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=MjAyNDA0MTExNTM3MjBfMzYyNA%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.
- 14 out of 15 identifiers in the sample were found in Reactome, where 496 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 MjAyNDA0MTExNTM3MjBfMzYyNA%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
TP53 Regulates Transcription of DNA Repair Genes	5 / 201	0.009	0.003	0.353	10 / 17	0.001
Defective Mismatch Repair Associated With MLH1	1 / 4	1.74e-04	0.006	0.353	1 / 1	6.72e-05
p75NTR negatively regulates cell cycle via SC1	1 / 9	3.91e-04	0.013	0.353	3 / 3	2.02e-04
DNA replication initiation	1 / 13	5.65e-04	0.018	0.353	2 / 2	1.34e-04
Polymerase switching	1 / 16	6.96e-04	0.023	0.353	4 / 4	2.69e-04
Leading Strand Synthesis	1 / 16	6.96e-04	0.023	0.353	4 / 4	2.69e-04
NFE2L2 regulating inflammation associated genes	1 / 16	6.96e-04	0.023	0.353	1 / 3	2.02e-04
Defective Mismatch Repair Associated With MSH6	1 / 18	7.83e-04	0.026	0.353	1 / 1	6.72e-05
PDH complex synthesizes acetyl-CoA from PYR	1 / 19	8.26e-04	0.027	0.353	3 / 3	2.02e-04
Defective Mismatch Repair Associated With MSH3	1 / 19	8.26e-04	0.027	0.353	1 / 1	6.72e-05
RUNX3 Regulates Immune Response and Cell Migration	1 / 19	8.26e-04	0.027	0.353	1 / 5	3.36e-04
G1/S-Specific Transcription	2 / 186	0.008	0.029	0.353	2 / 28	0.002
Removal of the Flap Intermediate	1 / 23	0.001	0.032	0.353	4 / 4	2.69e-04
BMAL1:CLOCK,NPAS2 activates circadian gene expression	4 / 199	0.009	0.033	0.353	3 / 20	0.001
Processive synthesis on the lagging strand	1 / 24	0.001	0.034	0.353	6 / 7	4.70e-04
Lagging Strand Synthesis	1 / 31	0.001	0.044	0.353	10 / 11	7.39e-04
HIV elongation arrest and recovery	1 / 34	0.001	0.048	0.353	3 / 3	2.02e-04
Pausing and recovery of HIV elongation	1 / 34	0.001	0.048	0.353	2 / 2	1.34e-04
Circadian Clock	6 / 609	0.026	0.056	0.353	5 / 59	0.004
SARS-CoV-1-mediated effects on programmed cell death	1 / 41	0.002	0.057	0.353	2 / 5	3.36e-04
Mismatch repair (MMR) directed by MSH2:MSH3 (MutSbeta)	2 / 42	0.002	0.059	0.353	5 / 9	6.05e-04
Regulation of pyruvate dehydrogenase (PDH) complex	1 / 43	0.002	0.06	0.353	2 / 6	4.03e-04
TRAF3 deficiency - HSE	1 / 46	0.002	0.064	0.353	1 / 1	6.72e-05

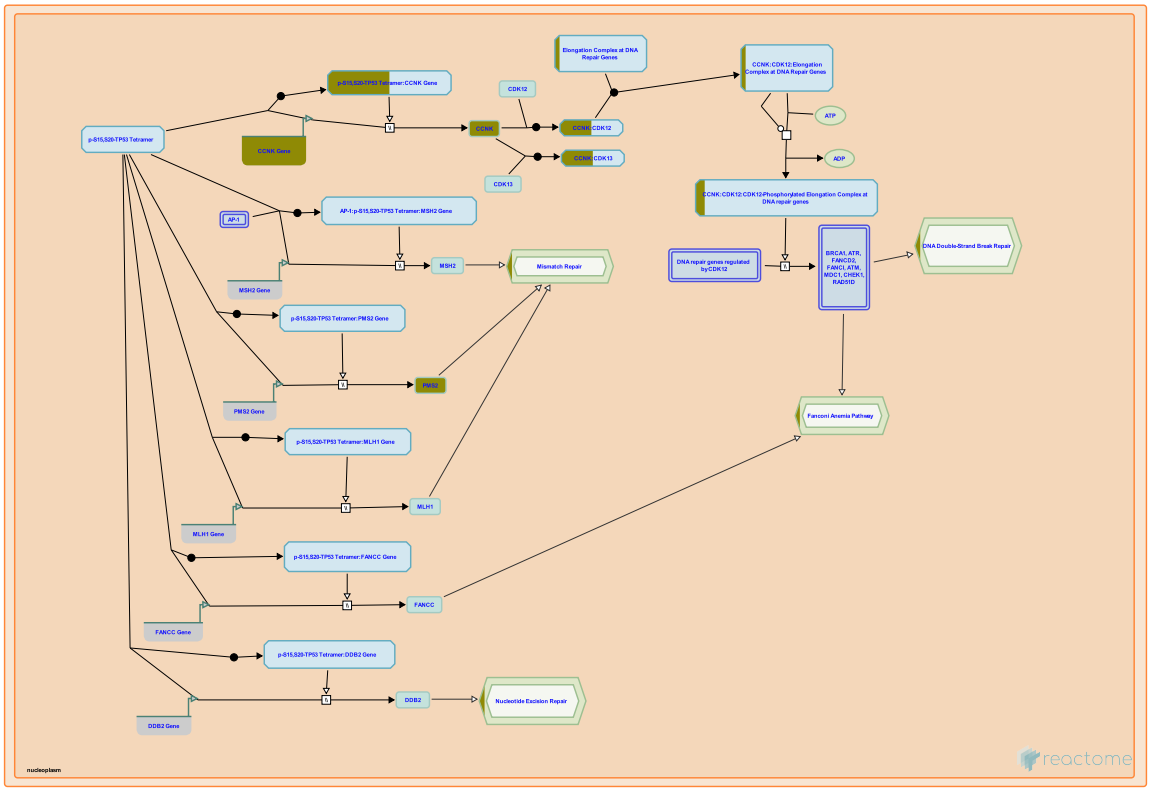
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
MyD88 deficiency (TLR2/4)	1 / 46	0.002	0.064	0.353	1 / 2	1.34e-04
Defective pyroptosis	1 / 51	0.002	0.071	0.353	1 / 3	2.02e-04

* 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. 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

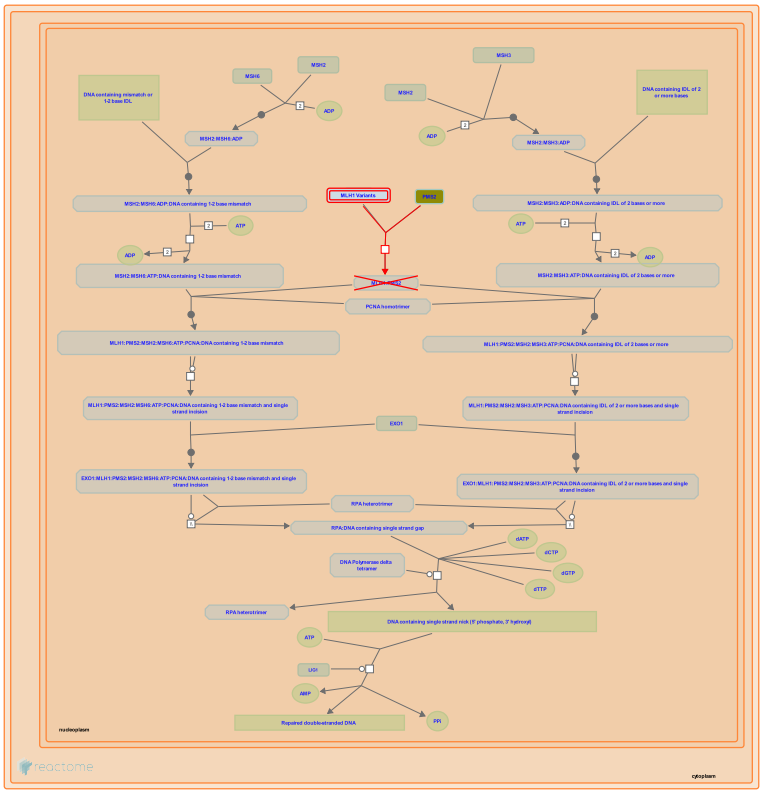
Input	UniProt Id	Input	UniProt Id
CCNK	O75909	PMS1	P54278

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	PMS1	P54277	P40692
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.

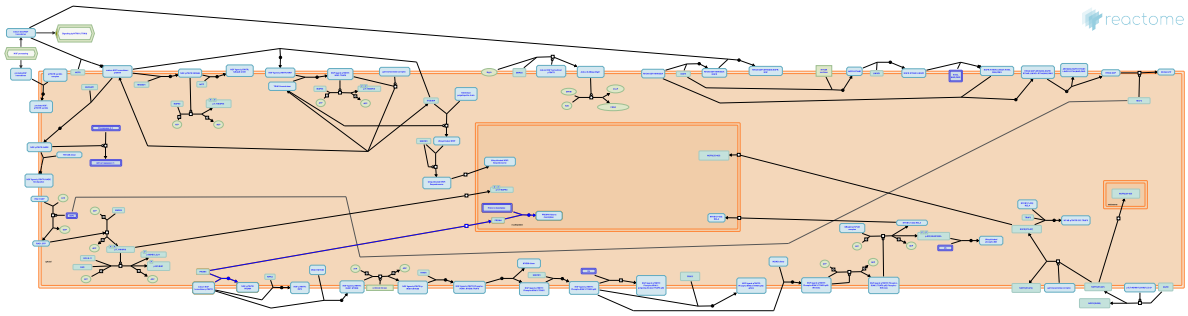
Edit history

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. p75NTR negatively regulates cell cycle via SC1 (R-HSA-193670)



SC1 (Schwann Cell factor 1; also called PR domain zinc finger protein 4, PRDM4) interacts with an NGF:p75NTR complex and signals cell cycle arrest by regulating the levels of cyclin E.

References

Frade JM & Lopez-Sanchez N (2002). Control of the cell cycle by neurotrophins: lessons from the p75 neurotrophin receptor. Histol Histopathol, 17, 1227-37.

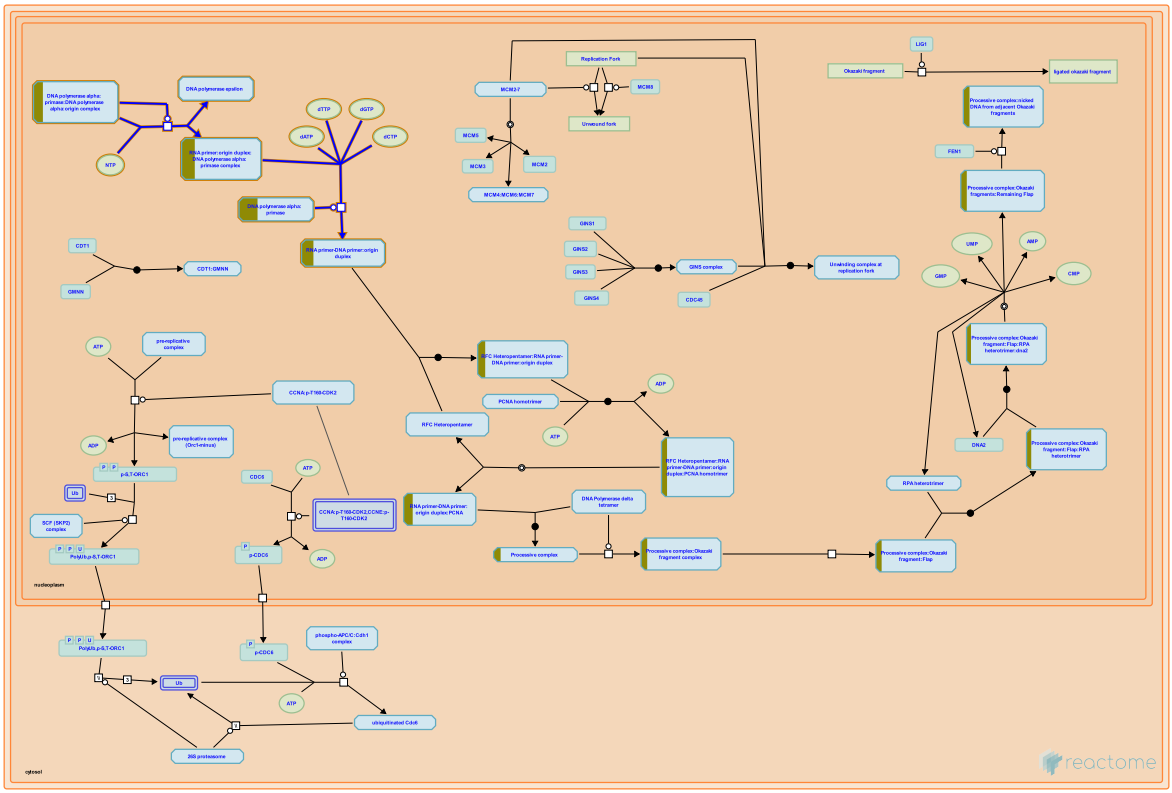
Edit history

Date	Action	Author
2006-10-10	Authored	Annibali D, Nasi S
2007-02-23	Created	Jassal B
2008-05-20	Edited	Jassal B
2008-05-20	Reviewed	Friedman WJ
2008-05-28	Reviewed	Chao MV
2023-03-08	Modified	Matthews L

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
ncs1	P62166	Q9UKN5			

4. DNA replication initiation (R-HSA-68952)



Cellular compartments: nucleoplasm.

DNA polymerases are not capable of de novo DNA synthesis and require synthesis of a primer, usually by a DNA-dependent RNA polymerase (primase) to begin DNA synthesis. In eukaryotic cells, the primer is synthesized by DNA polymerase alpha:primase. First, the DNA primase portion of this complex synthesizes approximately 6-10 nucleotides of RNA primer and then the DNA polymerase portion synthesizes an additional 20 nucleotides of DNA (Frick & Richardson 2002; Wang et al 1984).

References

Frick DN & Richardson CC (2002). DNA primases. Annu Rev Biochem, 70, 39-80.

Hu SZ, Korn D & Wang TS (1984). DNA primase from KB cells. Characterization of a primase activity tightly associated with immunoaffinity-purified DNA polymerase-alpha. J Biol Chem, 259, 1854-65.

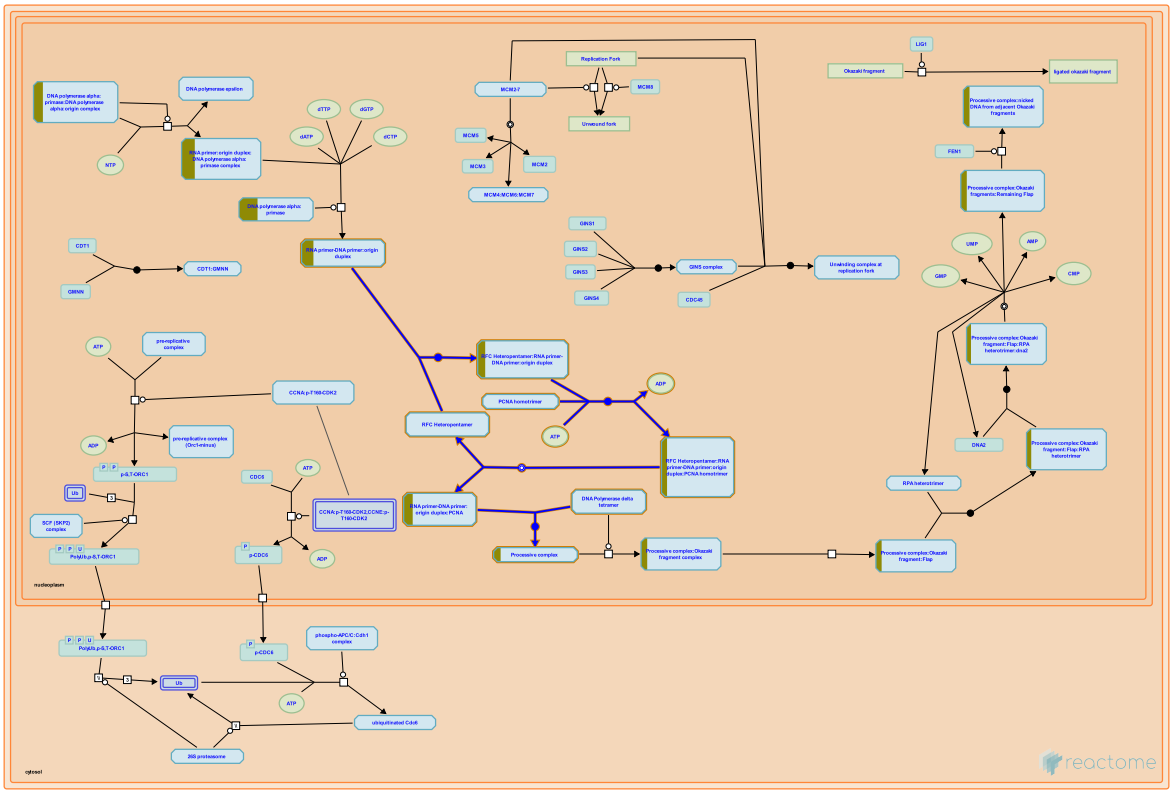
Edit history

Date	Action	Author
2003-06-05	Created	Davey MJ, O'Donnell M
2024-03-08	Modified	Wright A

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

Input	UniProt Id
POLA1	P09884

5. Polymerase switching (R-HSA-69091)



Cellular compartments: nucleoplasm.

After the primers are synthesized, Replication Factor C binds to the 3'-end of the initiator DNA to trigger polymerase switching. The non-processive nature of pol alpha catalytic activity and the tight binding of Replication Factor C to the primer-template junction presumably lead to the turnover of the pol alpha:primase complex. After the Pol alpha-primase primase complex is displaced from the primer, the proliferating cell nuclear antigen (PCNA) binds to form a "sliding clamp" structure. Replication Factor C then dissociates, and DNA polymerase delta binds and catalyzes the processive synthesis of DNA.

References

Stillman B & Tsurimoto T (1990). Functions of replication factor C and proliferating-cell nuclear antigen: functional similarity of DNA polymerase accessory proteins from human cells and bacteriophage T4. Proc Natl Acad Sci U S A, 87, 1023-7.

Hurwitz J, Kwong AD, Pan ZQ & Lee SH (1991). Studies on the activator 1 protein complex, an accessory factor for proliferating cell nuclear antigen-dependent DNA polymerase delta. J Biol Chem, 266, 594-602.

Stillman B & Tsurimoto T (1991). Replication factors required for SV40 DNA replication in vitro. II. Switching of DNA polymerase alpha and delta during initiation of leading and lagging strand synthesis. J Biol Chem, 266, 1961-8.

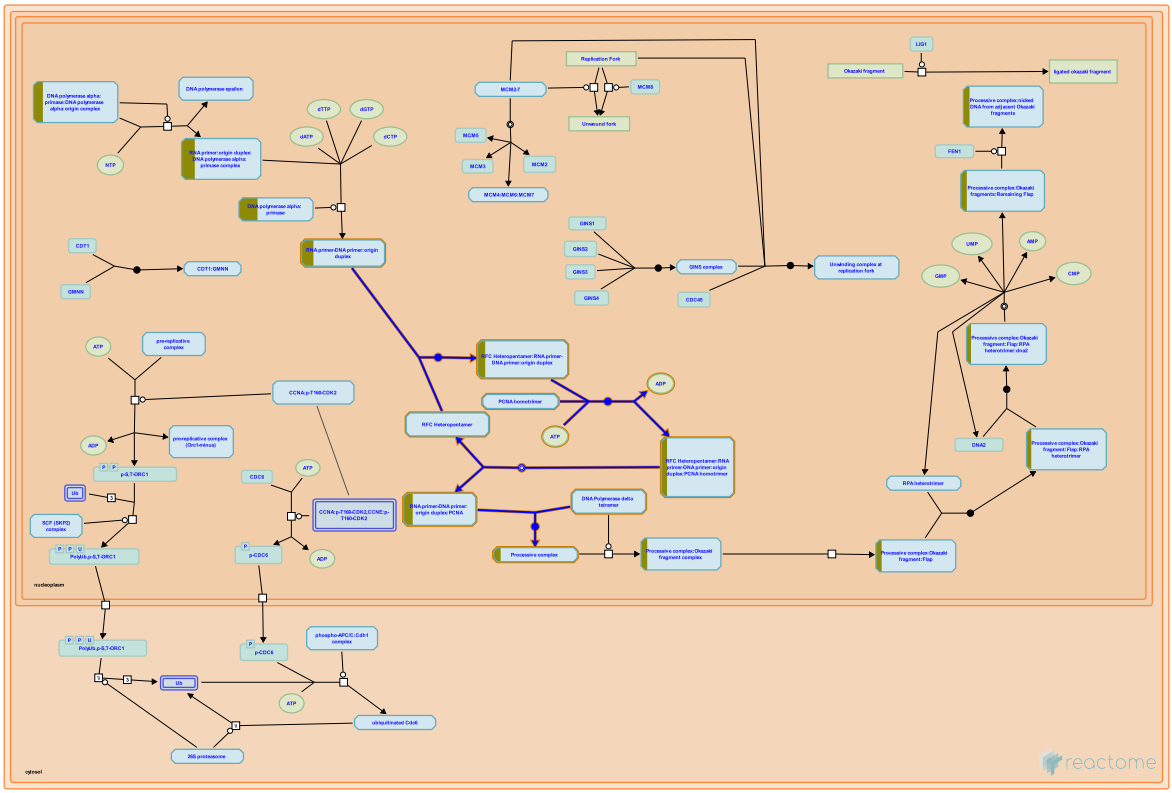
Edit history

Date	Action	Author
2024-03-08	Modified	Wright A

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

Input	UniProt Id
POLA1	P09884

6. Leading Strand Synthesis (R-HSA-69109)



Cellular compartments: nucleoplasm.

The processive complex is responsible for synthesizing at least 5-10 kb of DNA in a continuous manner during leading strand synthesis. The incorporation of nucleotides by pol delta is quite accurate. However, incorporation of an incorrect nucleotide does occur occasionally. Misincorporated nucleotides are removed by the 3' to 5' exonucleolytic proofreading capability of pol delta.

References

So AG, Downey KM, Tan CK & Lee MY (1980). Purification of deoxyribonucleic acid polymerase delta from calf thymus: partial characterization of physical properties. Biochemistry, 19, 2096-101.

Hurwitz J, Matsumoto T & Eki T (1991). Studies on the initiation and elongation reactions in the simian virus 40 DNA replication system. Proc Natl Acad Sci U S A, 87, 9712-6.

Hubscher U & Hindges R (1997). DNA polymerase delta, an essential enzyme for DNA transactions. Biol Chem, 378, 345-62.

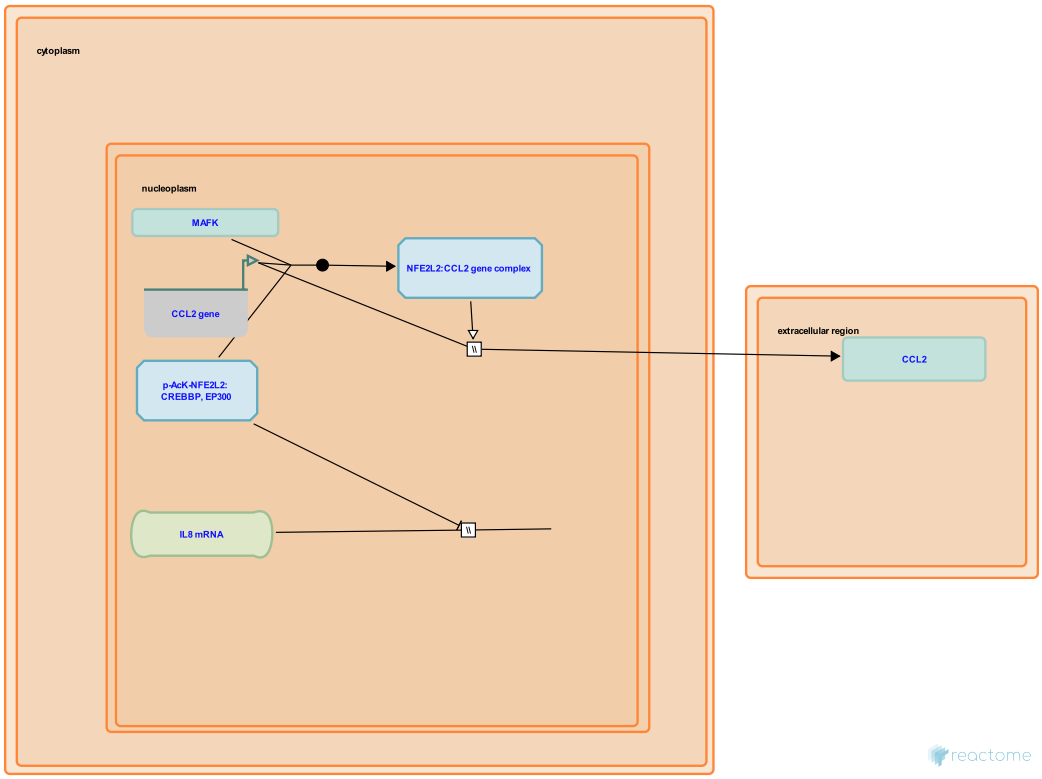
Edit history

Date	Action	Author
2024-03-08	Modified	Wright A

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

Input	UniProt Id
POLA1	P09884

7. 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

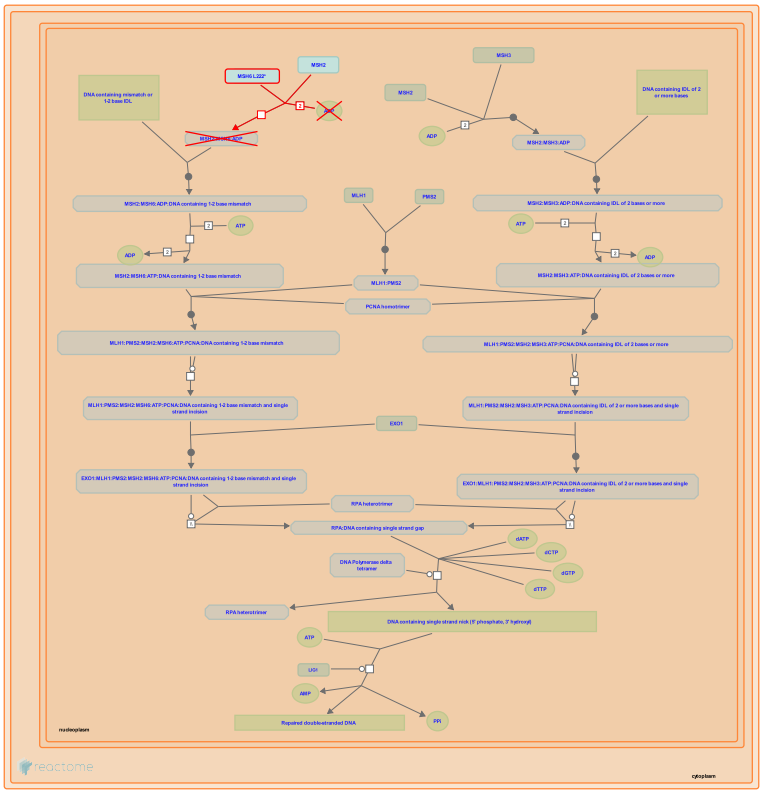
Edit history

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			

8. 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.

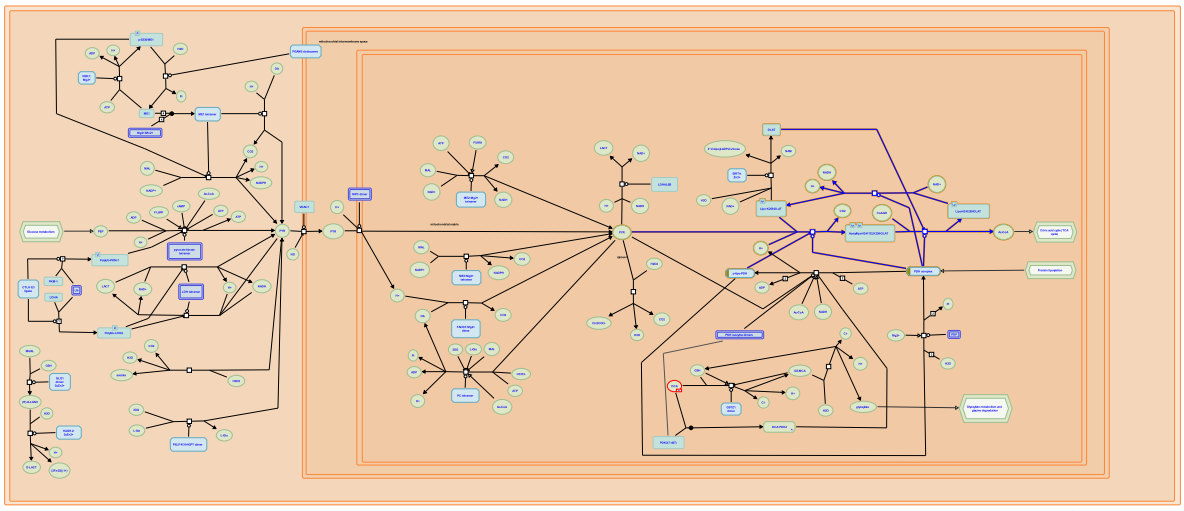
Edit history

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
SLX4	Q8IY92	P43246			

9. 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.

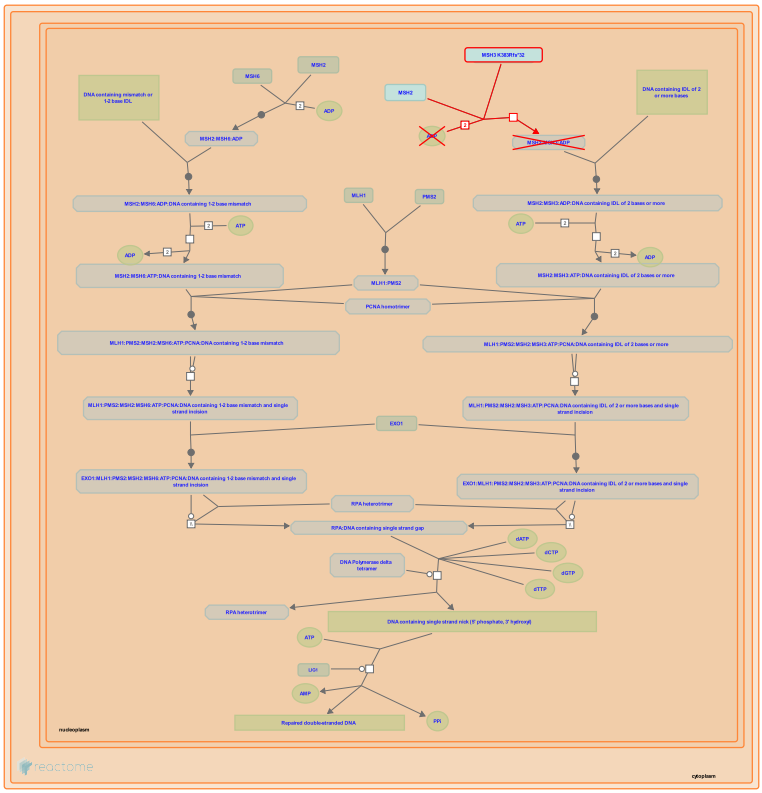
Edit history

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

10. 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.

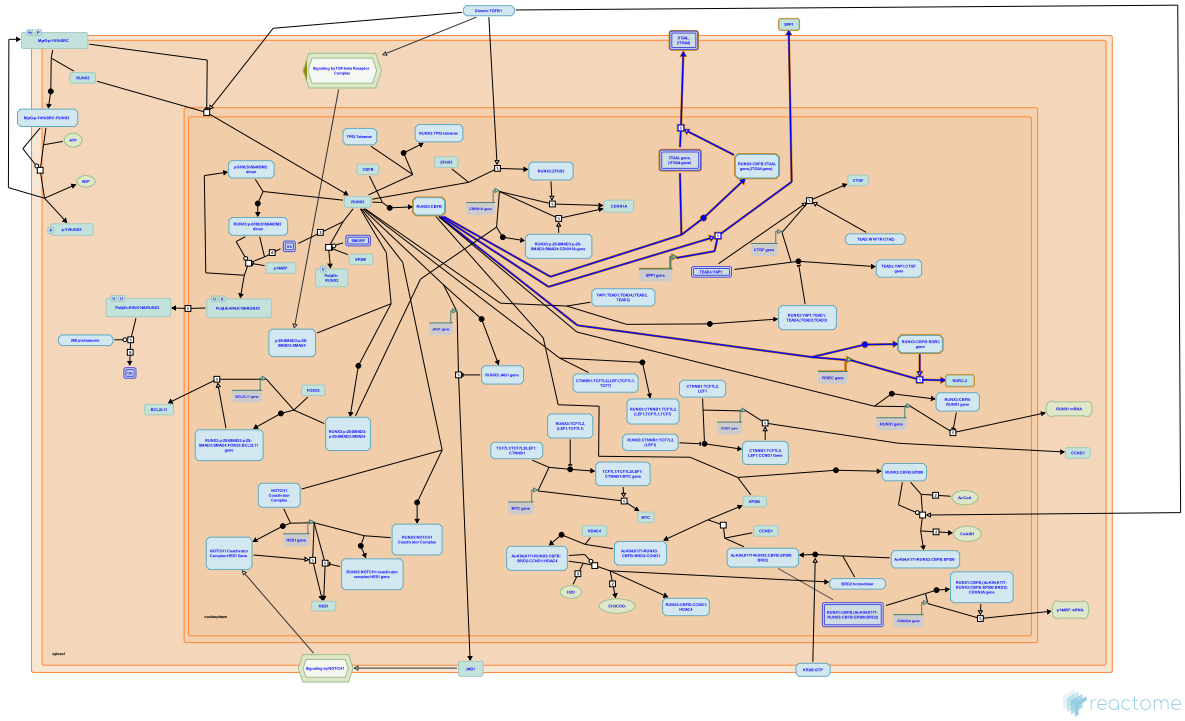
Edit history

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

Interactors found in this pathway (1)

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

11. RUNX3 Regulates Immune Response and Cell Migration (R-HSA-8949275)



RUNX3-mediated transcription regulates development of immune system cells. RUNX3 is necessary for the development of innate lymphoid cells (ILCs) of ILC1 and ILC3 lineages, which reside in the mucosa and are involved in response to external pathogens. RUNX3 exerts its role in the development of ILC1 and ILC3 lineages by stimulating expression of the RORC (RORgamma) gene, encoding nuclear retinoid-related orphan receptor-gamma (Ebihara et al. 2015).

RUNX3 regulates transcription of integrin genes ITGAL (CD11a) and ITGA4 (CD49d), involved in transendothelial migration of leukocytes during immune and inflammatory responses as well as co-stimulation of T cells (Domniguez-Soto et al. 2005). The RUNX3 splicing isoform p33 lacks the Runt domain and is unable to transactivate integrin genes. The p33 isoform is induced during maturation of monocyte-derived dendritic cells (MDDC), leading to reduced expression of genes involved in inflammatory responses, such as IL8 (interleukin-8) (Puig-Kroger et al. 2010).

RUNX3 positively regulates transcription of the SPP1 (osteopontin) gene, which contributes to invasiveness of pancreatic cancer cells (Whittle et al. 2015).

References

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Dopazo A, Corbí AL, Alonso Martín MJ, Sánchez-Cabo F, Martín-Gayo E, Puig-Kröger A, ... Domínguez-Soto A (2010). The novel RUNX3/p33 isoform is induced upon monocyte-derived dendritic cell maturation and downregulates IL-8 expression. Immunobiology, 215, 812-20.

Thorsen SM, DelGiorno KE, Hruban RH, Rani PG, Chang AE, Hingorani SR, ... Goggins M (2015). RUNX3 Controls a Metastatic Switch in Pancreatic Ductal Adenocarcinoma. Cell, 161, 1345-60.

Corbí AL, Puig-Kröger A, Relloso M, Vega MA & Domínguez-Soto A (2005). RUNX3 regulates the activity of the CD11a and CD49d integrin gene promoters. Immunobiology, 210, 133-9.

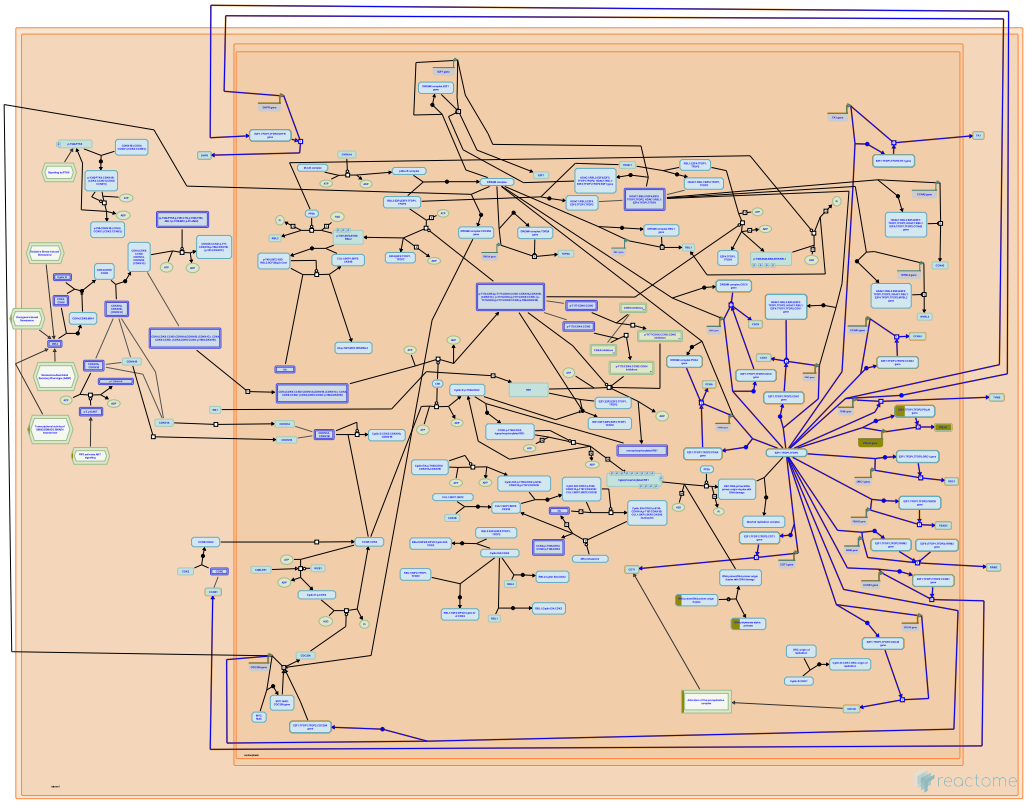
Edit history

Date	Action	Author
2016-11-21	Created	Orlic-Milacic M
2016-12-13	Authored	Orlic-Milacic M
2017-01-31	Edited	Orlic-Milacic M
2017-01-31	Reviewed	Ito Y, Chuang LS
2023-03-08	Modified	Matthews L

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
ncs1	P62166	P10451			

12. G1/S-Specific Transcription (R-HSA-69205)



Cellular compartments: nucleoplasm.

The E2F family of transcription factors regulate the transition from the G1 to the S phase in the cell cycle. E2F activity is regulated by members of the retinoblastoma protein (pRb) family, resulting in the tight control of the expression of E2F-responsive genes. Phosphorylation of pRb by cyclin D:CDK complexes releases pRb from E2F, inducing E2F-targeted genes such as cyclin E.

E2F1 binds to E2F binding sites on the genome activating the synthesis of the target proteins. For annotation purposes, the reactions regulated by E2F1 are grouped under this pathway and information about the target genes alone are displayed for annotation purposes.

Cellular targets for activation by E2F1 include thymidylate synthase (TYMS) (DeGregori et al. 1995), Rir2 (RRM2) (DeGregori et al. 1995, Giangrande et al. 2004), Dihydrofolate reductase (DHFR) (DeGregori et al. 1995, Wells et al. 1997, Darbinian et al. 1999), Cdc2 (CDK1) (Furukawa et al. 1994, DeGregori et al. 1995, Zhu et al. 2004), Cyclin A1 (CCNA1) (DeGregori et al. 1995, Liu et al. 1998), CDC6 (DeGregori et al. 1995, Yan et al. 1998; Ohtani et al. 1998), CDT1 (Yoshida and Inoue 2004), CDC45 (Arata et al. 2000), Cyclin E (CCNE1) (Ohtani et al. 1995), Emi1 (FBXO5) (Hsu et al. 2002), and ORC1 (Ohtani et al. 1996, Ohtani et al. 1998). The activation of TK1 (Dnk1) (Dou et al. 1994, DeGregori et al. 1995, Giangrande et al. 2004) and CDC25A (DeGregori et al. 1995, Vigo et al. 1999) by E2F1 is conserved in Drosophila (Duronio and O'Farrell 1994, Reis and Edgar 2004).

RRM2 protein is involved in dNTP level regulation and activation of this enzyme results in higher levels of dNTPs in anticipation of S phase. E2F activation of RRM2 has been shown also in Drosophila by Duronio and O'Farrell (1994). E2F1 activation of CDC45 is shown in mouse cells by using human E2F1 construct (Arata et al. 2000). Cyclin E is also transcriptionally regulated by E2F1. Cyclin E protein plays important role in the transition of G1 in S phase by associating with CDK2 (Ohtani et al. 1996). E2F1-mediated activation of PCNA has been demonstrated in Drosophila (Duronio and O'Farrell 1994) and in some human cells by using recombinant adenovirus constructs (DeGregori et al. 1995). E2F1-mediated activation of the DNA polymerase alpha subunit p180 (POLA1) has been demonstrated in some human cells. It has also been demonstrated in Drosophila by Ohtani and Nevins (1994). It has been observed in Drosophila that E2F1 induced expression of Orc1 stimulates ORC1 6 complex formation and binding to the origin of replication (Asano and Wharton 1999). ORC1 6 recruit CDC6 and CDT1 that are required to recruit the MCM2 7 replication helicases. E2F1 regulation incorporates a feedback mechanism wherein Geminin (GMNN) can inhibit MCM2 7 recruitment of ORC1 6 complex by interacting with CDC6/CDT1. The activation of CDC25A and TK1 (Dnk1) by E2F1 has been inferred from similar events in Drosophila (Duronio RJ and O'Farrell 1994; Reis and Edgar 2004). E2F1 activates string (CDC25) that in turn activates the complex of Cyclin B and CDK1. A similar phenomenon has been observed in mouse NIH 3T3 cells and in Rat1 cells.

References

Ohtani K, Ikeda M, Nakamura M & Tsujimoto A (1998). Regulation of cell growth-dependent expression of mammalian CDC6 gene by the cell cycle transcription factor E2F. Oncogene, 17, 1777-85.

Wang J, Dou QP, Pardee AB, Zhao S, Helin K & Levin AH (1994). G1/S-regulated E2F-containing protein complexes bind to the mouse thymidine kinase gene promoter. J. Biol. Chem., 269, 1306-13.

Hateboer G, Vigo E, Helin K, Prosperini E, Cartwright P, Moroni MC & Muller H (1999). CDC25A phosphatase is a target of E2F and is required for efficient E2F-induced S phase. Mol Cell Biol, 19, 6379-95.

Tretiakova A, Kundu M, Gallia GL, Khalili K, Giordano A, Shcherbik N & Darbinian N (1999). Association of Pur alpha and E2F-1 suppresses transcriptional activity of E2F-1. Oncogene, 18, 6398-402 .

Kijima S, Ohtani K, Fujita M, Arata Y & Kato JY (2000). Cdk2-dependent and -independent pathways in E2F-mediated S phase induction. J Biol Chem, 275, 6337-45.

Edit history

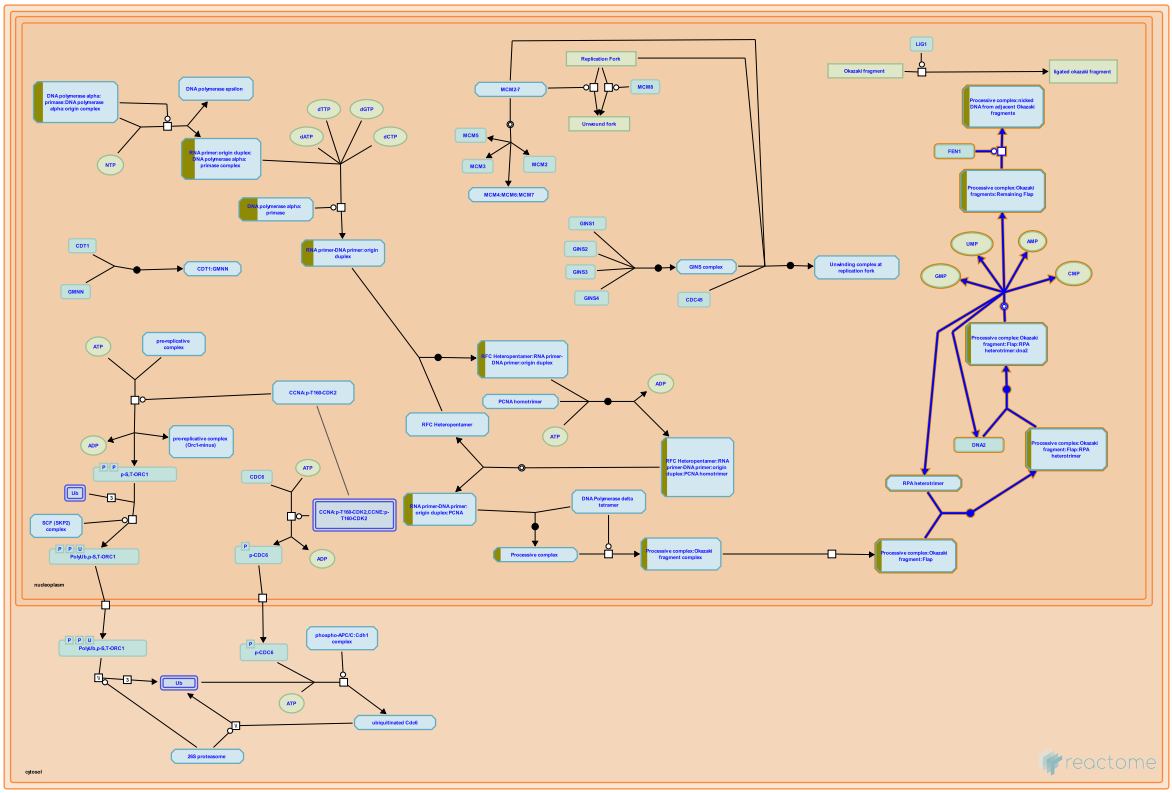
Date	Action	Author
2003-06-05	Created	Walworth N, O'Donnell M

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

Input	UniProt Id
POLA1	P09884

Input	Ensembl Id
POLA1	ENSG00000101868

13. Removal of the Flap Intermediate (R-HSA-69166)



Cellular compartments: nucleoplasm.

Two endonucleases, Dna2 and flap endonuclease 1 (FEN-1), are responsible for resolving the nascent flap structure (Tsurimoto and Stillman 1991). The Dna2 endonuclease/helicase in yeast is a monomer of approximately 172 kDa. Human FEN-1 is a single polypeptide of approximately 42 kDa. Replication Protein A regulates the switching of endonucleases during the removal of the displaced flap (Tsurimoto et al.1991).

References

Harrington JJ & Lieber MR (1994). The characterization of a mammalian DNA structure-specific endonuclease. EMBO J, 13, 1235-46.

Campbell JL & Budd ME (1995). A yeast gene required for DNA replication encodes a protein with homology to DNA helicases. Proc Natl Acad Sci U S A, 92, 7642-6.

Harrington JJ & Lieber MR (1994). Functional domains within FEN-1 and RAD2 define a family of structure-specific endonucleases: implications for nucleotide excision repair. Genes Dev, 8, 1344-55.

Edit history

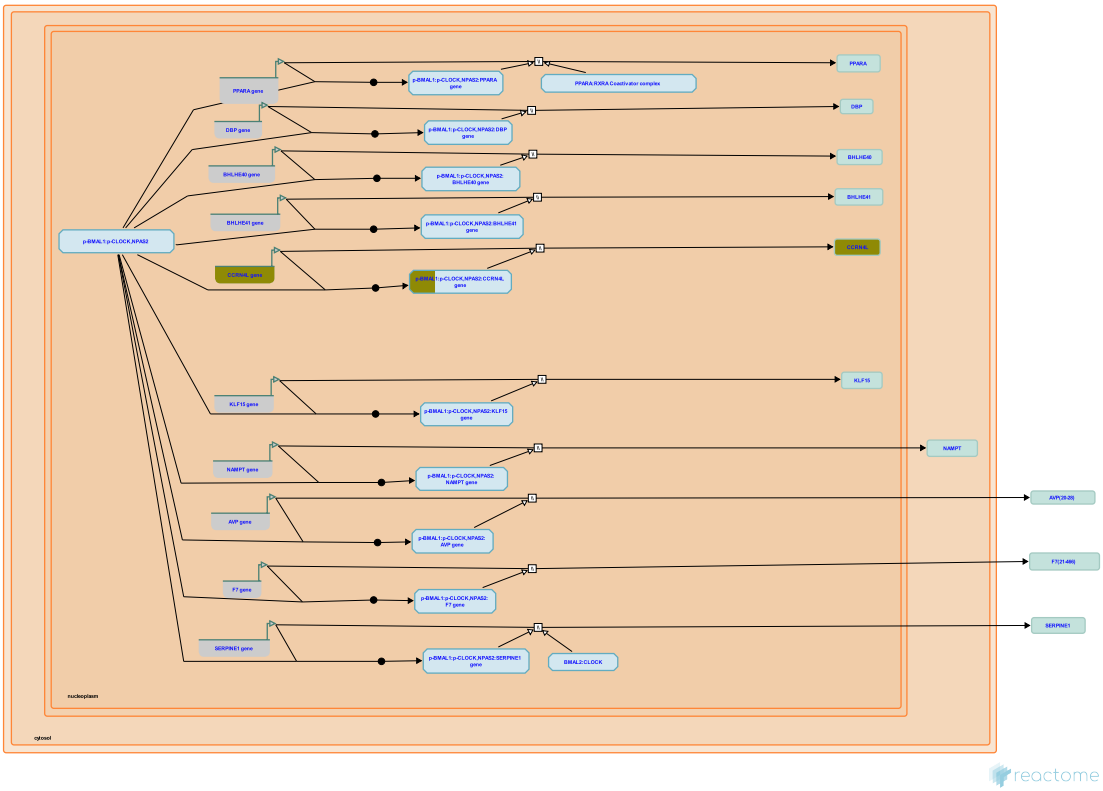
Date	Action	Author
2024-03-08	Modified	Wright A

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

Input	UniProt Id
POLA1	P09884

Input	UniProt Id

14. BMAL1:CLOCK,NPAS2 activates circadian gene expression (R-HSA-1368108)



Cellular compartments: nucleoplasm, extracellular region, endoplasmic reticulum lumen, cytosol.

As inferred from mouse, BMAL1:CLOCK (ARNTL:CLOCK) and BMAL1:NPAS2 (ARNTL:NPAS2) heterodimers bind to sequence elements (E boxes) in the promoters of target genes and enhance transcription (Gekakis et al. 1998, reviewed in Munoz and Baler 2003).

References

Muñoz E & Baler R (2003). The circadian E-box: when perfect is not good enough. Chronobiol Int, 20, 371-88.

King DP, Nguyen HB, Weitz CJ, Takahashi JS, Staknis D, Gekakis N, ... Wilsbacher LD (1998). Role of the CLOCK protein in the mammalian circadian mechanism. Science, 280, 1564-9.

Edit history

Date	Action	Author
2009-05-27	Reviewed	D'Eustachio P
2010-06-23	Reviewed	Hirota T, Delaunay F, Kay SA, Albrecht U
2011-06-22	Edited	May B
2011-06-22	Authored	May B
2011-06-30	Created	May B
2015-01-17	Revised	May B
2023-10-12	Modified	Weiser JD

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

Input	UniProt Id
CCRN4L	Q9UK39

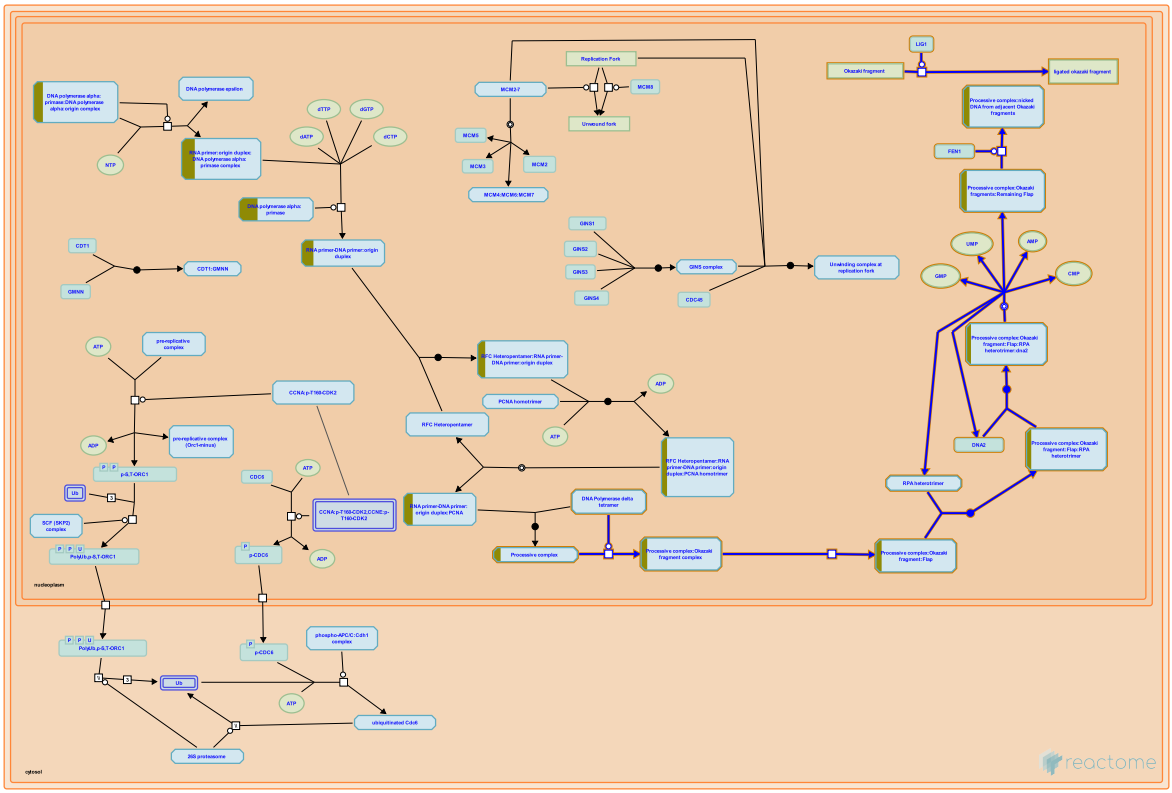
Input	Ensembl Id
CCRN4L	ENSG00000151014

Interactors found in this pathway (2)

Input	UniProt Id	Interacts with
CCNK	O75909	O14503

Input	UniProt Id	Interacts with
CREM	Q03060-25	O14503

15. Processive synthesis on the lagging strand (R-HSA-69183)



Cellular compartments: nucleoplasm.

The key event that allows the processive synthesis on the lagging strand, is polymerase switching from pol alpha to pol delta, as on the leading strand. However, the processive synthesis on the lagging strand proceeds very differently. DNA synthesis is discontinuous, and involves the formation of short fragments called the Okazaki fragments. During the synthesis of Okazaki fragments, the RNA primer is folded into a single-stranded flap, which is removed by endonucleases. This is followed by the ligation of adjacent Okazaki fragments.

References

Stillman B & Tsurimoto T (1991). Replication factors required for SV40 DNA replication in vitro. II. Switching of DNA polymerase alpha and delta during initiation of leading and lagging strand synthesis. J Biol Chem, 266, 1961-8.

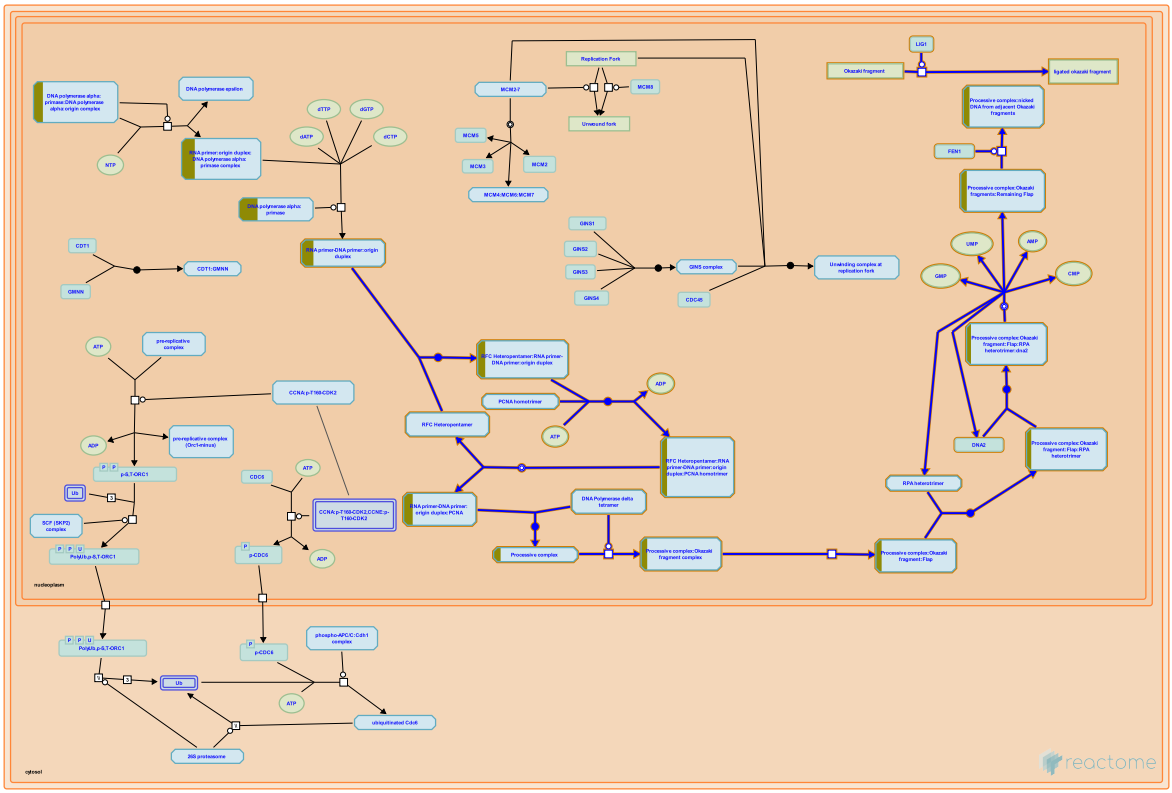
Edit history

Date	Action	Author
2024-03-08	Modified	Wright A

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

Input	UniProt Id
POLA1	P09884

16. Lagging Strand Synthesis (R-HSA-69186)



Cellular compartments: nucleoplasm.

Due to the antiparallel nature of DNA, DNA polymerization is unidirectional, and one strand is synthesized discontinuously. This strand is called the lagging strand. Although the polymerase switching on the lagging strand is very similar to that on the leading strand, the processive synthesis on the two strands proceeds quite differently. Short DNA fragments, about 100 bases long, called Okazaki fragments are synthesized on the RNA-DNA primers first. Strand-displacement synthesis occurs, whereby the primer-containing 5'-terminus of the adjacent Okazaki fragment is folded into a single-stranded flap structure. This flap structure is removed by endonucleases, and the adjacent Okazaki fragments are joined by DNA ligase.

References

Bambara RA, Murante RS & Henricksen LA (1997). Enzymes and reactions at the eukaryotic DNA replication fork. J Biol Chem, 272, 4647-50.

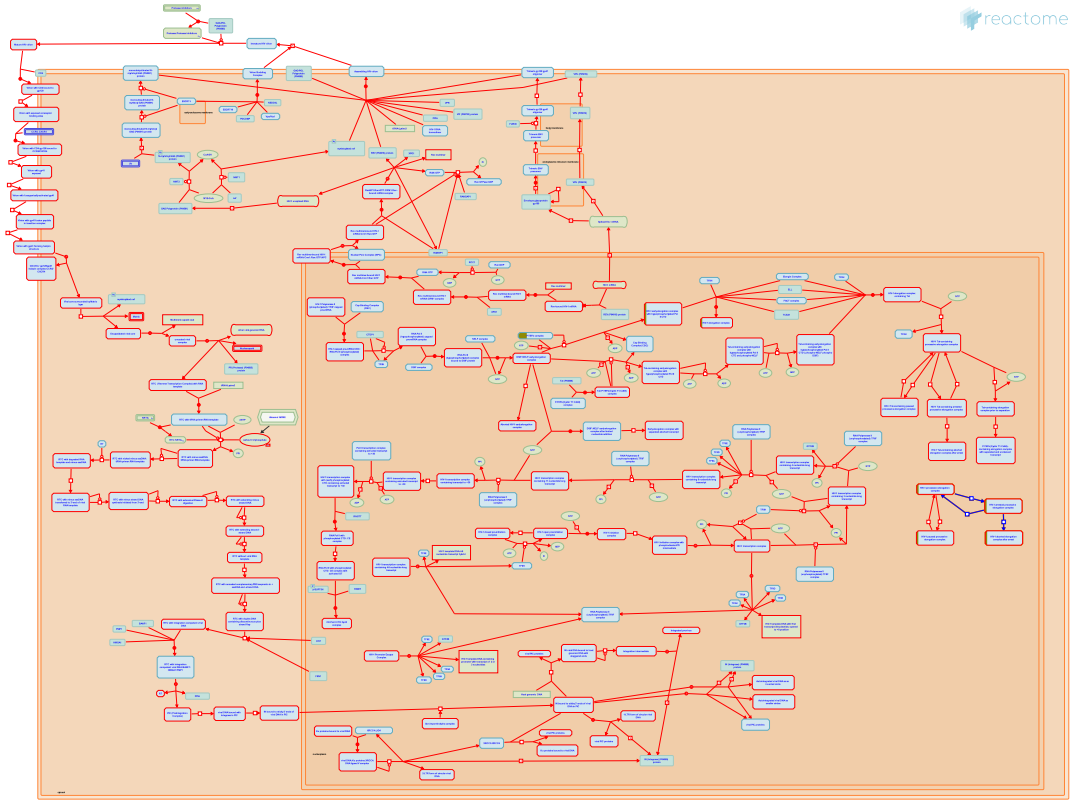
Edit history

Date	Action	Author
2024-03-08	Modified	Wright A

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

Input	UniProt Id
POLA1	P09884

17. HIV elongation arrest and recovery (R-HSA-167287)



Cellular compartments: nucleoplasm.

Diseases: Human immunodeficiency virus infectious disease.

RNA Pol II arrest is believed to be a result of irreversible backsliding of the enzyme by ~7-14 nucleotides. TFIIS reactivates arrested RNA Pol II by promoting the excision of nascent transcript ~7-14 nucleotides upstream of the 3' end.

References

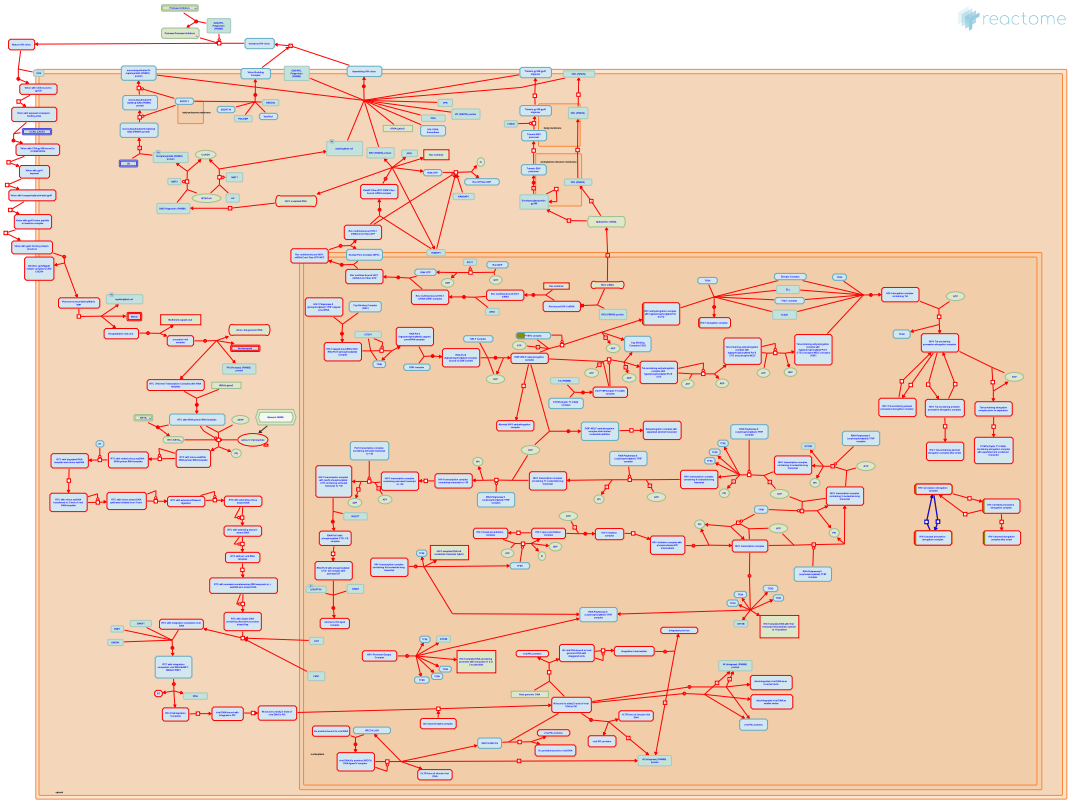
Edit history

Date	Action	Author
2005-10-14	Created	Matthews L
2023-10-12	Modified	Weiser JD

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

Input	UniProt Id
CCNK	O75909

18. Pausing and recovery of HIV elongation (R-HSA-167290)



Cellular compartments: nucleoplasm.

Diseases: Human immunodeficiency virus infectious disease.

After Pol II pauses by back tracking 2 -4 nuleotides on the HIV-1 template, elongation of the HIV-1 transcript resumes.

References

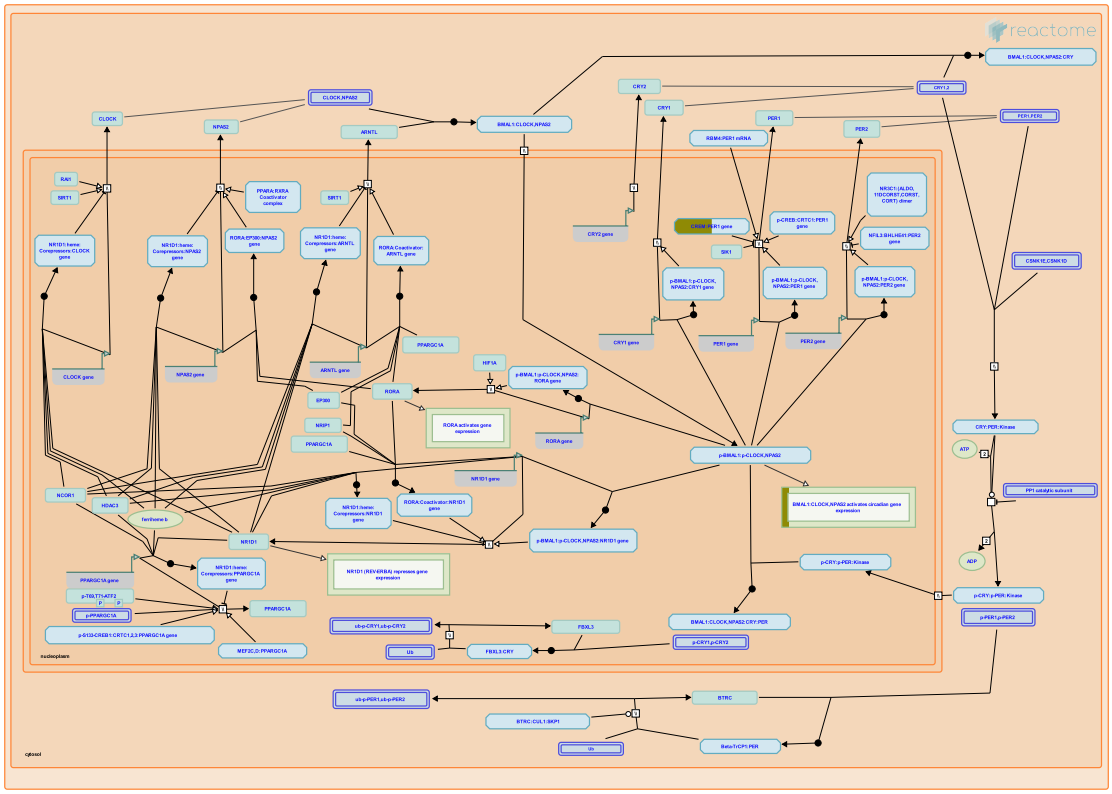
Edit history

Date	Action	Author
2005-10-14	Created	Matthews L
2023-10-12	Modified	Weiser JD

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

Input	UniProt Id
CCNK	O75909

19. Circadian Clock (R-HSA-400253)



Cellular compartments: cytosol, nucleoplasm.

At the center of the mammalian circadian clock is a negative transcription/translation-based feedback loop: The BMAL1:CLOCK/NPAS2 (ARNTL:CLOCK/NPAS2) heterodimer transactivates CRY and PER genes by binding E-box elements in their promoters; the CRY and PER proteins then inhibit transactivation by BMAL1:CLOCK/NPAS2. BMAL1:CLOCK/NPAS2 activates transcription of CRY, PER, and several other genes in the morning. Levels of PER and CRY proteins rise during the day and inhibit expression of CRY, PER, and other BMAL1:CLOCK/NPAS2-activated genes in the afternoon and evening. During the night CRY and PER proteins are targeted for degradation by phosphorylation and polyubiquitination, allowing the cycle to commence again in the morning.

Transcription of the BMAL1 (ARNTL) gene is controlled by ROR-alpha and REV-ERBA (NR1D1), both of which are targets of BMAL1:CLOCK/NPAS2 in mice and both of which compete for the same element (RORE) in the BMAL1 promoter. ROR-alpha (RORA) activates transcription of BMAL1; REV-ERBA represses transcription of BMAL1. This mutual control forms a secondary, reinforcing loop of the circadian clock. REV-ERBA shows strong circadian rhythmicity and confers circadian expression on BMAL1.

BMAL1 can form heterodimers with either CLOCK or NPAS2, which act redundantly but show different tissue specificity. The BMAL1:CLOCK and BMAL1:NPAS2 heterodimers activate a set of genes that possess E-box elements (consensus CACGTG) in their promoters. This confers circadian expression on the genes. The PER genes (PER1, PER2, PER3) and CRY genes (CRY1, CRY2) are among those activated by BMAL1:CLOCK and BMAL1:NPAS2. PER and CRY mRNA accumulates during the morning and the proteins accumulate during the afternoon. PER and CRY proteins form complexes in the cytosol and these are bound by either CSNK1D or CSNK1E kinases which phosphorylate PER and CRY. The phosphorylated PER:CRY:kinase complex is translocated into the nucleus due to the nuclear localization signal of PER and CRY. Within the nucleus the PER:CRY complexes bind BMAL1:CLOCK and BMAL1:NPAS2, inhibiting their transactivation activity and their phosphorylation. This reduces expression of the target genes of BMAL1:CLOCK and BMAL1:NPAS2 during the afternoon and evening.

PER:CRY complexes also traffic out of the nucleus into the cytosol due to the nuclear export signal of PER. During the night PER:CRY complexes are polyubiquitinated and degraded, allowing the cycle to begin again. Phosphorylated PER is bound by Beta-TrCP1, a cytosolic F-box type component of some SCF E3 ubiquitin ligases. CRY is bound by FBXL3, a nucleoplasmic F-box type component of some SCF E3 ubiquitin ligases. Phosphorylation of CRY1 by Adenosine monophosphate-activated kinase (AMPK) enhances degradation of CRY1. PER and CRY are subsequently polyubiquitinated and proteolyzed by the 26S proteasome.

The circadian clock is cell-autonomous and some, but not all cells of the body exhibit circadian rhythms in metabolism, cell division, and gene transcription. The suprachiasmatic nucleus (SCN) in the hypothalamus is the major clock in the body and receives its major input from light (via retinal neurons) and a minor input from nutrient intake. The SCN and other brain tissues determine waking and feeding cycles and influence the clocks in other tissues by hormone secretion and nervous stimulation. Independently of the SCN, other tissues such as liver receive inputs from signals from the brain and from nutrients.

References

Hastings MH, Maywood ES & O'Neill JS (2008). Cellular circadian pacemaking and the role of cytosolic rhythms. Curr Biol, 18, R805-R815.

Bass J, Green CB & Takahashi JS (2008). The meter of metabolism. Cell, 134, 728-42.

Hong HK, Ko CH, Takahashi JS & McDearmon EL (2008). The genetics of mammalian circadian order and disorder: implications for physiology and disease. Nat Rev Genet, 9, 764-75.

Ko CH & Takahashi JS (2006). Molecular components of the mammalian circadian clock. Hum Mol Genet, 15, R271-7.

Edit history

Date	Action	Author
2009-03-24	Created	May B
2009-05-18	Edited	May B
2009-05-18	Authored	May B
2009-05-27	Reviewed	D'Eustachio P
2010-06-23	Reviewed	Hirota T, Delaunay F, Kay SA, Albrecht U

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

Input	UniProt Id
CCRN4L	Q9UK39

Input	UniProt Id
CREM	Q03060-6

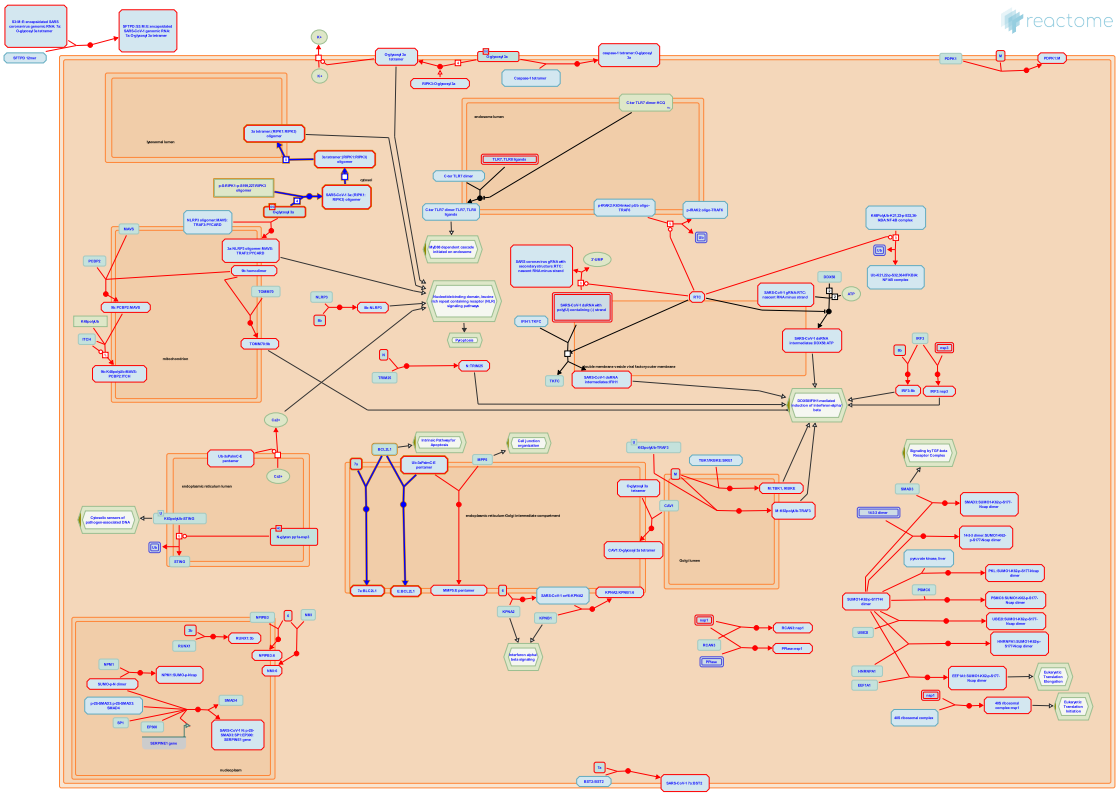
Input	Ensembl Id
CCRN4L	ENSG00000151014

Interactors found in this pathway (3)

Input	UniProt Id	Interacts with
CCNK	O75909	O14503
RNF4	P78317	P15336

Input	UniProt Id	Interacts with
CREM	Q03060-25	O14503

20. SARS-CoV-1-mediated effects on programmed cell death (R-HSA-9692913)



Diseases: severe acute respiratory syndrome.

Programmed cell death (PCD) pathways, including pyroptosis, apoptosis, and necroptosis, are induced in infected host cells as an integral part of host defense to restrict microbial infections and regulate inflammatory responses (reviewed in Jorgensen I et al. 2017; Galluzzi L et al. 2018). Apoptosis is a noninflammatory form of cell death driven by the initiator caspase‐mediated cleavage of executioner caspase‐3 and ‐7. It facilitates degradation of the cellular contents but these are not released to the extracellular space. Necroptosis and pyroptosis are highly inflammatory forms of cell death that lead to cell lysis and release of pro‐inflammatory cytokines such as interleukin (IL)‐1‐, tumour necrosis factor alpha (TNF‐), IL6, IL18 and cellular contents, which can cause severe inflammation (reviewed in Jorgensen I et al. 2017; Galluzzi L et al. 2018; Pasparakis M & Vandenabeele P 2015). Gasdermins (GSDMs) exert pore‐forming activity in inflammasome‐dependent pyroptosis, while the mixed lineage kinase domain‐like (MLKL) protein functions as the executioner during necroptosis (Shi J et AL. 2015; Upton JW et al. 2017). Inflammation is a fundamental protective mechanism in elimination of microorganisms, and is normally tightly regulated by certain mediators, in particular IL10, to promote resolution of inflammation (reviewed in Sugimoto MA et al. 2016). Microbial pathogens are able to trigger and/or modulate host PCD and inflammatory response through multiple mechanisms.

This Reactome module describes the roles of severe acute respiratory syndrome‐associated coronavirus type 1 (SARS‐CoV‐1) 3a, E, and 7a proteins in the induction of host cell death pathways. SARS‐CoV‐1 open reading frame‐3a (3a) binds host receptor interacting serine/threonine protein kinase 3 (RIPK3), facilitating RIPK3 oligomerization and the ion channel functionality of viral 3a, inducing inflammatory cell death and release of cellular contents (Yue Y et al. 2018). Enhanced production and release of proinflammatory cytokines leads to the cytokine storm that is considered to play a major role in SARS‐CoV type 1and 2 infections (reviewed in Channappanavar R & Perlman S 2017; Yang L et al. 2020). The module also describes induction of apoptosis by SARS‐CoV‐1 E and 7a proteins through their interaction with anti‐apoptotic BCL2L1 (Yang Y et al. 2005; Tan YX et al. 2007). Low levels of BCL2L1 may lead to enhanced function of pro‐apoptotic molecules, contributing to the depletion of T lymphocytes by apoptosis (Yang Y et al. 2005). This may lead to the lymphopenia observed in SARS patients, particularly in severe cases (Diao B et al. 2020; Chen Z & Wherry EJ 2020).

References

Yang F, Lu H, Wang H, Zhang S, Brendese J, Yan Y, ... Xiong Z (2005). Bcl-xL inhibits T-cell apoptosis induced by expression of SARS coronavirus E protein in the absence of growth factors, 392, 135-43.

Birch C, Lee MJ, Catton M, Tan TH, Yu VC, Tham PY, ... Tan YX (2007). Induction of apoptosis by the severe acute respiratory syndrome coronavirus 7a protein is dependent on its interaction with the Bcl-XL protein, 81, 6346-55.

Shi CS, Hwang IY, Kehrl JH, Xiao X, Kamenyeva O, Nabar NR, ... Wang M (2018). SARS-Coronavirus Open Reading Frame-3a drives multimodal necrotic cell death. Cell Death Dis, 9, 904.

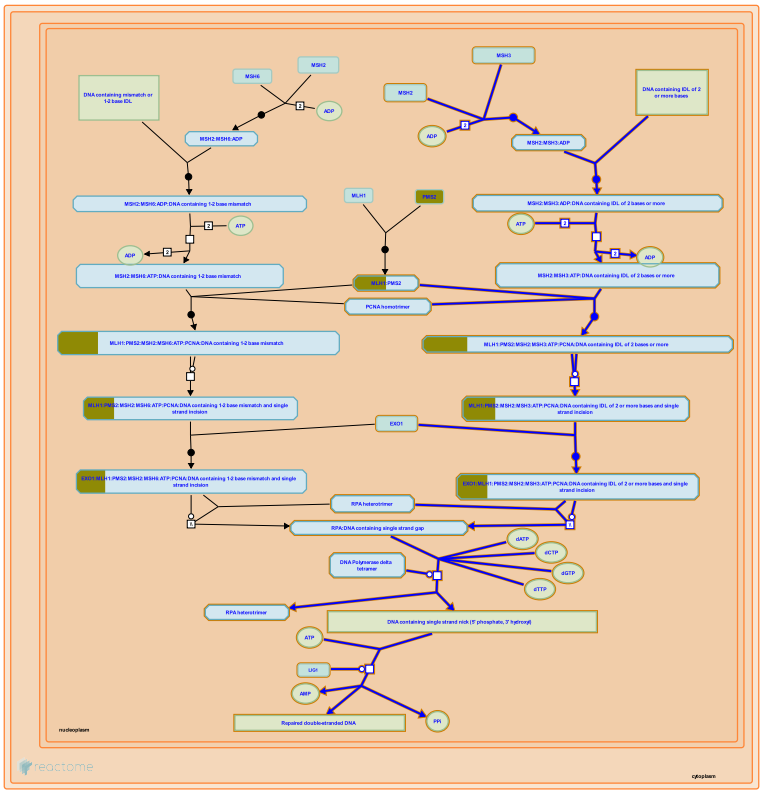
Edit history

Date	Action	Author
2020-06-25	Authored	Shamovsky V
2020-06-26	Created	Shamovsky V
2021-01-26	Reviewed	D'Eustachio P
2022-08-11	Edited	Shamovsky V
2023-03-08	Modified	Matthews L

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
RNF4	P78317	Q07817			

21. 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

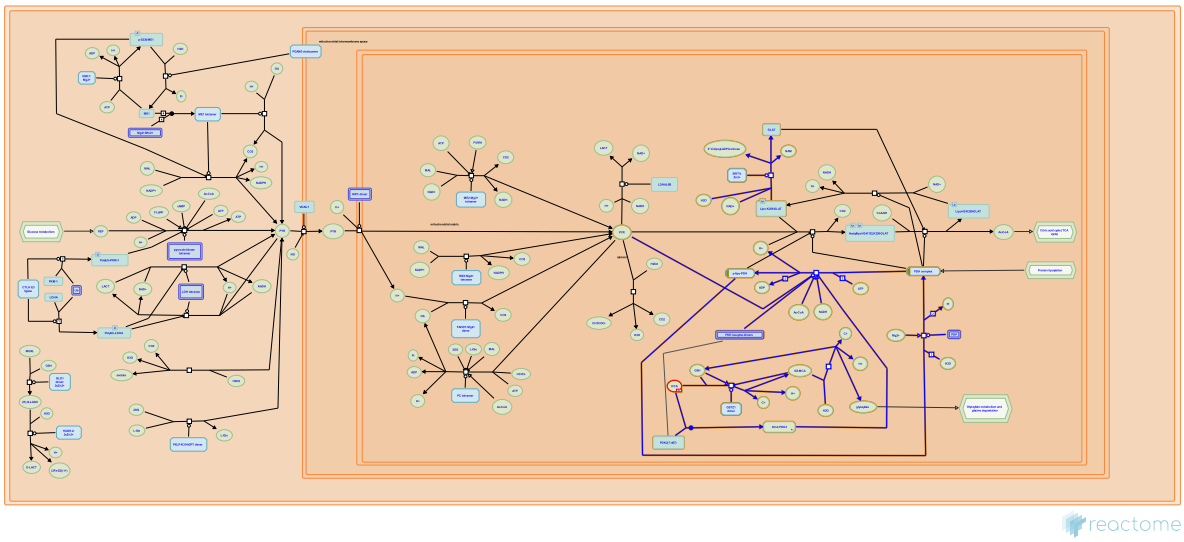
1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
PMS1	P54278

Interactors found in this pathway (1)

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

22. 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.

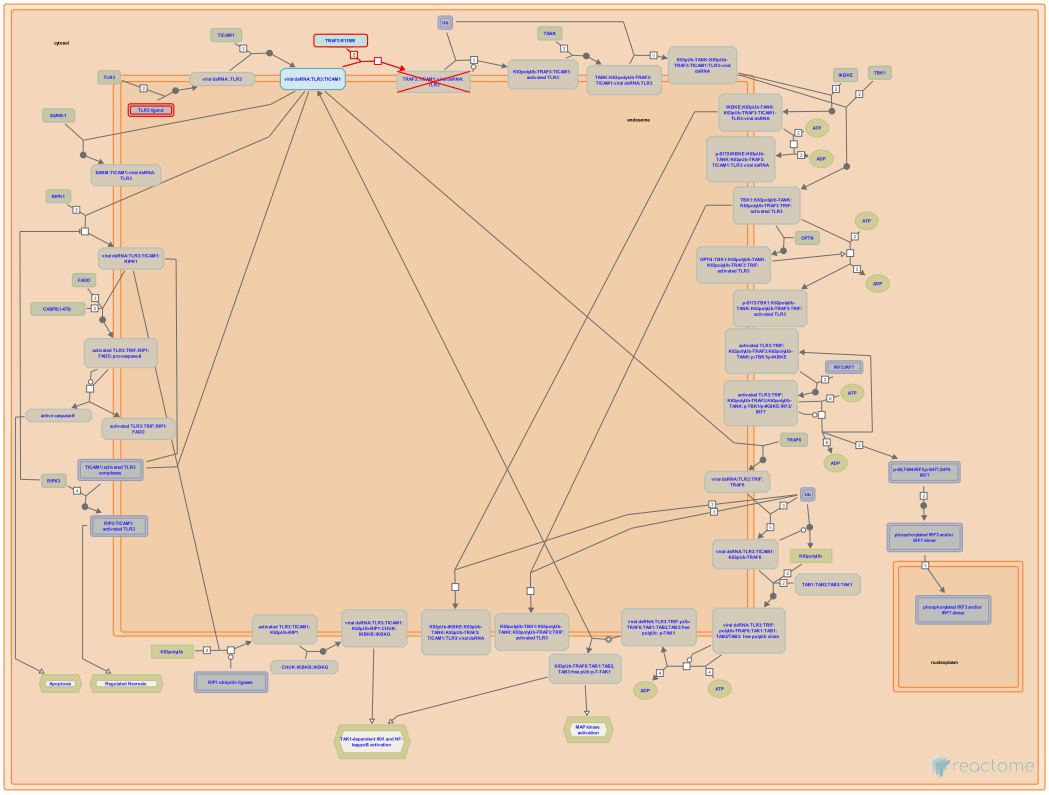
Edit history

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

23. TRAF3 deficiency - HSE (R-HSA-5602571)



Diseases: primary immunodeficiency disease.

TNF Receptor Associated Factor 3 (TRAF3) is a cytoplasmic adaptor protein utilized by the tumor necrosis factor receptor superfamily and toll-like receptors (TLRs). TRAF3 deficiency is thought to mimic the previously reported TLR3 deficiency in terms of susceptibility to herpes simplex virus type 1 (HSV1) encephalitis (HSE) via impaired TLR3-mediated immunity against HSV1 infection of central nervous system (CNS) (Pérez de Diego R et al. 2010; Guo Y et al. 2011).

References

Abel L, Lebon P, Bravo J, Al-Muhsen S, Pérez de Diego R, Herman M, ... Tardieu M (2010). Human TRAF3 adaptor molecule deficiency leads to impaired Toll-like receptor 3 response and susceptibility to herpes simplex encephalitis. Immunity, 33, 400-11.

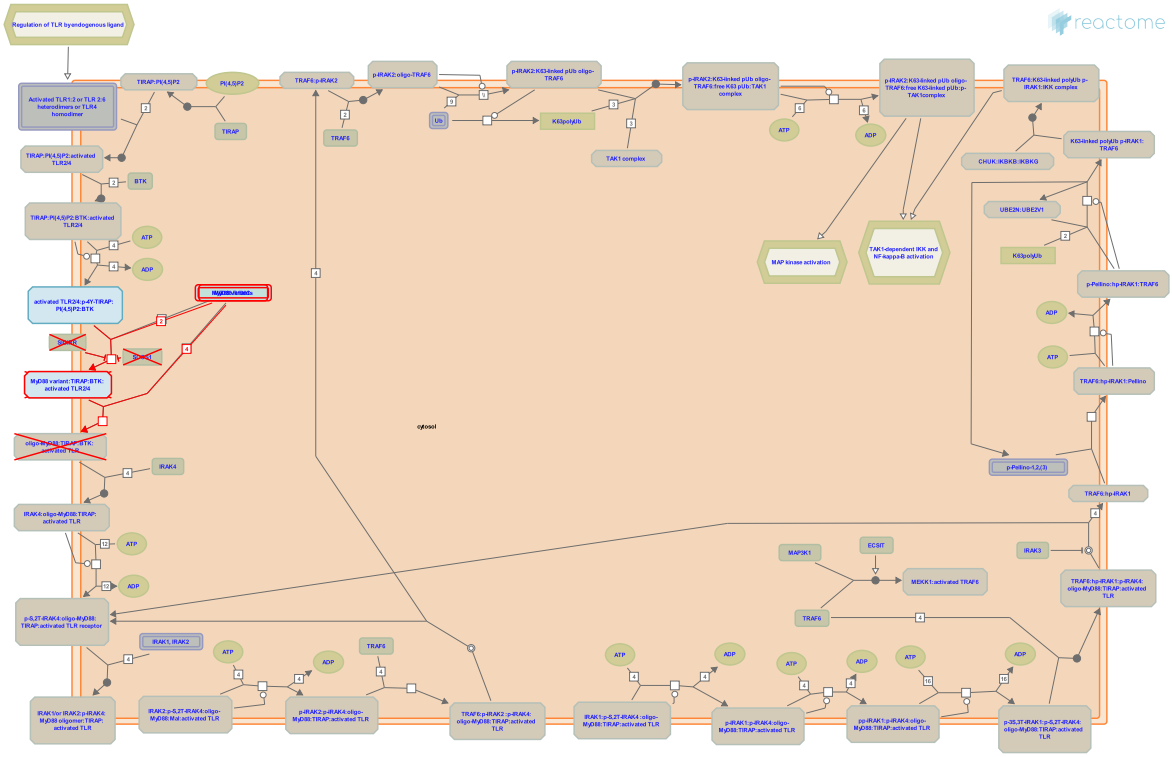
Edit history

Date	Action	Author
2014-05-21	Authored	Shamovsky V
2014-06-24	Created	Shamovsky V
2014-09-06	Reviewed	D'Eustachio P
2015-02-10	Edited	Shamovsky V
2015-02-15	Reviewed	McDonald DR
2023-03-08	Modified	Matthews L

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
RNF4	P78317	Q13114			

24. MyD88 deficiency (TLR2/4) (R-HSA-5602498)



Diseases: primary immunodeficiency disease.

Myeloid differentiation primary response (MyD88) is an adaptor protein that mediates intracellular signaling pathways evoked by all Toll-like receptors (TLRs) except for TLR3 and by several interleukin-1 receptors (IL-1Rs) (Medzhitov R et al. 1998). Upon ligand binding, TLRs hetero- or homodimerize and recruit MyD88 through their respective TIR domains. Then, MyD88 oligomerizes via its death domain (DD) and TIR domain and interacts with the interleukin-1 receptor-associated kinases (IRAKs) to form the Myddosome complex (MyD88:IRAK4:IRAK1/2) (Motshwene PG et al. 2009; Lin SC et al. 2010). The Myddosome complex transmits the signal leading to activation of transcription factors such as nuclear factor-kappaB (NFkB) and activator protein 1 (AP1).

Studies have identified patients with autosomal recessive (AR) form of MyD88 deficiency caused by homozygous or compound heterozygous mutations in MYD88 gene leading to abolished protein production (von Bernuth et al. 2008). AR MyD88 deficiency is a type of a primary immunodeficiency characterized by greater susceptibility to pyogenic bacteria (such as Streptococcus pneumoniae, Staphylococcus aureus or Pseudomonas aeruginosa) manifested in infancy and early childhood. Patients with MyD88 deficiency show delayed or weak signs of inflammation (Picard C et al. 2010; Picard C et al. 2011).

Functional assessment of MyD88 deficiency revealed that cytokine responses were impaired in patient-derived blood cells upon stimulation with the agonists of TLR2 and TLR4 (PAM2CSK4 and LPS respectively), although some were produced in response to LPS. (von Bernuth et al. 2008). NFkB luciferase reporter gene assays using human embryonic kidney 293 (HEK293T) cells showed that MyD88 variants, S34Y, E52del, E53X, L93P, R98C, and R196C, were compromised in their ability to enhance NFkB activation (Yamamoto T et al. 2014). The molecular basis for the observed functional effects (reported for selected mutations) probably faulty Myddosome formation due to impaired MyD88 oligomerization and/or interaction with IRAK4 (George J et al. 2011; Nagpal K et al. 2011; Yamamoto T et al. 2014).

While MyD88-deficiency might be expected to perturb MyD88?IRAK4 dependent TLR7 and TLR8 signaling events associated with the sensing viral infections, patients with MyD88 and IRAK4 deficiencies have so far not been reported to be susceptible to viral infection.

References

Devon RS, Reid GS, Currie AJ, MacDonald KL, Speert DP, Bharya S & Davidson DJ (2004). Primary immunodeficiency to pneumococcal infection due to a defect in Toll-like receptor signaling. J. Pediatr., 144, 512-8.

Kondo N, Shirakawa M, Ohnishi H, Tochio H, Kato Z, Tsutsumi N, ... Yamamoto T (2014). Functional assessment of the mutational effects of human IRAK4 and MyD88 genes. Mol. Immunol., 58, 66-76.

Abel L, Li X, von Bernuth H, Jin Z, Camcioglu Y, Pascal M, ... Rose Y (2008). Pyogenic bacterial infections in humans with MyD88 deficiency. Science, 321, 691-6.

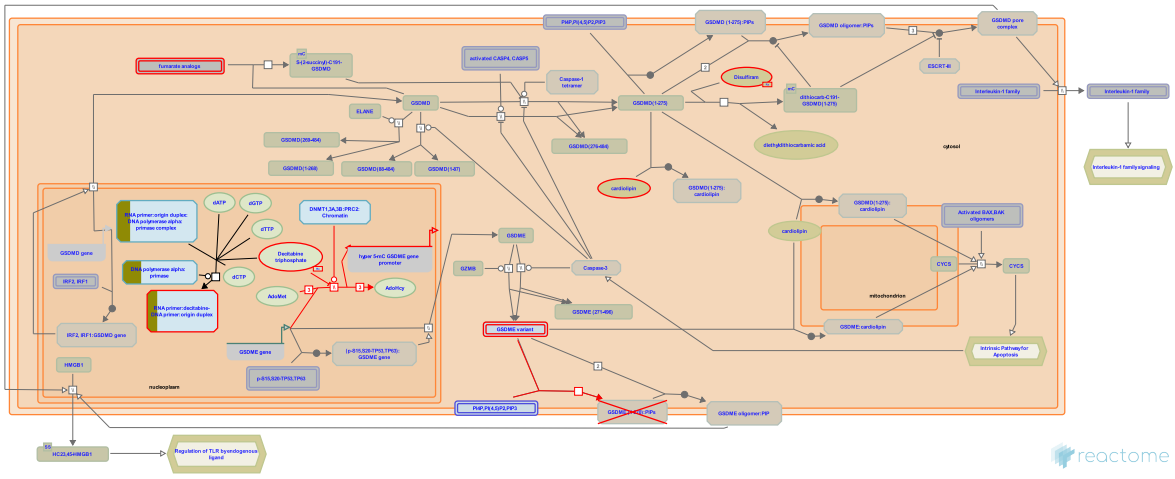
Edit history

Date	Action	Author
2014-05-21	Authored	Shamovsky V
2014-06-24	Created	Shamovsky V
2014-09-06	Reviewed	D'Eustachio P
2015-02-10	Edited	Shamovsky V
2015-02-15	Reviewed	McDonald DR

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
RNF4	P78317	Q99836			

25. Defective pyroptosis (R-HSA-9710421)



Diseases: gastric adenocarcinoma, breast carcinoma, lung adenocarcinoma, colon adenocarcinoma, melanoma, cancer, head and neck squamous cell carcinoma.

Pyroptosis is a form of lytic inflammatory programmed cell death that is mediated by the pore‐forming gasdermins (GSDMs) (Shi J et al. 2017) to stimulate immune responses through the release of pro‐inflammatory interleukin (IL)‐1‐, IL‐18 (mainly in GSDMD-mediated pyroptosis) as well as danger signals such as adenosine triphosphate (ATP) or high mobility group protein B1 (HMGB1) (reviewed in Shi J et al. 2017; Man SM et al. 2017; Tang D et al. 2019; Lieberman J et al. 2019). Pyroptosis protects the host from microbial infection but can also lead to pathological inflammation if overactivated or dysregulated (reviewed in Orning P et al. 2019; Tang L et al. 2020). During infections, the excessive production of cytokines can lead to a cytokine storm, which is associated with acute respiratory distress syndrome (ARDS) and systemic inflammatory response syndrome (SIRS) (reviewed in Tisoncik JR et al. 2012; Karki R et al. 2020; Ragab D et al. 2020). Pyroptosis has a close but complicated relationship to tumorigenesis, affected by tissue type and genetic background. Pyroptosis can trigger potent antitumor immune responses or serve as an effector mechanism in antitumor immunity (Wang Q et al. 2020; Zhou Z et al. 2020; Zhang Z et al. 2020), while in other cases, as a type of proinflammatory death, pyroptosis can contribute to the formation of a microenvironment suitable for tumor cell growth (reviewed in Xia X et al. 2019; Jiang M et al. 2020; Zhang Z et al. 2021).

This Reactome module describes the defective GSDME function caused by cancer‐related GSDME mutations (Zhang Z et al. 2020). It also shows epigenetic inactivation of GSDME due to hypermethylation of the GSDME promoter region (Akino K et al. 2007; Kim MS et al. 2008a,b; Croes L et al. 2017, 2018; Ibrahim J et al. 2019). Aberrant promoter methylation is considered to be a hallmark of cancer (Ehrlich M et al. 2002; Dong Y et al. 2014; Lam K et al. 2016; Croes L et al. 2018). Treatment with the DNA methyltransferase inhibitor decitabine (5‐aza‐2'‐deoxycytidine or DAC) may elevate GSDME expression in certain cancer cells (Akino K et al. 2007; Fujikane T et al. 2009; Wang Y et al. 2017).

References

Mok TMY, Sengupta S, Li S, Meza-Sosa KF, Junqueira C, Zhang Y, ... Xia S (2020). Gasdermin E suppresses tumour growth by activating anti-tumour immunity. Nature, 579, 415-420.

Suls A, Croes L, Van Camp G, Fransen E, Vanden Berghe W, Beyens M, ... Op de Beeck K (2019). Methylation analysis of Gasdermin E shows great promise as a biomarker for colorectal cancer. Cancer Med, 8, 2133-2145.

Zheng G, Tang L, Burgering BM & Lu C (2020). Emerging insights on the role of gasdermins in infection and inflammatory diseases. Clin Transl Immunology, 9, e1186.

Edit history

Date	Action	Author
2020-11-09	Authored	Shamovsky V
2020-12-30	Created	Shamovsky V
2021-02-17	Edited	Shorser S
2021-02-17	Reviewed	Kanneganti TD, D'Eustachio P, Zhang Z
2021-04-22	Reviewed	Shao F
2023-10-12	Modified	Weiser JD

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

Input	UniProt Id
POLA1	P09884

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 17 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CBR4	Q8N4T8	CCNK	O75909	CCRN4L	Q9UK39
CREM	Q03060-6	DDX3X	O00571	GEMIN5	Q8TEQ6
PAN3	Q58A45	PDHX	O00330	PMS1	P54278
PNPLA2	Q96AD5	POLA1	P09884	RNF4	P78317
RNF8	O76064	SLX4	Q8IY92		

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
CCNK	ENSG00000090061	CCRN4L	ENSG00000151014	POLA1	ENSG00000101868

Interactors (15)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
CCDC17	Q96LX7-5	P54252	CCNK	O75909	Q9NYV4, Q14004
CREM	Q03060-25	O14503	DDX3X	O00571	P04608
FAM154B	Q658L1	Q14192	GEMIN5	Q8TEQ6	P06730
KLHL26	Q53HC5	O75593	PAN3	Q58A45	Q8NDV7
PDHX	O00330	Q8IWL3	PMS1	P54277	P40692
PNPLA2	Q96AD5	P00533	RNF4	P78317	P13500
RNF8	O76064	P50570, O00401	SLX4	Q8IY92	P43246
ncs1	P62166	Q9UKN5			

7. Identifiers not found

These 1 identifiers were not found neither mapped to any entity in Reactome.

MXRA5