing events alter the coding properties of mRNA.

RNA editing can be generally defined as the co- or post transcriptional modification of the primary sequence of RNA from that encoded in the genome through nucleotide deletion, insertion, or base modification mechanisms.

There are two pathways of RNA editing: the substitution/conversion pathway and the insertion/deletion pathway. The insertion/deletion editing occurs in protozoans like Trypanosoma, Leishmania; in slime molds like Physarum spp., and in some viral categories like paramyxoviruses, Ebola virus etc. To date, the substitution/conversion pathway has been observed in human along with other mammals, Drosophila, and some plants. The RNA editing processes are known to create diversity in proteins involved in various pathways like lipid transport, metabolism etc. and may act as potential targets for therapeutic intervention (Smith et al., 1997).

The reaction mechanisms of cytidine and adenosine deaminases is represented below. In both these reactions, NH3 is presumed to be released:

References

Emeson RB & Gott JM (2001). Functions and mechanisms of RNA editing. Annu Rev Genet, 34, 499-531.

Panigrahi AK & Stuart K (2002). RNA editing: complexity and complications. Mol Microbiol, 45, 591-6.

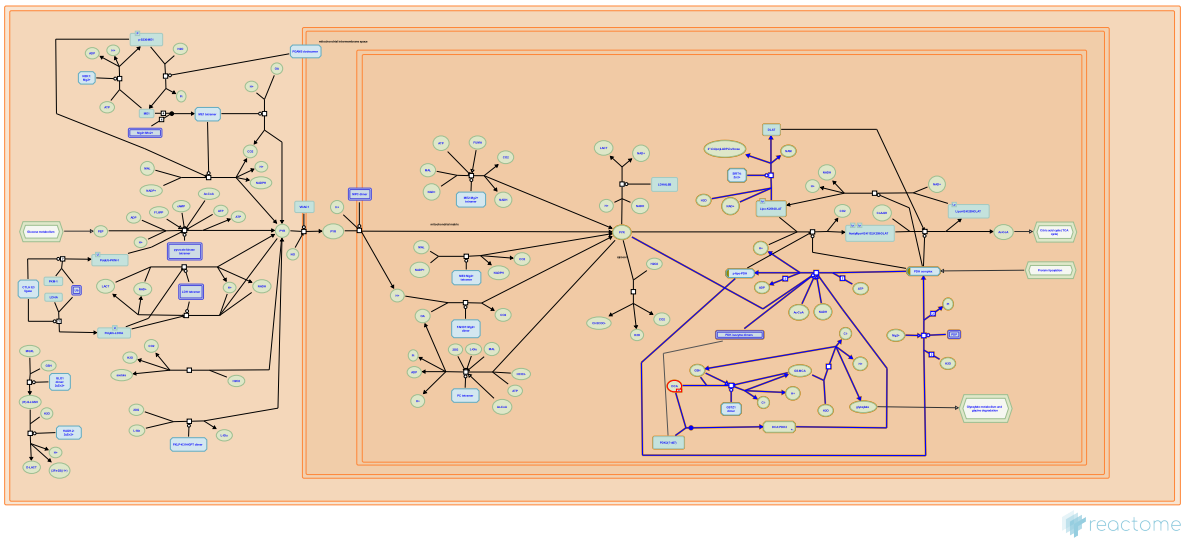
Edit history

Date	Action	Author
2003-08-22	Authored	Carmichael GG
2003-08-22	Created	Carmichael GG
2024-03-06	Edited	Gopinathrao G
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			

24. Regulation of pyruvate dehydrogenase (PDH) complex (R-HSA-204174)



Cellular compartments: mitochondrial matrix.

The mitochondrial pyruvate dehydrogenase (PDH) complex catalyzes the oxidative decarboxylation of pyruvate, linking glycolysis to the tricarboxylic acid cycle and fatty acid synthesis. PDH inactivation is crucial for glucose conservation when glucose is scarce, while adequate PDH activity is required to allow both ATP and fatty acid production from glucose. The mechanisms that control human PDH activity include its phosphorylation (inactivation) by pyruvate dehydrogenase kinases (PDK 1-4) and its dephosphorylation (activation, reactivation) by pyruvate dehydrogenase phosphate phosphatases (PDP 1 and 2). Isoform-specific differences in kinetic parameters, regulation, and phosphorylation site specificity of the PDKs introduce variations in the regulation of PDC activity in differing endocrine and metabolic states (Sugden and Holness 2003). Further, PDH is inhibited by SIRT4 and the drug dichloroacetic acid (DCA).

References

Holness MJ & Sugden MC (2003). Recent advances in mechanisms regulating glucose oxidation at the level of the pyruvate dehydrogenase complex by PDKs. Am J Physiol Endocrinol Metab, 284, E855-62.

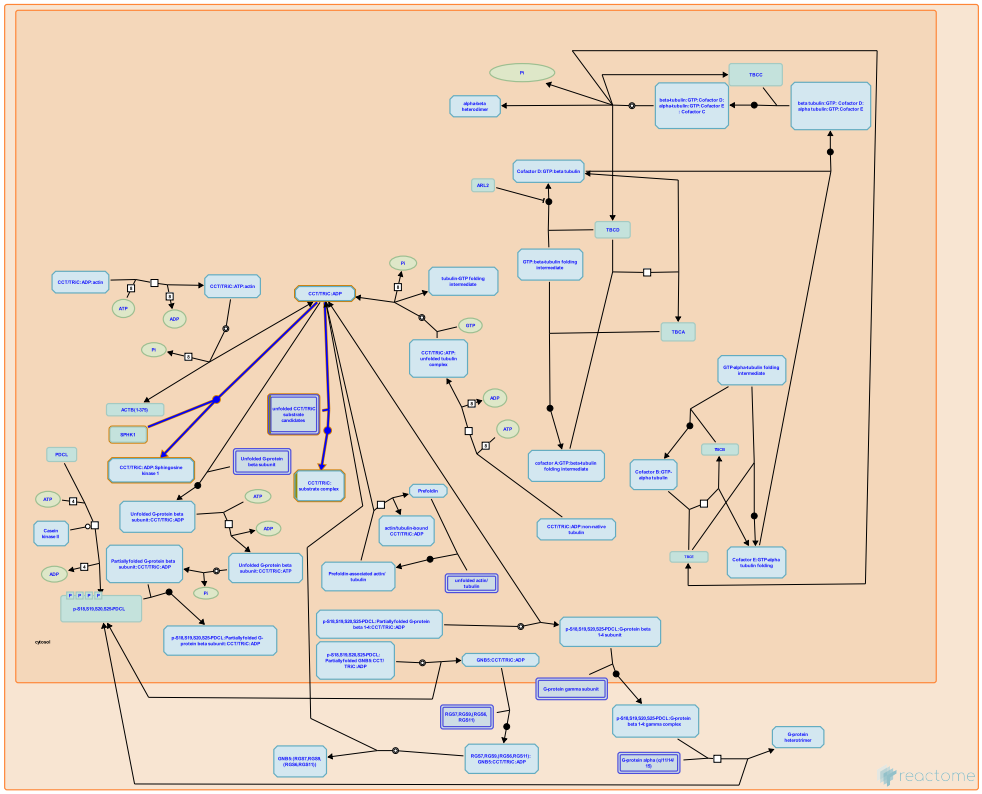
Edit history

Date	Action	Author
2007-11-27	Authored	Gopinathrao G
2007-11-27	Created	Gopinathrao G
2008-01-12	Reviewed	D'Eustachio P
2009-12-18	Revised	D'Eustachio P
2024-02-21	Edited	Stephan R
2024-02-23	Reviewed	Hill DP
2024-03-08	Modified	Wright A

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

Input	UniProt Id
PDHX	O00330

25. Association of TriC/CCT with target proteins during biosynthesis (R-HSA-390471)



Cellular compartments: cytosol.

TRiC has broad recognition specificities, but in the cell it interacts with only a defined set of substrates (Yam et al. 2008). Many of its substrates that are targeted during biosynthesis are conserved between mammals and yeast (Yam et al. 2008).

References

Lin HT, Burlingame A, Frydman J, Xia Y, Gerstein M & Yam AY (2008). Defining the TRiC/CCT interactome links chaperonin function to stabilization of newly made proteins with complex topologies. Nat Struct Mol Biol, 15, 1255-62.

Edit history

Date	Action	Author
2008-12-01	Authored	Matthews L
2009-01-21	Reviewed	Cowan NJ
2009-02-09	Created	Matthews L
2009-02-21	Edited	Matthews L
2024-03-08	Modified	Wright A

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

Input	UniProt Id
FBXW10	Q5XX13

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.

14 of the submitted entities were found, mapping to 15 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CREM	Q03060-6	FBXW10	Q5XX13	INO80C	Q6PI98
JUN	P05412	MEAF6	Q9HAF1	MSH3	P20585
MSH4	O15457	PAN3	Q58A45	PDHX	O00330
PMS1	P54278	SLX4	Q8IY92	TDRD12	Q587J7
TFDP1	Q14186	TP53INP1	Q96A56		

Input	Ensembl Id
TP53INP1	ENSG00000164938

Interactors (13)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
CCDC17	Q96LX7-5	P54252	CREM	EBI-10048213	P08047
INO80C	Q6PI98	P50454	JUN	P05412	P78563
MEAF6	Q9HAF1	P40937	MSH3	P20585	P43246
MSH4	O15457	O43196	PAN3	Q58A45	Q8NDV7
PDHX	O00330	Q8IWL3	PMS1	P54277	P40692
SLX4	Q8IY92	P43246	TFDP1	Q14186	Q01094
ZMYND8	Q9ULU4	P41182			

7. Identifiers not found

These 3 identifiers were not found neither mapped to any entity in Reactome.

LMNTD1 PMFBP1 TMEM135