



Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 79 on 26/02/2022. The web link to these results is:

<https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMjAyMjYwMjU2NTBfMTcyOTg%3D>

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

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1. Introduction

Reactome is a curated database of pathways and reactions in human biology. Reactions can be considered as pathway 'steps'. Reactome defines a 'reaction' as any event in biology that changes the state of a biological molecule. Binding, activation, translocation, degradation and classical biochemical events involving a catalyst are all reactions. Information in the database is authored by expert biologists, entered and maintained by Reactome's team of curators and editorial staff. Reactome content frequently cross-references other resources e.g. NCBI, Ensembl, UniProt, KEGG (Gene and Compound), ChEBI, PubMed and GO. Orthologous reactions inferred from annotation for *Homo sapiens* are available for 17 non-human species including mouse, rat, chicken, puffer fish, worm, fly, yeast, rice, and *Arabidopsis*. Pathways are represented by simple diagrams following an SBGN-like format.

Reactome's annotated data describe reactions possible if all annotated proteins and small molecules were present and active simultaneously in a cell. By overlaying an experimental dataset on these annotations, a user can perform a pathway over-representation analysis. By overlaying quantitative expression data or time series, a user can visualize the extent of change in affected pathways and its progression. A binomial test is used to calculate the probability shown for each result, and the p-values are corrected for the multiple testing (Benjamini–Hochberg procedure) that arises from evaluating the submitted list of identifiers against every pathway.

To learn more about our Pathway Analysis, please have a look at our relevant publications:

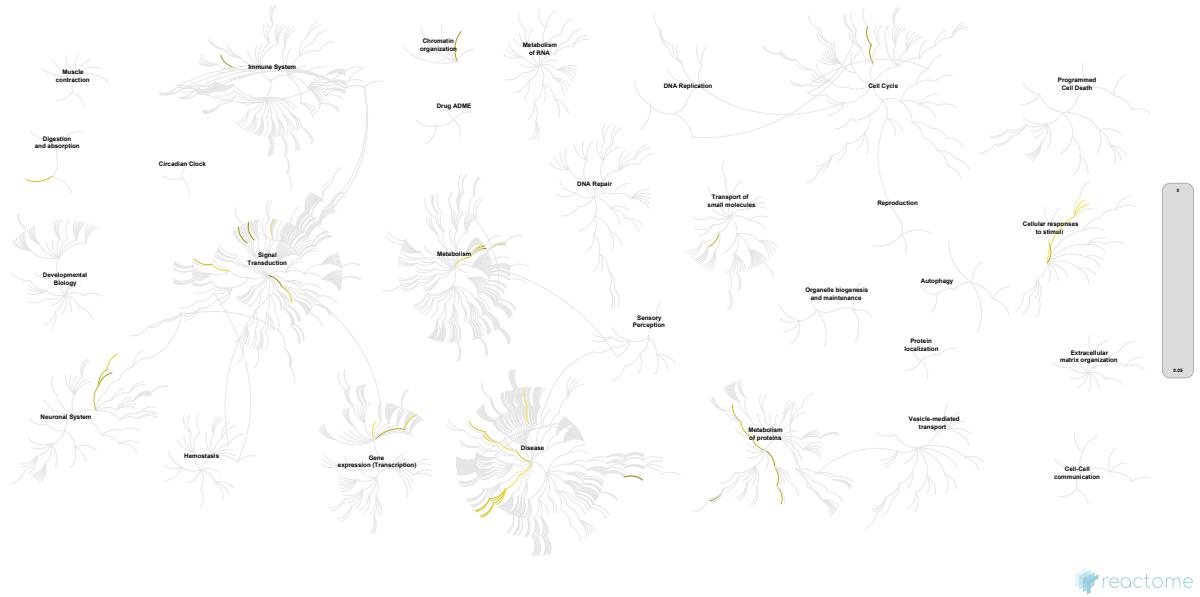
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

Fabregat A, Sidiropoulos K, Viteri G, Forner O, Marin-Garcia P, Arnau V, ... Hermjakob H (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC Bioinformatics*, 18.

2. Properties

- This is an **overrepresentation** analysis: A statistical (hypergeometric distribution) test that determines whether certain Reactome pathways are over-represented (enriched) in the submitted data. It answers the question 'Does my list contain more proteins for pathway X than would be expected by chance?' This test produces a probability score, which is corrected for false discovery rate using the Benjamani-Hochberg method. ↗
- 49 out of 72 identifiers in the sample were found in Reactome, where 384 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent. ↗
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAyMjAyMjYwMjU2NTBfMTcyOTg%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
Oncogene Induced Senescence	6 / 42	0.003	2.23e-07	8.73e-05	13 / 19	0.001
Oxidative Stress Induced Senescence	7 / 114	0.008	5.68e-06	0.001	14 / 40	0.003
Cellular Senescence	7 / 200	0.013	1.93e-04	0.018	20 / 90	0.007
Transcriptional Regulation by VENTX	4 / 48	0.003	2.02e-04	0.018	4 / 13	9.53e-04
Diseases of Cellular Senescence	2 / 4	2.65e-04	2.72e-04	0.018	3 / 3	2.20e-04
Diseases of cellular response to stress	2 / 4	2.65e-04	2.72e-04	0.018	3 / 3	2.20e-04
FBXW7 Mutants and NOTCH1 in Cancer	2 / 6	3.98e-04	6.07e-04	0.029	1 / 1	7.33e-05
Loss of Function of FBXW7 in Cancer and NOTCH1 Signaling	2 / 6	3.98e-04	6.07e-04	0.029	1 / 1	7.33e-05
Defective Intrinsic Pathway for Apoptosis	3 / 33	0.002	0.001	0.045	4 / 24	0.002
ChREBP activates metabolic gene expression	2 / 9	5.97e-04	0.001	0.053	6 / 6	4.40e-04
Class B/2 (Secretin family receptors)	4 / 99	0.007	0.003	0.102	4 / 20	0.001
RUNX3 regulates p14-ARF	2 / 16	0.001	0.004	0.133	2 / 8	5.86e-04
NR1H2 & NR1H3 regulate gene expression linked to lipogenesis	2 / 17	0.001	0.005	0.14	2 / 8	5.86e-04
Evasion of Oxidative Stress Induced Senescence Due to p14ARF Defects	1 / 1	6.64e-05	0.006	0.153	1 / 1	7.33e-05
Evasion of Oncogene Induced Senescence Due to p14ARF Defects	1 / 1	6.64e-05	0.006	0.153	1 / 1	7.33e-05
Trafficking of GluR2-containing AMPA receptors	2 / 23	0.002	0.008	0.2	3 / 3	2.20e-04
Integration of energy metabolism	4 / 145	0.01	0.011	0.219	23 / 62	0.005
Defective Intrinsic Pathway for Apoptosis Due to p14ARF Loss of Function	1 / 2	1.33e-04	0.012	0.219	1 / 1	7.33e-05
Evasion of Oxidative Stress Induced Senescence Due to Defective p16INK4A binding to CDK4	1 / 2	1.33e-04	0.012	0.219	1 / 1	7.33e-05
Evasion of Oncogene Induced Senescence Due to Defective p16INK4A binding to CDK4	1 / 2	1.33e-04	0.012	0.219	1 / 1	7.33e-05
WNT ligand biogenesis and trafficking	2 / 28	0.002	0.012	0.219	8 / 12	8.79e-04
Neurodegenerative Diseases	2 / 30	0.002	0.014	0.228	3 / 22	0.002

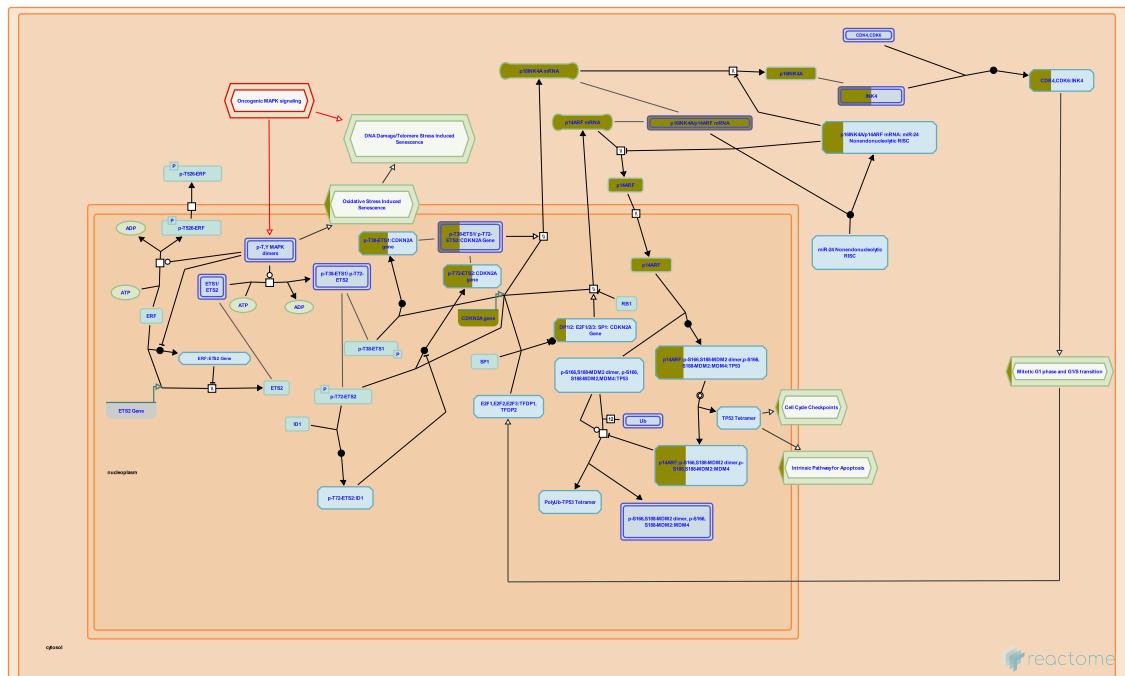
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models	2 / 30	0.002	0.014	0.228	3 / 22	0.002
Diseases of programmed cell death	3 / 90	0.006	0.017	0.228	4 / 28	0.002
Intestinal lipid absorption	1 / 3	1.99e-04	0.018	0.228	3 / 3	2.20e-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. Oncogene Induced Senescence (R-HSA-2559585)



Oncogene-induced senescence (OIS) is triggered by high level of RAS/RAF/MAPK signaling that can be caused, for example, by oncogenic mutations in RAS or RAF proteins, or by oncogenic mutations in growth factor receptors, such as EGFR, that act upstream of RAS/RAF/MAPK cascade. Oncogene-induced senescence can also be triggered by high transcriptional activity of E2F1, E2F2 or E2F3 which can be caused, for example, by the loss-of-function of RB1 tumor suppressor.

Oncogenic signals trigger transcription of CDKN2A locus tumor suppressor genes: p16INK4A and p14ARF. p16INK4A and p14ARF share exons 2 and 3, but are expressed from different promoters and use different reading frames (Quelle et al. 1995). Therefore, while their mRNAs are homologous and are both translationally inhibited by miR-24 microRNA (Lal et al. 2008, To et al. 2012), they share no similarity at the amino acid sequence level and perform distinct functions in the cell. p16INK4A acts as the inhibitor of cyclin-dependent kinases CDK4 and CDK6 which phosphorylate and inhibit RB1 protein thereby promoting G1 to S transition and cell cycle progression (Serrano et al. 1993). Increased p16INK4A level leads to hypophosphorylation of RB1, allowing RB1 to inhibit transcription of E2F1, E2F2 and E2F3-target genes that are needed for cell cycle progression, which results in cell cycle arrest in G1 phase. p14-ARF binds and destabilizes MDM2 ubiquitin ligase (Zhang et al. 1998), responsible for ubiquitination and degradation of TP53 (p53) tumor suppressor protein (Wu et al. 1993, Fuchs et al. 1998, Fang et al. 2000). Therefore, increased p14-ARF level leads to increased level of TP53 and increased expression of TP53 target genes, such as p21, which triggers p53-mediated cell cycle arrest and, depending on other factors, may also lead to p53-mediated apoptosis. CDKN2B locus, which encodes an inhibitor of CDK4 and CDK6, p15INK4B, is located in the vicinity of CDKN2A locus, at the chromosome band 9p21. p15INK4B, together with p16INK4A, contributes to senescence of human T-lymphocytes (Erickson et al. 1998) and mouse fibroblasts (Malumbres et al. 2000). SMAD3, activated by TGF-beta-1 signaling, controls senescence in the mouse multistage carcinogenesis model through regulation of MYC and p15INK4B gene expression (Vijayachandra et al. 2003). TGF-beta-induced p15INK4B expression is also important for the senescence of hepatocellular carcinoma cell lines (Senturk et al. 2010).

MAP kinases MAPK1 (ERK2) and MAPK3 (ERK1), which are activated by RAS signaling, phosphorylate ETS1 and ETS2 transcription factors in the nucleus (Yang et al. 1996, Seidel et al. 2002, Foulds et al. 2004, Nelson et al. 2010). Phosphorylated ETS1 and ETS2 are able to bind RAS response elements (RREs) in the CDKN2A locus and stimulate p16INK4A transcription (Ohtani et al. 2004). At the same time, activated ERKs (MAPK1 i.e. ERK2 and MAPK3 i.e. ERK1) phosphorylate ERF, the repressor of ETS2 transcription, which leads to translocation of ERF to the cytosol and increased transcription of ETS2 (Sgouras et al. 1995, Le Gallic et al. 2004). ETS2 can be sequestered and inhibited by binding to ID1, resulting in inhibition of p16INK4A transcription (Ohtani et al. 2004).

Transcription of p14ARF is stimulated by binding of E2F transcription factors (E2F1, E2F2 or E2F3) in complex with SP1 to p14ARF promoter (Parisi et al. 2002).

Oncogenic RAS signaling affects mitochondrial metabolism through an unknown mechanism, leading to increased generation of reactive oxygen species (ROS), which triggers oxidative stress induced senescence pathway. In addition, increased rate of cell division that is one of the consequences of oncogenic signaling, leads to telomere shortening which acts as another senescence trigger.

While OIS has been studied to considerable detail in cultured cells, establishment of in vivo role of OIS has been difficult due to lack of specific biomarkers and its interconnectedness with other senescence pathways (Baek and Ryeom 2017, reviewed in Sharpless and Sherr 2015).

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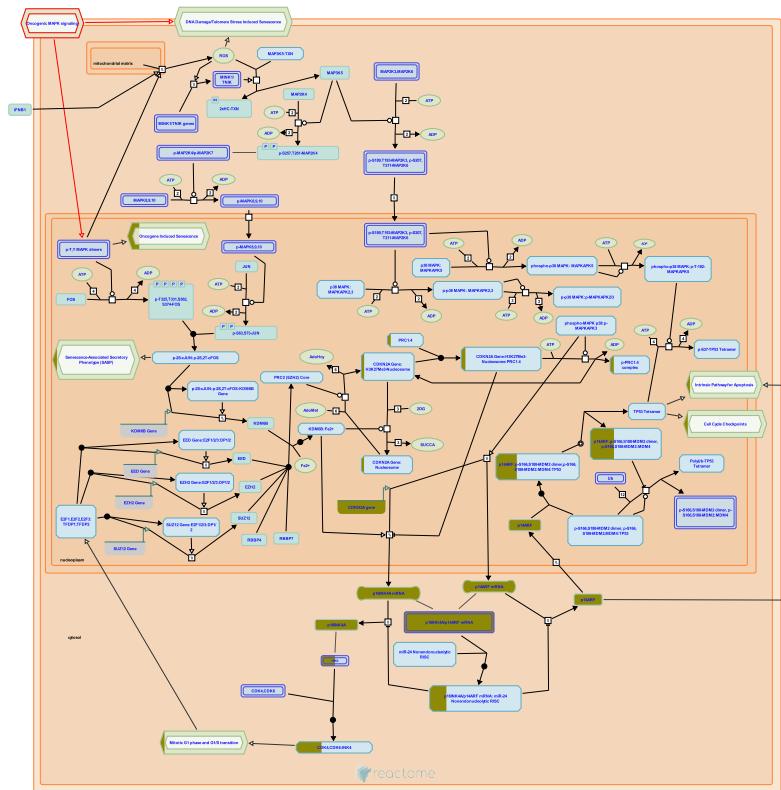
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2013-07-15	Edited	Matthews L, D'Eustachio P
2013-07-15	Authored	Orlic-Milacic M
2013-09-03	Reviewed	Samarajiwa S
2022-01-09	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 6 Reactome entities

Input	UniProt Id
CDKN2A	P42771, P42772, Q8N726

Input	Ensembl Id
CDKN2A	ENSG00000147889, ENST00000304494, ENST00000579755

2. Oxidative Stress Induced Senescence (R-HSA-2559580)



Oxidative stress, caused by increased concentration of reactive oxygen species (ROS) in the cell, can happen as a consequence of mitochondrial dysfunction induced by the oncogenic RAS (Moiseeva et al. 2009) or independent of oncogenic signaling. Prolonged exposure to interferon-beta (IFNB, IFN-beta) also results in ROS increase (Moiseeva et al. 2006). ROS oxidize thioredoxin (TXN), which causes TXN to dissociate from the N-terminus of MAP3K5 (ASK1), enabling MAP3K5 to become catalytically active (Saitoh et al. 1998). ROS also stimulate expression of Ste20 family kinases MINK1 (MINK) and TNIK through an unknown mechanism, and MINK1 and TNIK positively regulate MAP3K5 activation (Nicke et al. 2005).

MAP3K5 phosphorylates and activates MAP2K3 (MKK3) and MAP2K6 (MKK6) (Ichijo et al. 1997, Takekawa et al. 2005), which act as p38 MAPK kinases, as well as MAP2K4 (SEK1) (Ichijo et al. 1997, Matsuura et al. 2002), which, together with MAP2K7 (MKK7), acts as a JNK kinase.

MKK3 and MKK6 phosphorylate and activate p38 MAPK alpha (MAPK14) and beta (MAPK11) (Raingeaud et al. 1996), enabling p38 MAPKs to phosphorylate and activate MAPKAPK2 (MK2) and MAPKAPK3 (MK3) (Ben-Levy et al. 1995, Clifton et al. 1996, McLaughlin et al. 1996, Sithanandam et al. 1996, Meng et al. 2002, Lukas et al. 2004, White et al. 2007), as well as MAPKAPK5 (PRAK) (New et al. 1998 and 2003, Sun et al. 2007).

Phosphorylation of JNKs (MAPK8, MAPK9 and MAPK10) by MAP3K5-activated MAP2K4 (Deacon and Blank 1997, Fleming et al. 2000) allows JNKs to migrate to the nucleus (Mizukami et al. 1997) where they phosphorylate JUN. Phosphorylated JUN binds FOS phosphorylated by ERK1 or ERK2, downstream of activated RAS (Okazaki and Sagata 1995, Murphy et al. 2002), forming the activated protein 1 (AP-1) complex (FOS:JUN heterodimer) (Glover and Harrison 1995, Ainbinder et al. 1997).

Activation of p38 MAPKs and JNKs downstream of MAP3K5 (ASK1) ultimately converges on transcriptional regulation of CDKN2A locus. In dividing cells, nucleosomes bound to the CDKN2A locus are trimethylated on lysine residue 28 of histone H3 (HIST1H3A) by the Polycomb repressor complex 2 (PRC2), creating the H3K27Me3 (Me3K-28-HIST1H3A) mark (Bracken et al. 2007, Kotake et al. 2007). The expression of Polycomb constituents of PRC2 (Kuzmichev et al. 2002) - EZH2, EED and SUZ12 - and thereby formation of the PRC2, is positively regulated in growing cells by E2F1, E2F2 and E2F3 (Weinmann et al. 2001, Bracken et al. 2003). H3K27Me3 mark serves as a docking site for the Polycomb repressor complex 1 (PRC1) that contains BMI1 (PCGF4) and is therefore named PRC1.4, leading to the repression of transcription of p16INK4A and p14ARF from the CDKN2A locus, where PRC1.4 mediated repression of p14ARF transcription in humans may be context dependent (Voncken et al. 2005, Dietrich et al. 2007, Agherbi et al. 2009, Gao et al. 2012). MAPKAPK2 and MAPKAPK3, activated downstream of the MAP3K5-p38 MAPK cascade, phosphorylate BMI1 of the PRC1.4 complex, leading to dissociation of PRC1.4 complex from the CDKN2A locus and upregulation of p14ARF transcription (Voncken et al. 2005). AP-1 transcription factor, formed as a result of MAP3K5-JNK signaling, as well as RAS signaling, binds the promoter of KDM6B (JMJD3) gene and stimulates KDM6B expression. KDM6B is a histone demethylase that removes H3K27Me3 mark i.e. demethylates lysine K28 of HIST1H3A, thereby preventing PRC1.4 binding to the CDKN2A locus and allowing transcription of p16INK4A (Agger et al. 2009, Barradas et al. 2009, Lin et al. 2012).

p16INK4A inhibits phosphorylation-mediated inactivation of RB family members by CDK4 and CDK6, leading to cell cycle arrest (Serrano et al. 1993). p14ARF inhibits MDM2-mediated degradation of TP53 (p53) (Zhang et al. 1998), which also contributes to cell cycle arrest in cells undergoing oxidative stress. In addition, phosphorylation of TP53 by MAPKAPK5 (PRAK) activated downstream of MAP3K5-p38 MAPK signaling, activates TP53 and contributes to cellular senescence (Sun et al. 2007).

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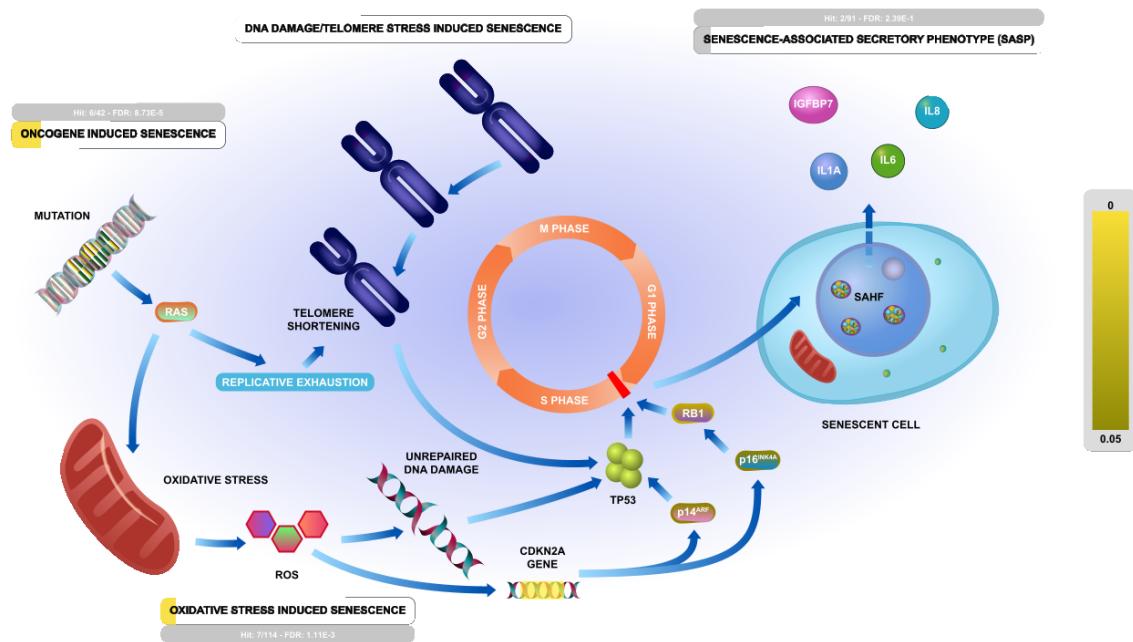
Date	Action	Author
2013-09-03	Reviewed	Samarajiwa S
2021-11-28	Modified	Weiser JD

2 submitted entities found in this pathway, mapping to 7 Reactome entities

Input	UniProt Id	Input	UniProt Id
CBX6	O95503	CDKN2A	P42771, P42772, Q8N726

Input	Ensembl Id
CDKN2A	ENSG0000147889, ENST0000304494, ENST0000579755

3. Cellular Senescence (R-HSA-2559583)



Cellular senescence involves irreversible growth arrest accompanied by phenotypic changes such as enlarged morphology, reorganization of chromatin through formation of senescence-associated heterochromatic foci (SAHF), and changes in gene expression that result in secretion of a number of proteins that alter local tissue environment, known as senescence-associated secretory phenotype (SASP).

Senescence is considered to be a cancer protective mechanism and is also involved in aging. Senescent cells accumulate in aged tissues (reviewed by Campisi 1997 and Lopez-Otin 2013), which may be due to an increased senescence rate and/or decrease in the rate of clearance of senescent cells. In a mouse model of accelerated aging, clearance of senescent cells delays the onset of age-related phenotypes (Baker et al. 2011).

Cellular senescence can be triggered by the aberrant activation of oncogenes or loss-of-function of tumor suppressor genes, and this type of senescence is known as the oncogene-induced senescence, with RAS signaling-induced senescence being the best studied. Oxidative stress, which may or may not be caused by oncogenic RAS signaling, can also trigger senescence. Finally, the cellular senescence program can be initiated by DNA damage, which may be caused by reactive oxygen species (ROS) during oxidative stress, and by telomere shortening caused by replicative exhaustion which may be due to oncogenic signaling. The senescent phenotype was first reported by Hayflick and Moorhead in 1961, when they proposed replicative senescence as a mechanism responsible for the cessation of mitotic activity and morphological changes that occur in human somatic diploid cell strains as a consequence of serial passaging, preventing the continuous culture of untransformed cells—the Hayflick limit (Hayflick and Moorhead 1961).

Secreted proteins that constitute the senescence-associated secretory phenotype (SASP), also known as the senescence messaging secretome (SMS), include inflammatory and immune-modulatory cytokines, growth factors, shed cell surface molecules and survival factors. The SASP profile is not significantly affected by the type of senescence trigger or the cell type (Coppe et al. 2008), but the persistent DNA damage may be a deciding SASP initiator (Rodier et al. 2009). SASP components function in an autocrine manner, reinforcing the senescent phenotype (Kuilman et al. 2008, Acosta et al. 2008), and in the paracrine manner, where they may promote epithelial-to-mesenchymal transition (EMT) and malignancy in the nearby premalignant or malignant cells (Coppe et al. 2008).

Senescent cells may remain viable for years, such as senescent melanocytes of moles and nevi, or they can be removed by phagocytic cells. The standard marker for immunohistochemical detection of senescent cells is senescence-associated beta-galactosidase (SA-beta-Gal), a lysosomal enzyme that is not required for senescence.

For reviews of this topic, please refer to Collado et al. 2007, Adams 2009, Kuilman et al. 2010. For a review of differential gene expression between senescent and immortalized cells, please refer to Fridman and Tainsky 2008.

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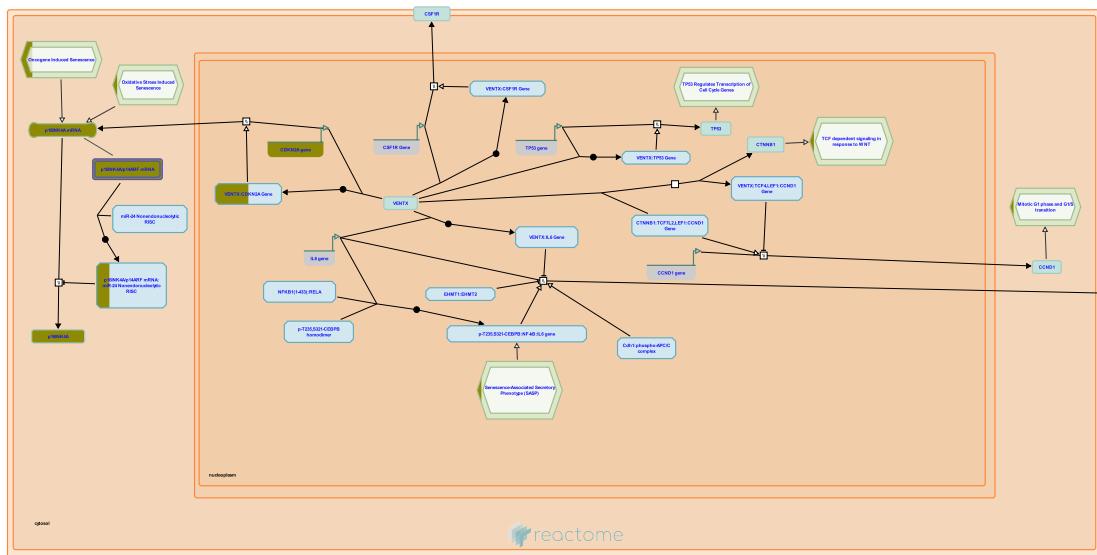
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2013-09-30	Revised	Orlic-Milacic M
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Input	Ensembl Id
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4. Transcriptional Regulation by VENTX (R-HSA-8853884)



The VENTX (also known as VENT homeobox or VENTX2) gene is a member of the homeobox family of transcription factors. The ortholog of VENTX was first described in Xenopus where it participates in BMP and Nanog signaling pathways and controls dorsoventral mesoderm patterning (Onichtchouk et al. 1996, Scerbo et al. 2012). The zebrafish ortholog of VENTX is also involved in dorsoventral patterning in the early embryo (Imai et al. 2001). Rodents lack the VENTX ortholog (Zhong and Holland 2011). VENTX is expressed in human blood cells (Moretti et al. 2001) and appears to play an important role in hematopoiesis. The role of VENTX in hematopoiesis was first suggested based on its role in mesoderm patterning in Xenopus and zebrafish (Davidson and Zon 2000). VENTX promotes cell cycle arrest and differentiation of hematopoietic stem cells and/or progenitor cells (Wu, Gao, Ke, Giese and Zhu 2011, Wu et al. 2014). Ventx suppression leads to expansion of hematopoietic stem cells and multi-progenitor cells (Gao et al., J. Biol. Chem., 2012). VENTX induces transcription of cell cycle inhibitors TP53 (p53) and p16INK4A and activates tumor suppressor pathways regulated by TP53 and p16INK4A (Wu, Gao, Ke, Hager et al. 2011), as well as macrophage colony stimulating factor receptor (CSF1R) (Wu, Gao, Ke, Giese and Zhu 2011) and inhibits transcription of cyclin D1 (CCND1) (Gao et al. 2010) and Interleukin-6 (IL6) (Wu et al. 2014). ChIP showed that EGR3 transcription factor directly binds to the promoter of IL6 and IL8 genes (Baron VT et al., BJC 2015). While VENTX expression may suppress lymphocytic leukemia (Gao et al. 2010), high levels of VENTX have been reported in acute myeloid leukemia cells, with a positive effect on their proliferation (Rawat et al. 2010). Another homeobox transcription factor that regulates differentiation of hematopoietic stem cells is DLX4 (Bon et al. 2015). Studies on colon cancer showed that VentX regulates tumor associated macrophages and reverts immune suppression in tumor microenvironment (Le et al. 2018). MEK1 is required for Xenopus Ventx2 asymmetric distribution during blastula cell division. Ventx2 inhibition by MEK1 is required for embryonic cell commitment (Scerbo et al., eLife, 2017). VENTX induces TP53-independent apoptosis in cancer cells (Gao H, Oncotarget, 2016). During Xenopus embryonic development, VENTX ortholog regulates transcription of the sox3 gene (Rogers et al. 2007) as well as the early neuronal gene zic3 (Umair et al. 2018).

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Wu B, Le Y, Gao H & Zhu Z (2016). Homeobox protein VentX induces p53-independent apoptosis in cancer cells. *Oncotarget*, 7, 39719-39729. [\[View\]](#)

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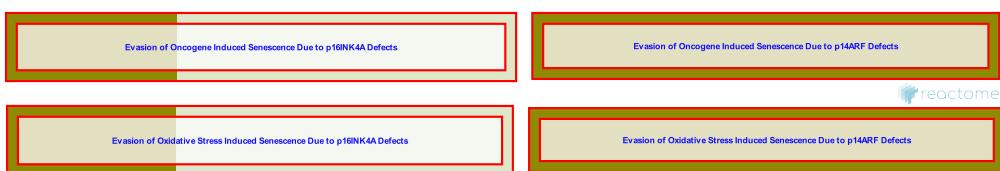
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2019-06-28	Authored	Orlic-Milacic M
2019-10-18	Reviewed	Vegi NM
2019-11-01	Edited	Orlic-Milacic M
2021-11-27	Modified	Weiser JD

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

Input	UniProt Id
CDKN2A	P42771

Input	Ensembl Id
CDKN2A	ENSG00000147889, ENST00000304494, ENST00000579755

5. Diseases of Cellular Senescence (R-HSA-9630747)



Diseases: cancer.

Cellular senescence plays an important role in normal aging, as well as in age-related diseases. Impaired cellular senescence contributes to malignant transformation and cancer development. Presence of an excessive number of senescent cells that are not cleared by the immune system, however, promotes tissue inflammation and creates a microenvironment suitable for growth of neighboring malignant cells. Besides cancer, senescence is also involved in atherosclerosis, osteoarthritis and diabetes (Childs et al. 2015, He and Sharpless 2017).

References

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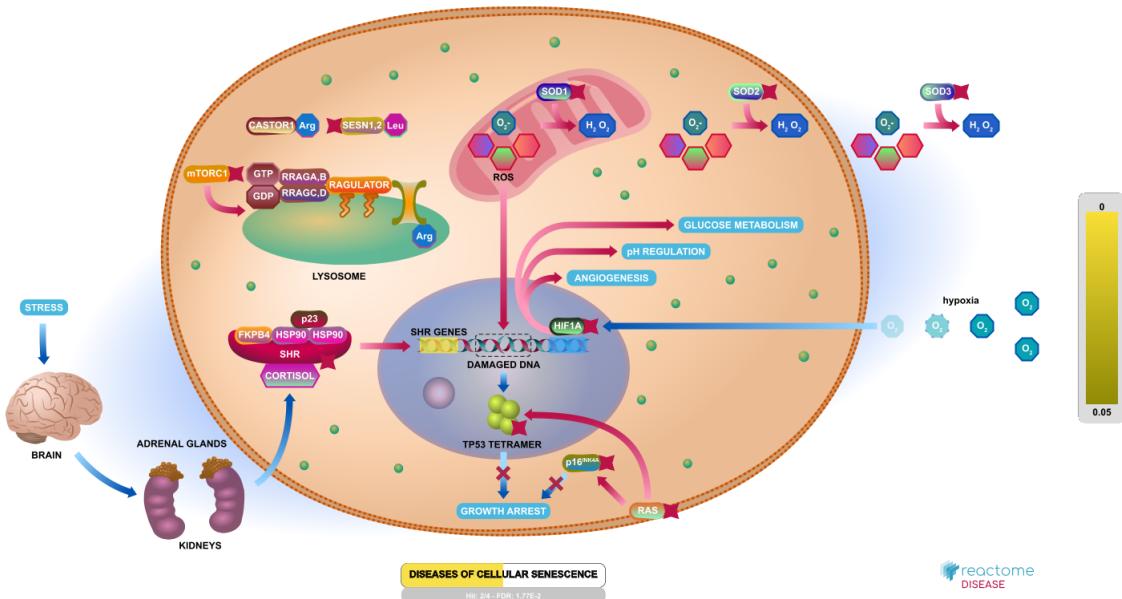
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Date	Action	Author
2018-12-03	Created	Orlic-Milacic M
2018-12-24	Authored	Orlic-Milacic M
2019-04-23	Reviewed	Bennett DC
2019-05-07	Edited	Orlic-Milacic M
2019-06-03	Reviewed	Nathan V, Hayward NK
2019-06-11	Modified	Orlic-Milacic M

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

Input	UniProt Id
CDKN2A	P42771, Q8N726

6. Diseases of cellular response to stress (R-HSA-9675132)



Cells are subject to external and internal stressors, such as foreign molecules that perturb metabolic or signaling processes, cellular respiration-generated reactive oxygen species that can cause DNA damage, oxygen and nutrient deprivation, and changes in temperature or pH. The ability of cells and tissues to respond to stress is essential to the maintenance of tissue homeostasis (Kultz 2005) and dysregulation of cellular response to stress is involved in disease.

So far, we have captured diseases of cellular senescence.

Impaired cellular senescence contributes to malignant transformation and cancer development by enabling continuous proliferation of damaged cells. On the other hand, presence of an excessive number of senescent cells that are not cleared by the immune system promotes tissue inflammation and creates a microenvironment suitable for growth of neighboring malignant cells. In addition to cancer, senescence is also involved in other age-related diseases such as atherosclerosis, osteoarthritis, chronic obstructive lung disease, and diabetes (Childs et al. 2015, He and Sharpless 2017, Hamsanathan et al. 2019, Faget et al. 2019, Gorgoulis et al. 2019, Rhinn et al. 2019). Senotherapy is a new field of pharmacology that aims to therapeutically target senescence to improve healthy aging and age-related diseases (Schmitt 2017, Gorgoulis et al. 2019).

References

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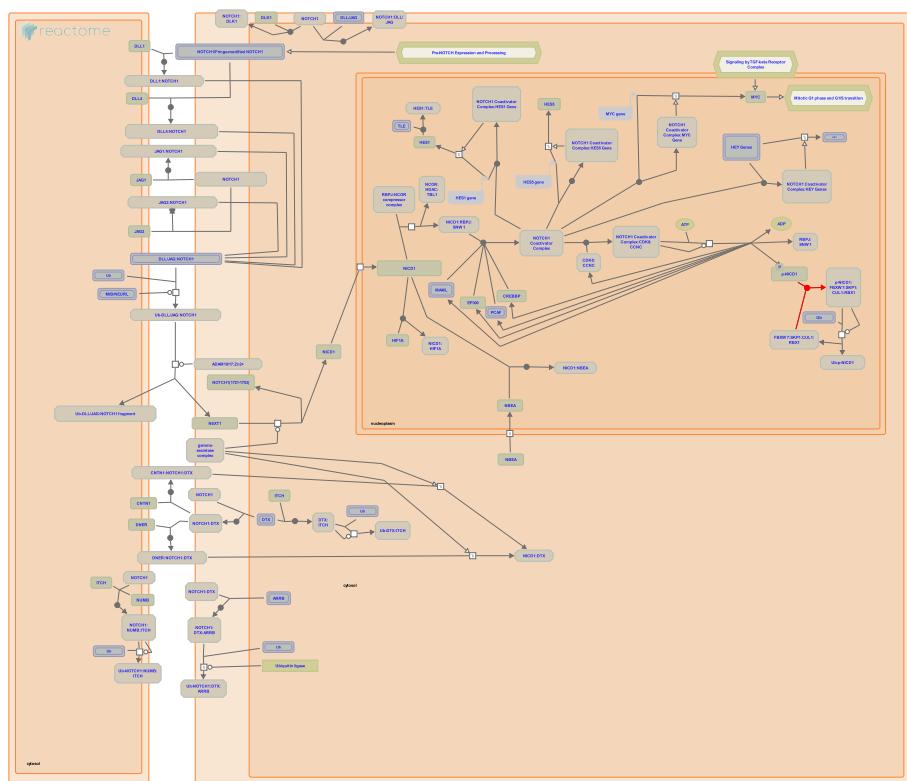
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Date	Action	Author
2020-01-31	Created	Orlic-Milacic M
2020-02-21	Authored	Orlic-Milacic M
2020-02-24	Edited	Orlic-Milacic M
2020-02-24	Reviewed	D'Eustachio P
2020-08-25	Modified	Matthews L

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

Input	UniProt Id
CDKN2A	P42771, Q8N726

7. FBXW7 Mutants and NOTCH1 in Cancer (R-HSA-2644605)



Diseases: cancer.

FBXW7 (FBW7) is a component of the SCF (SKP1, CUL1, and F-box protein) ubiquitin ligase complex SCF-FBW7 which is involved in the degradation of NOTCH1 (Oberg et al. 2001, Wu et al. 2001, Fryer et al. 2004). Loss of function mutations in FBXW7 are frequently found in T-cell acute lymphoblastic leukemia (Akhoondi et al. 2007, Thompson et al. 2007, O'Neil et al. 2007) and are mutually exclusive with NOTCH1 PEST domain mutations (Thompson et al. 2007, O'Neil et al. 2007).

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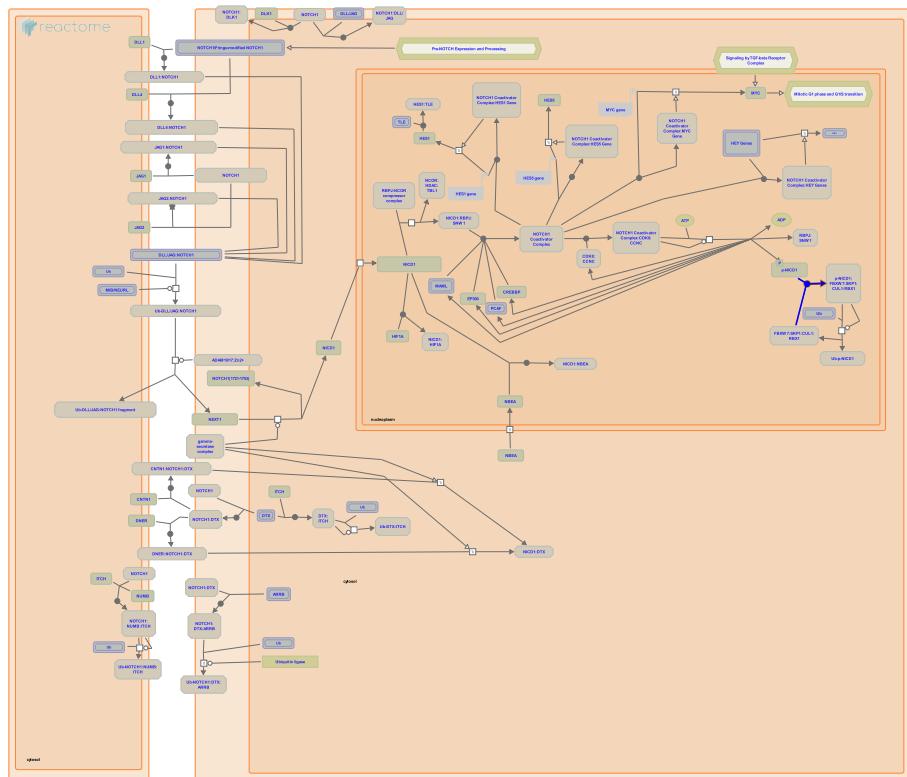
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2013-01-04	Authored	Orlic-Milacic M
2013-01-09	Edited	Jassal B
2013-02-10	Reviewed	Haw R
2015-02-09	Modified	Wu G

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

Input	UniProt Id
FBXW7	Q969H0-1, Q969H0-4

8. Loss of Function of FBXW7 in Cancer and NOTCH1 Signaling (R-HSA-2644607)



Diseases: cancer.

Loss of function mutations found in FBXW7 in T-cell acute lymphoblastic leukemia are predominantly dominant negative missense mutations that target one of the three highly conserved arginine residues in the WD repeats of FBXW7 (Thompson et al. 2007, O'Neil et al. 2007). These three arginine residues are part of the FBXW7 substrate binding pocket and each one of them contacts the phosphorylated threonine residue in the conserved substrate phosphodegron region (Orlicky et al. 2003). Specifically, FBXW7 interacts with the PEST domain of NOTCH1 upon phosphorylation of the PEST domain by CDK8 (Fryer et al. 2004). FBXW7 mutants are therefore unable to bind and promote ubiquitination of the NOTCH1 intracellular domain (NICD1), leading to prolonged NICD1 transcriptional activity (Thompson et al. 2007, O'Neil et al. 2007).

References

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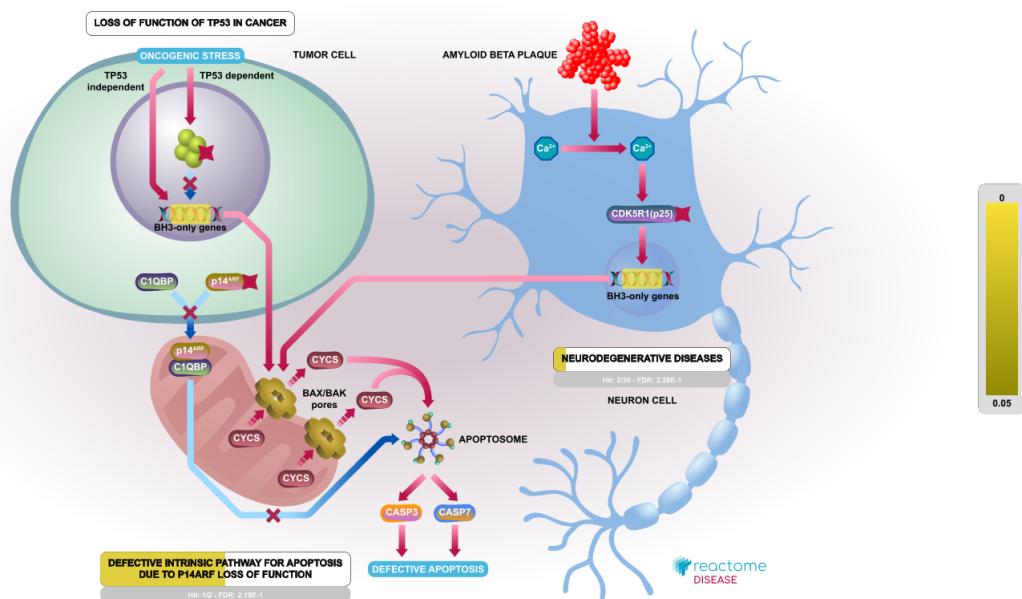
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2013-01-09	Edited	Jassal B
2013-02-10	Reviewed	Haw R
2013-02-11	Modified	Orlic-Milacic M

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

Input	UniProt Id
FBXW7	Q969H0-1, Q969H0-4

9. Defective Intrinsic Pathway for Apoptosis (R-HSA-9734009)



Diseases: neurodegenerative disease, cancer.

Defects in the regulation of the intrinsic pathway for apoptosis are involved in diseases associated with increased cell loss, such as neurodegenerative diseases, as well as in diseases associated with impaired elimination of harmful cells, such as cancer and autoimmunity. For review, please refer to Reed 2001, Lavrik et al. 2009, and Tuzlak et al. 2016.

So far, Reactome has annotated apoptosis defects associated with the loss of function of the CDKN2A gene product p14ARF in cancer, loss of function of TP53 in cancer, and CDK5 dysregulation in neurodegenerative diseases.

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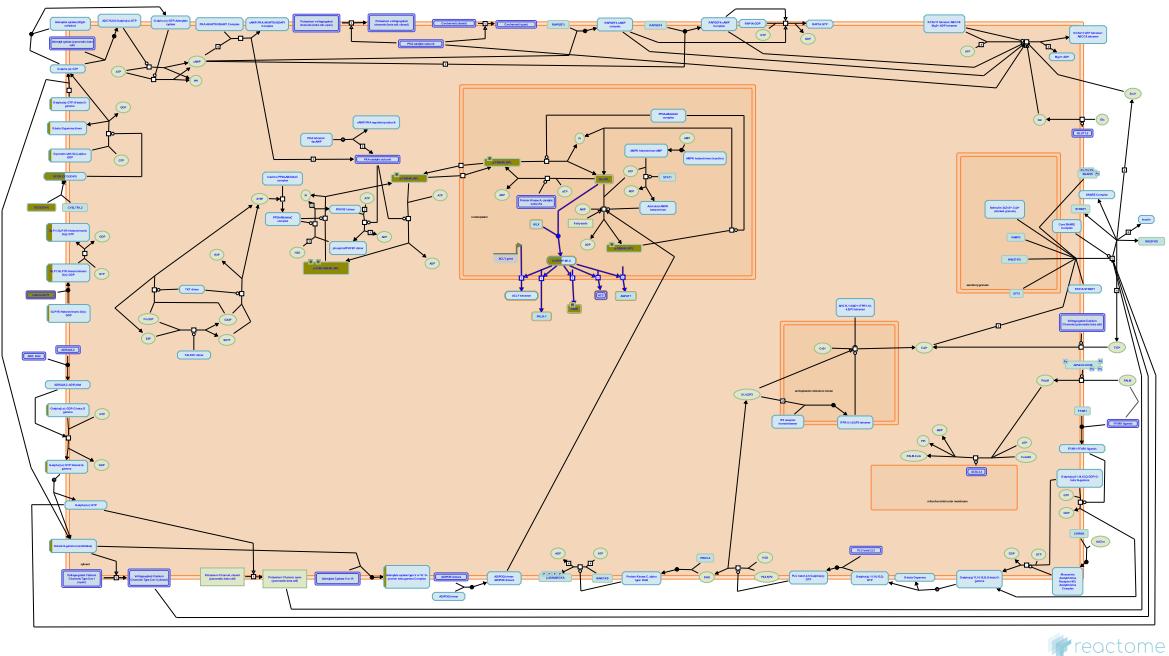
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2021-06-14	Created	Orlic-Milacic M
2021-08-18	Modified	Orlic-Milacic M
2021-08-18	Edited	Orlic-Milacic M
2021-08-18	Reviewed	D'Eustachio P

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

Input	UniProt Id	Input	UniProt Id
CAPNS1	P04632, Q96L46	CDKN2A	Q8N726

10. ChREBP activates metabolic gene expression (R-HSA-163765)



 reactome

Cellular compartments: endoplasmic reticulum membrane, nucleoplasm, cytosol.

ChREBP (Carbohydrate Response Element Binding Protein) is a large multidomain protein containing a nuclear localization signal near its amino terminus, polyproline domains, a basic helix-loop-helix-leucine zipper domain, and a leucine-zipper-like domain (Uyeda et al., 2002). Its dephosphorylation in response to molecular signals associated with the well-fed state allows it to enter the nucleus, interact with MLX protein, and bind to ChRE DNA sequence motifs near Acetyl-CoA carboxylase, Fatty acid synthase, and Pyruvate kinase (L isoform) genes (Ishi et al. 2004). This sequence of events is outlined schematically in the picture below (adapted from Kawaguchi et al. (2001) - copyright (2001) National Academy of Sciences, U.S.A.).

References

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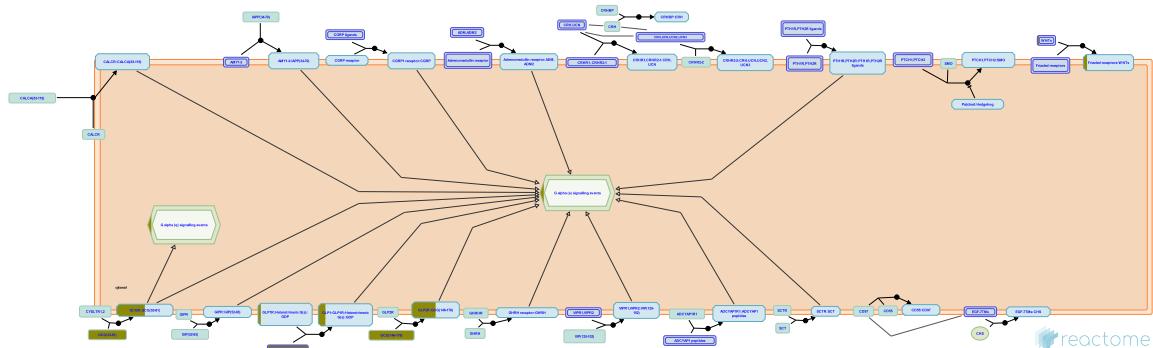
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Date	Action	Author
2005-05-06	Created	Gopinathrao G
2005-05-13	Authored	Gopinathrao G
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
FASN	P49327	MLXIPL	Q9NP71

11. Class B/2 (Secretin family receptors) (R-HSA-373080)



This family is known as Family B (secretin-receptor family, family 2) G-protein-coupled receptors. Family B GPCRs include secretin, calcitonin, parathyroid hormone/parathyroid hormone-related peptides and vasoactive intestinal peptide receptors; all of which activate adenylyl cyclase and the phosphatidyl-inositol-calcium pathway (Harmar AJ, 2001).

References

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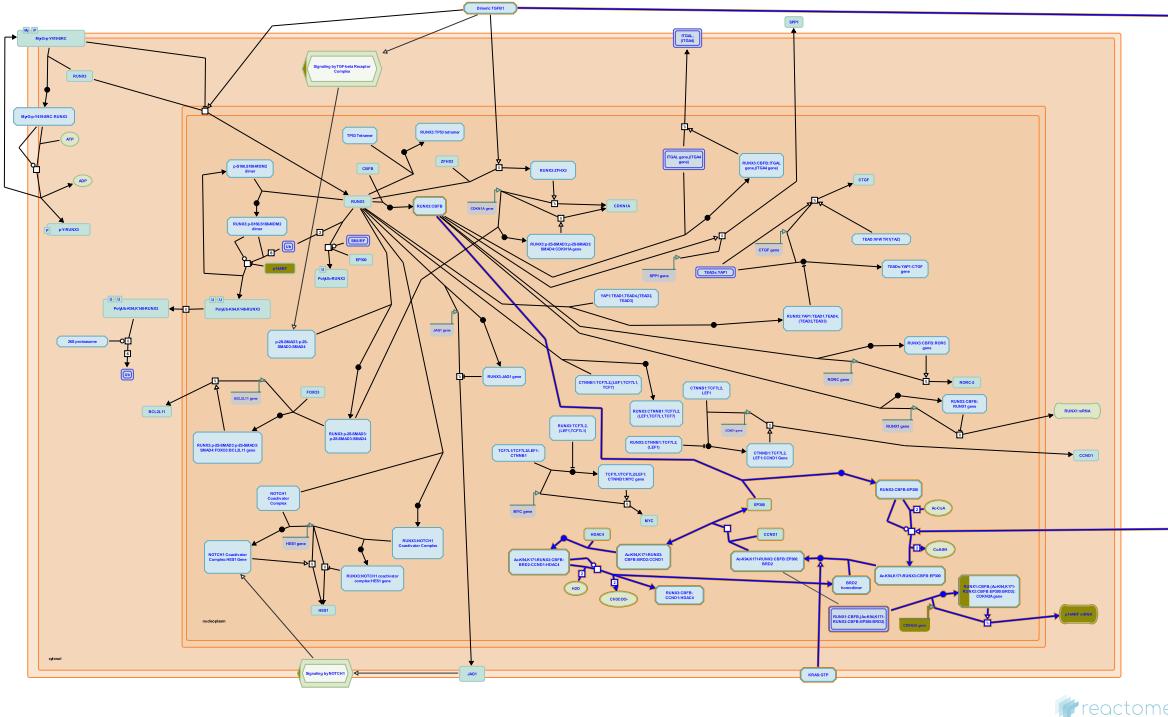
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Date	Action	Author
2008-07-14	Edited	Jassal B
2008-07-14	Authored	Jassal B
2008-07-14	Created	Jassal B
2009-05-29	Reviewed	D'Eustachio P
2021-11-27	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
GCG	P01275	GNB2	P62879	WNT4	O96014, P56705

12. RUNX3 regulates p14-ARF (R-HSA-8951936)



reactome

Acetylation of RUNX3 by the histone acetyl transferase p300 (EP300) and the subsequent association of acetylated RUNX3 with BRD2 correlates with upregulation of p14-ARF transcription from the CDKN2A locus. Cyclin D1 (CCND1) negatively regulates RUNX3-facilitated induction of p14-ARF by recruiting histone deacetylase HDAC4 to RUNX3, leading to RUNX3 deacetylation (Lee et al. 2013).

References

Lee JW, Lee YS, Chuang LS, Kim JH, Bae SC, Jang JW, ... Kim MK (2013). Runx3 inactivation is a crucial early event in the development of lung adenocarcinoma. *Cancer Cell*, 24, 603-16.

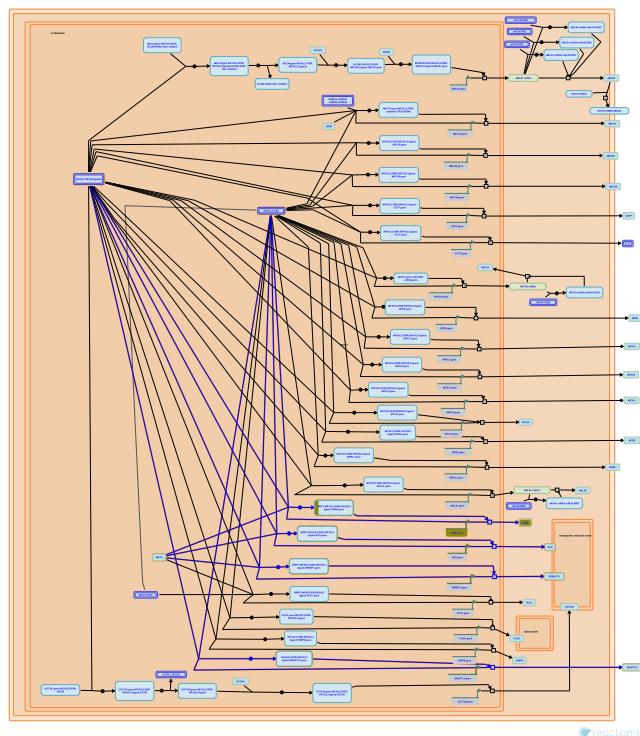
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Date	Action	Author
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2016-12-13	Created	Orlic-Milacic M
2017-01-31	Edited	Orlic-Milacic M
2017-01-31	Reviewed	Ito Y, Chuang LS
2021-11-27	Modified	Weiser JD

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

Input	Ensembl Id
CDKN2A	ENSG00000147889, ENST00000579755

13. NR1H2 & NR1H3 regulate gene expression linked to lipogenesis (R-HSA-9029558)



Cellular compartments: nucleoplasm.

The liver X receptor $\hat{1}\pm$ (LXR $\hat{1}\pm$ or NR1H3) and LXR $\hat{1}^2$ (NR1H2) are nuclear receptors that are activated by endogenous oxidized derivatives of cholesterol known as oxysterols (Janowski BA et al. 1999; Jakobsson T et al. 2012). NR1H2 and NR1H3 act as whole-body cholesterol sensors and their activation results in a net elimination of cholesterol from the body and amelioration of the plasma lipoprotein profile by mobilizing cholesterol from the periphery (Venkateswaran A et al. 2000; Repa JJ et al. 2000a; Ishibashi M et al. 2013). NR1H3 (LXR $\hat{1}\pm$) and NR1H2 (LXR $\hat{1}^2$) also contribute to lowering of whole-body cholesterol levels by shifting acetyl-CoA units from cholesterol de novo biosynthesis to fatty acid synthesis. NR1H2 or 3-induced hepatic lipogenesis in rodents and humans is mediated by direct upregulation of sterol regulatory element-binding protein 1 (SREBF1), the main regulator of hepatic lipogenesis that controls the transcription of genes involved in fatty acid biosynthesis (Schultz JR et al. 2000). NR1H2 & NR1H3 may activate lipogenic gene transcription directly by bidding LXR responsive element (LXRE) found in the promoter regions of several genes, such as fatty acid synthase (FAS or FASN) and stearoyl-CoA desaturase 1 (SCD1) (Repa JJ et al. 2000b; Yoshikawa T et al. 2001; Joseph SB et al. 2002; Chu K et al. 2006). Mice carrying a targeted disruption in the NR1H3 (LXR $\hat{1}\pm$) gene were deficient in expression of FAS, SCD1, ACC, and SREBF1 (Peet DJ et al. 1998). Mice ablated of both NR1H3 and NR1H2 showed defective hepatic lipid metabolism decreasing lipogenesis by 80% and were resistant to obesity (Repa JJ et al. 2000; Kalaany NY et al. 2005; Beaven SW et al. 2013). Further, the administration of the synthetic NR1H2 or NR1H3 ligands to mice triggered induction of the lipogenic pathway and raised plasma triglyceride levels (Schultz JR et al. 2000). These studies demonstrate the role of NR1H3 (LXR $\hat{1}\pm$) and NR1H2 (LXR $\hat{1}^2$) in the control of lipogenesis.

References

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Herzog B, Parker MG, Hallberg M, Woods A, White R & Seth A (2007). The nuclear receptor cofactor, receptor-interacting protein 140, is required for the regulation of hepatic lipid and glucose metabolism by liver X receptor. Mol. Endocrinol., 21, 2687-97. ↗

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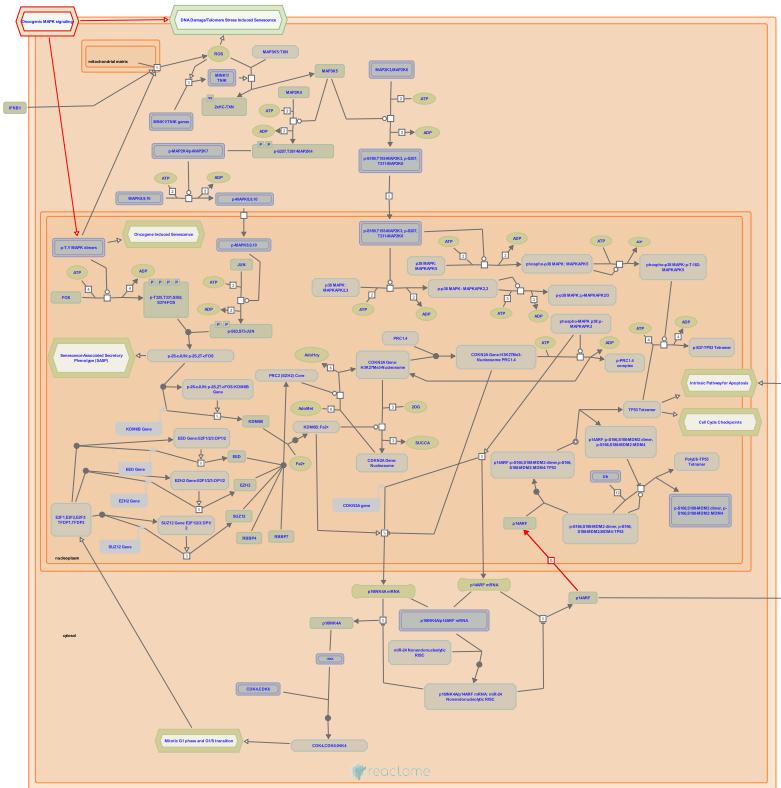
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2017-11-21	Created	Shamovsky V
2018-01-19	Authored	Shamovsky V
2018-12-29	Reviewed	D'Eustachio P
2019-08-09	Edited	Shamovsky V
2019-08-09	Reviewed	Repa JJ, Cummins CL
2019-08-12	Modified	Shamovsky V

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

Input	UniProt Id
FASN	P49327

Input	Ensembl Id
FASN	ENSG00000169710

14. Evasion of Oxidative Stress Induced Senescence Due to p14ARF Defects (R-HSA-9646304)



Diseases: cancer.

One of the two main protein products of the CDKN2A gene, p14ARF (CDKN2A transcript 4, CDKN2A-4, ARF), contributes to oxidative stress induced cellular senescence by stabilizing TP53 (p53). The function of p14ARF in p53 stabilization through sequestration of MDM2, a p53 ubiquitin ligase, depends on the nuclear localization of p14ARF and its ability to interact with MDM2. The nuclear localization signal and the MDM2 interaction domain map to the first 15 amino acids of the N-terminus of p14ARF. This region is encoded by the p14ARF-specific exon 1beta of CDKN2A. An independent MDM2-binding domain is localized at the C-terminus of p14ARF (Lohrum et al. 2000). Insertion of 16 nucleotides in exon 1beta results in a frameshift truncation of p14ARF, responsible for a familial melanoma syndrome in which the p16INK4A product of the CDKN2A gene is unaffected. This mutation is rare and has so far been reported in one family only. The mutant protein, p14ARF R21RfsTER47 has the nucleotide localization signal and the N-terminal MDM2 interaction region preserved, but is unable to translocate from the cytosol to the nucleus, possibly due to aberrant conformation (Rizos, Puig et al. 2001), and also lacks the C-terminal MDM2 interaction region. Relocation of wild type p14ARF to the cytosol has been observed in melanoma (Rizos, Darmanian et al. 2001) and aggressive thyroid papillary carcinoma (Ferru et al. 2006). Genomic deletion of exon 1beta, with exons 1alpha, 2 and 3 intact, has been reported in about 30% of melanoma cases with genomic deletions involving the CDKN2A locus (Freedberg et al. 2008). Several different familial melanoma germline mutations map to the exon 1beta splice donor site (Harland et al. 2005).

The ability of p14ARF to localize to the nucleolus also plays a role in p14ARF-mediated stabilization of p53. Mutations in exon 2 of the CDKN2A gene can lead to missense mutations in p14ARF that affect its nucleolar localization and p53 stabilization, but the exact mechanism has not been fully elucidated (Zhang and Xiong 1999, reviewed by Fontana et al. 2019).

References

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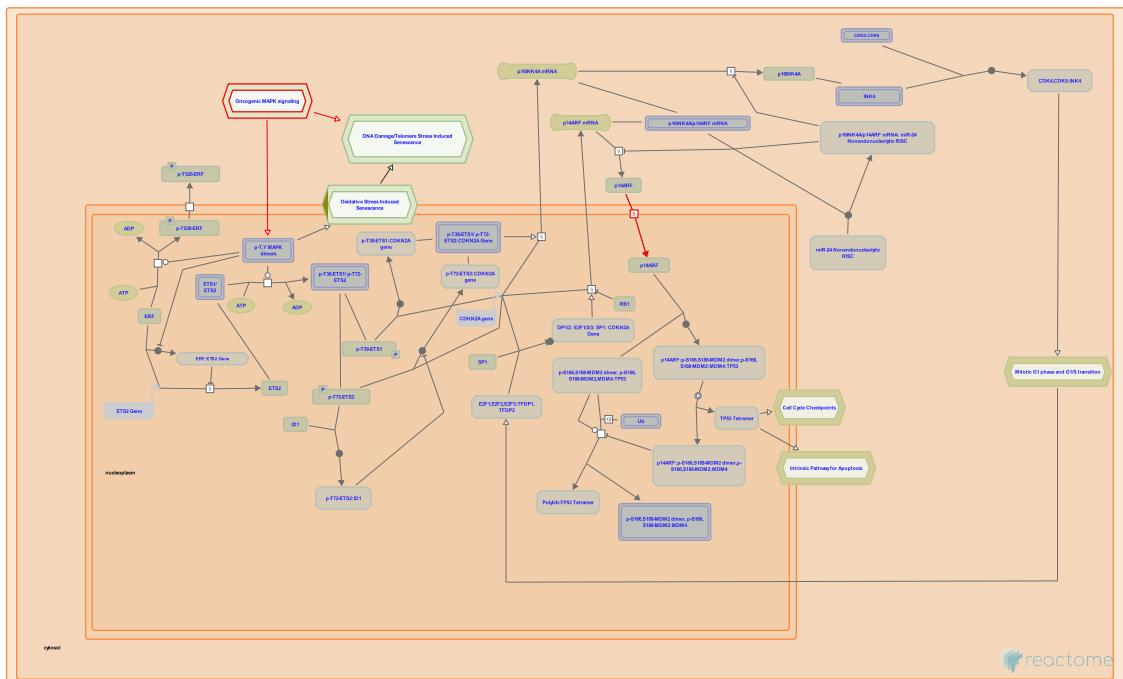
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2019-06-28	Authored	Orlic-Milacic M
2019-07-08	Reviewed	Rizos H
2019-07-16	Edited	Orlic-Milacic M
2019-08-12	Reviewed	Bennett DC
2019-08-14	Edited	Orlic-Milacic M
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
CDKN2A	Q8N726

15. Evasion of Oncogene Induced Senescence Due to p14ARF Defects (R-HSA-9646303)



Diseases: cancer.

In cell culture, p14ARF (CDKN2A transcript 4, CDKN2A-4, ARF), one of the two main protein products of the CDKN2A gene, contributes to oncogene induced senescence by stabilizing TP53 (p53). The function of p14ARF in p53 stabilization through sequestration of MDM2, a p53 ubiquitin ligase, depends on the nuclear localization of p14ARF and its ability to interact with MDM2. The nuclear localization signal and the MDM2 interaction domain map to the first 15 amino acids of the N-terminus of p14ARF. This region is encoded by the p14ARF-specific exon 1beta of CDKN2A. An independent MDM2-binding domain localized to the C-terminus of p14ARF (Lohrum et al. 2000). Insertion of 16 nucleotides in exon 1beta results in a frameshift truncation of p14ARF, responsible for a familial melanoma syndrome in which the p16INK4A product of the CDKN2A gene is unaffected. This mutation is rare and has so far been reported in one family only. The mutant protein, p14ARF R21RfsTER47 has the nucleotide localization signal and the N-terminal MDM2 interaction region preserved, but is unable to translocate from the cytosol to the nucleus, possibly due to aberrant conformation (Rizos, Puig et al. 2001), and also lacks the C-terminal MDM2 interaction region. Relocation of wild type p14ARF to the cytosol has been observed in melanoma (Rizos, Darmanian et al. 2001) and aggressive thyroid papillary carcinoma (Ferru et al. 2006). Genomic deletion of exon 1beta, with exons 1alpha, 2 and 3 intact, has been reported in about 30% of melanoma cases with genomic deletions involving the CDKN2A locus (Freedberg et al. 2008). Several different familial melanoma germline mutations map to the exon 1beta splice donor site (Harland et al. 2005).

The ability of p14ARF to localize to the nucleolus also plays a role in p14ARF-mediated stabilization of p53. Mutations in exon 2 of the CDKN2A gene can lead to missense mutations in p14ARF that affect its nucleolar localization and p53 stabilization, but the exact mechanism has not been fully elucidated (Zhang and Xiong 1999, reviewed by Fontana et al. 2019).

References

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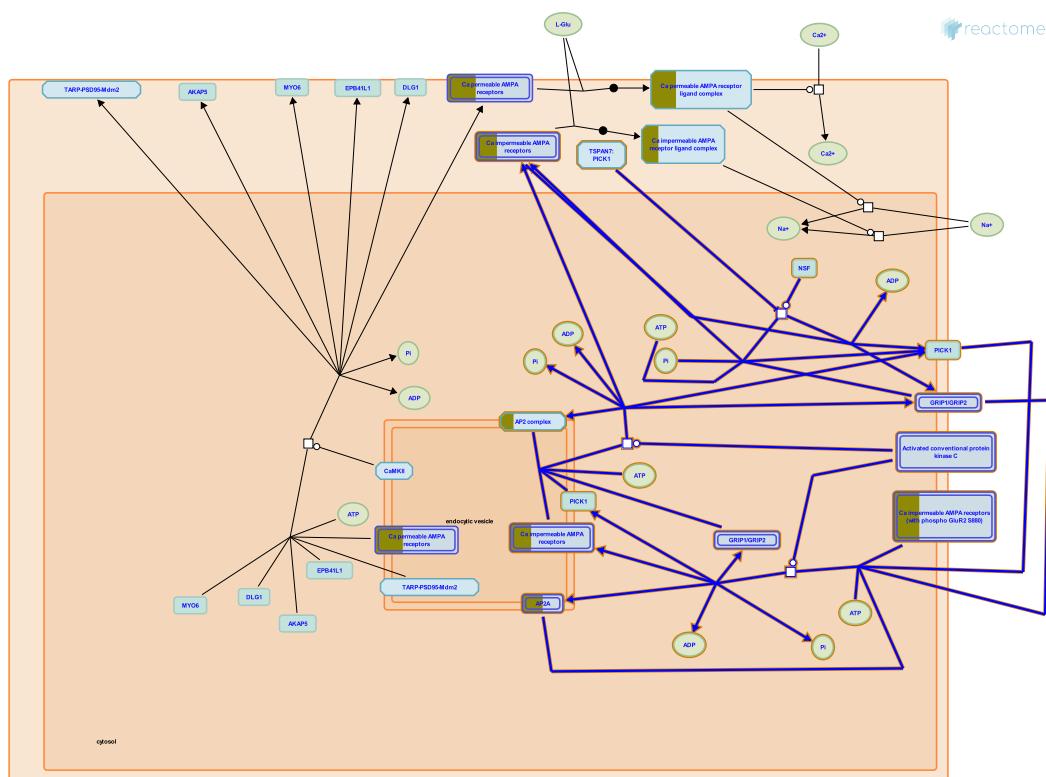
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2019-07-08	Reviewed	Rizos H
2019-07-16	Edited	Orlic-Milacic M
2019-08-12	Reviewed	Bennett DC
2019-08-14	Edited	Orlic-Milacic M
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
CDKN2A	Q8N726

16. Trafficking of GluR2-containing AMPA receptors (R-HSA-416993)



Trafficking of GluR2-containing receptors is governed by protein-protein interactions that are regulated by phosphorylation events. GluR2 binds NSF and AP2 in the proximal C-terminal region and binds PICK and GRIP1/2 in the extreme C-terminal region. GluR2 interaction with NSF is necessary to maintain the synaptic levels of GluR2-containing AMPA receptors both at basal levels and under conditions of synaptic activity. GluR2 interaction with GRIP helps anchor AMPA receptors at the synapse. Phosphorylation of GluR2 at S880 disrupts GRIP interaction but allows binding of PICK. PICK is activated by Ca-sensitive Protein Kinase C (PKC). Under basal conditions, in hippocampal synapse, GluR2-containing AMPA receptors (GluR2/GluR3) constitutively recycle between the synapse and the endosome by endocytosis and exocytosis. GRIP anchors the receptors at the synapse while PICK interaction internalizes the receptors and NSF helps maintain the synaptic receptors. Cerebellar stellate cells mainly contain GluR3 homomers as Ca-permeable receptors. The interaction of GluR3 and GRIP is disrupted by PICK interaction by phosphorylation of equivalent of S880 residue in GluR3. Under conditions of repetitive presynaptic activity, there is PICK-dependent removal of GluR2-lacking AMPA receptors and selective incorporation of GluR2-containing AMPA receptors at the synapse. The GluR2-containing AMPA receptors are first delivered to the surface by PICK and mobilized to the synapse by NSF-dependent mechanism (Liu SJ and Cull-Candy SG Nat Neurosci. 2005 Jun;8(6):768-75).

References

Glauser L, Kropf M, Johnsson K, Rey G, Hirling H & Kulangara K (2008). Subunit-specific surface mobility of differentially labeled AMPA receptor subunits. Eur J Cell Biol, 87, 763-78. [\[link\]](#)

Edit history

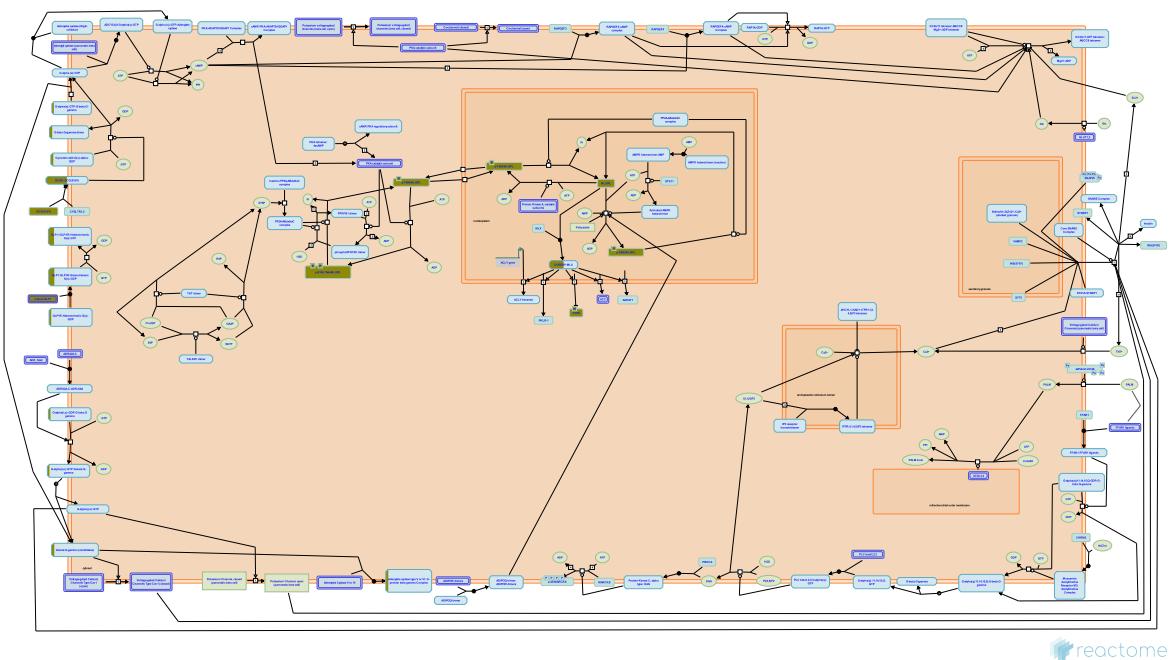
Date	Action	Author
2008-01-14	Edited	Mahajan SS

Date	Action	Author
2008-01-14	Authored	Mahajan SS
2009-04-07	Created	Mahajan SS
2009-05-15	Reviewed	Ziff EB
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
AP2A2	O94973-3	GRIA3	P42263

17. Integration of energy metabolism (R-HSA-163685)



Cellular compartments: cytosol.

Many hormones that affect individual physiological processes including the regulation of appetite, absorption, transport, and oxidation of foodstuffs influence energy metabolism pathways. While **insulin** mediates the storage of excess nutrients, **glucagon** is involved in the mobilization of energy resources in response to low blood glucose levels, principally by stimulating hepatic glucose output. Small doses of glucagon are sufficient to induce significant glucose elevations. These hormone-driven regulatory pathways enable the body to sense and respond to changed amounts of nutrients in the blood and demands for energy.

Glucagon and Insulin act through various metabolites and enzymes that target specific steps in metabolic pathways for sugar and fatty acids. The processes responsible for the long-term control of fat synthesis and short term control of glycolysis by key metabolic products and enzymes are annotated in this module as six specific pathways:

Pathway 1. Glucagon signalling in metabolic pathways: In response to low blood glucose, pancreatic alpha-cells release glucagon. The binding of glucagon to its receptor results in increased cAMP synthesis, and Protein Kinase A (PKA) activation.

Pathway 2. PKA mediated phosphorylation: PKA phosphorylates key enzymes, e.g., 6-Phosphofructo-2-kinase /Fructose-2,6-bisphosphatase (PF2K-Pase) at serine 36, and regulatory proteins, e.g., Carbohydrate Response Element Binding Protein (ChREBP) at serine 196 and threonine 666.

In brief, the binding of insulin to its receptor leads to increased protein phosphatase activity and to hydrolysis of cAMP by cAMP phosphodiesterase. These events counteract the regulatory effects of glucagon.

Pathway 3: Insulin stimulates increased synthesis of Xylulose-5-phosphate (Xy-5-P). Activation of the insulin receptor results indirectly in increased Xy-5-P synthesis from Glyceraldehyde-3-phosphate and Fructose-6-phosphate. Xy-5-P, a metabolite of the pentose phosphate pathway, stimulates protein phosphatase PP2A.

Pathway 4: AMP Kinase (AMPK) mediated response to high AMP:ATP ratio: In response to diet with high fat content or low energy levels, the cytosolic AMP:ATP ratio is increased. AMP triggers a complicated cascade of events. In this module we have annotated only the phosphorylation of ChREBP by AMPK at serine 568, which inactivates this transcription factor.

Pathway 5: Dephosphorylation of key metabolic factors by PP2A: Xy-5-P activated PP2A efficiently dephosphorylates phosphorylated PF2K-Pase resulting in the higher output of F-2,6-P2 that enhances PFK activity in the glycolytic pathway. PP2A also dephosphorylates (and thus activates) cytosolic and nuclear ChREBP.

Pathway 6: Transcriptional activation of metabolic genes by ChREBP: Dephosphorylated ChREBP activates the transcription of genes involved in glucose metabolism such as pyruvate kinase, and lipogenic genes such as acetyl-CoA carboxylase, fatty acid synthetase, acyl CoA synthase and glycerol phosphate acyl transferase.

The illustration below summarizes this network of events. Black lines are metabolic reactions, red lines are negative regulatory events, and green lines are positive regulatory events (figure reused with permission from Veech (2003) - Copyright (2003) National Academy of Sciences, U.S.A.).

References

- Hardie DG (2004). The AMP-activated protein kinase pathway--new players upstream and downstream. *J Cell Sci*, 117, 5479-87. [🔗](#)
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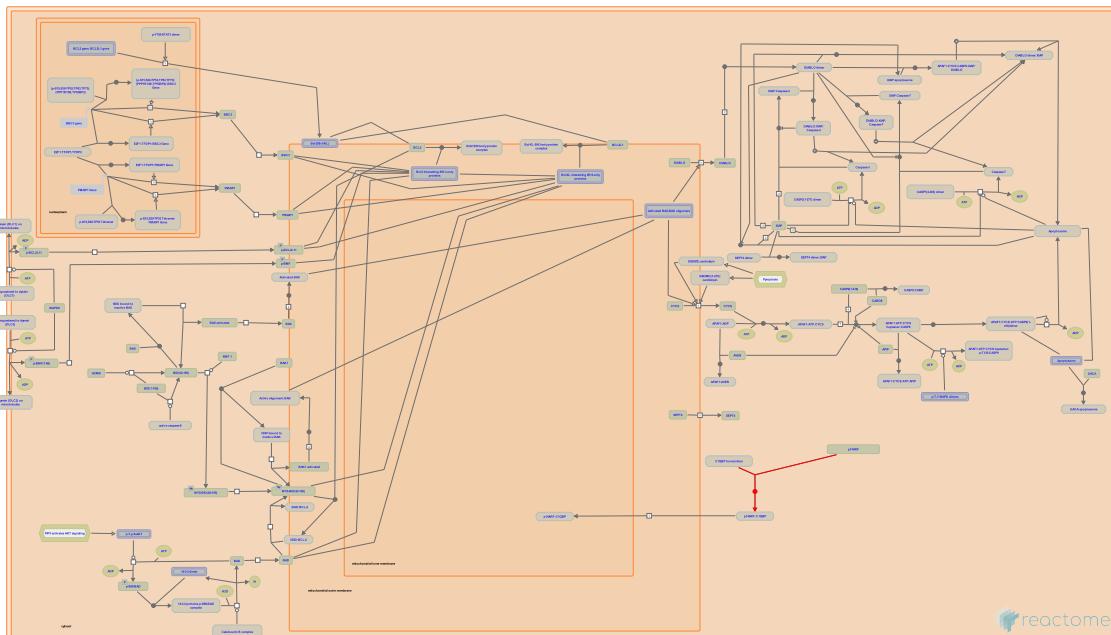
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Date	Action	Author
2005-05-11	Authored	Gopinathrao G, D'Eustachio P
2005-05-11	Created	Gopinathrao G, D'Eustachio P
2005-09-10	Reviewed	Rush MG
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
FASN	P49327	GCG	P01275
GNB2	P62879	MLXIPL	Q9NP71

18. Defective Intrinsic Pathway for Apoptosis Due to p14ARF Loss of Function (R-HSA-9645722)



Diseases: cancer.

Cancer-derived missense mutations in the CDKN2A gene that affect the C-terminal arginine-rich region of p14ARF (also known as CDKN2A transcription isoform 4, CDKN2A-4, p14 or ARF) impair p14ARF binding to the mitochondrial matrix protein C1QBP and interfere with p53-mediated apoptosis. Many mutations in the CDKN2A locus that affect C-terminal arginines of p14ARF are silent in p16INK4A (CDKN2A-1) (Itahana and Zhang 2008).

References

Itahana K & Zhang Y (2008). Mitochondrial p32 is a critical mediator of ARF-induced apoptosis. *Cancer Cell*, 13, 542-53. [View](#)

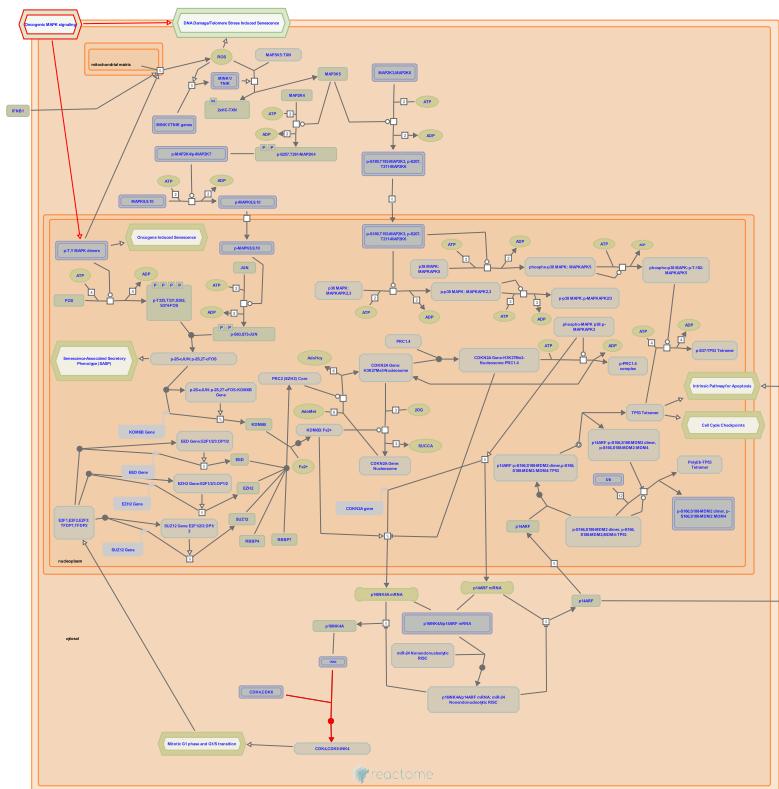
Edit history

Date	Action	Author
2019-05-17	Created	Orlic-Milacic M
2019-06-28	Authored	Orlic-Milacic M
2019-07-08	Reviewed	Rizos H
2019-07-16	Edited	Orlic-Milacic M
2019-08-12	Reviewed	Bennett DC
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
CDKN2A	Q8N726

19. Evasion of Oxidative Stress Induced Senescence Due to Defective p16INK4A binding to CDK4 (R-HSA-9632697)



Diseases: cancer.

Missense mutations and small indels in the CDKN2A gene, which result in amino acid changes in p16INK4A that impair its ability to bind to CDK4, interfere with p16INK4A-mediated, oxidative stress-induced, cellular senescence (Chen 2000, Vurusanker et al. 2012).

Loss-of-function mutations in p16INK4A can also contribute to cancer by interfering with p16INK4A-mediated inhibition of NFkB signaling (Becker et al. 2005).

References

- Chen QM (2000). Replicative senescence and oxidant-induced premature senescence. Beyond the control of cell cycle checkpoints. Ann. N. Y. Acad. Sci., 908, 111-25. [\[CrossRef\]](#)
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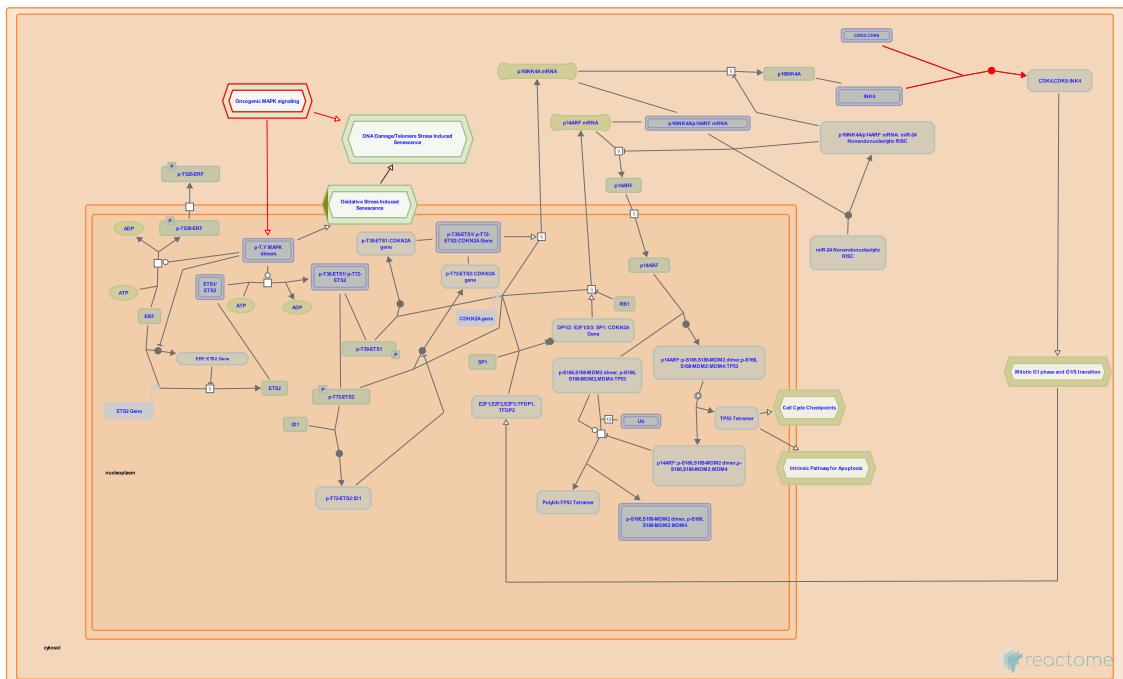
Date	Action	Author
2018-12-21	Created	Orlic-Milacic M
2018-12-24	Authored	Orlic-Milacic M
2019-04-23	Reviewed	Bennett DC
2019-05-07	Edited	Orlic-Milacic M
2019-06-03	Reviewed	Nathan V, Hayward NK

Date	Action	Author
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
CDKN2A	P42771

20. Evasion of Oncogene Induced Senescence Due to Defective p16INK4A binding to CDK4 (R-HSA-9630791)



Diseases: cancer.

Missense mutations and small indels in the CDKN2A gene, which result in amino acid changes in p16INK4A that impair its ability to bind to CDK4, interfere with p16INK4A-mediated induction of cellular senescence in response to oncogenic signaling (Jones et al. 2007).

Loss-of-function mutations in p16INK4A can also contribute to cancer by interfering with p16INK4A-mediated inhibition of NF κ B signaling (Becker et al. 2005).

References

Peters G, Jones R, Delia D, Moulin S, Brookes S, Manoukian S, ... Rowe J (2007). A CDKN2A mutation in familial melanoma that abrogates binding of p16INK4a to CDK4 but not CDK6. *Cancer Res.*, 67, 9134-41. [View](#)

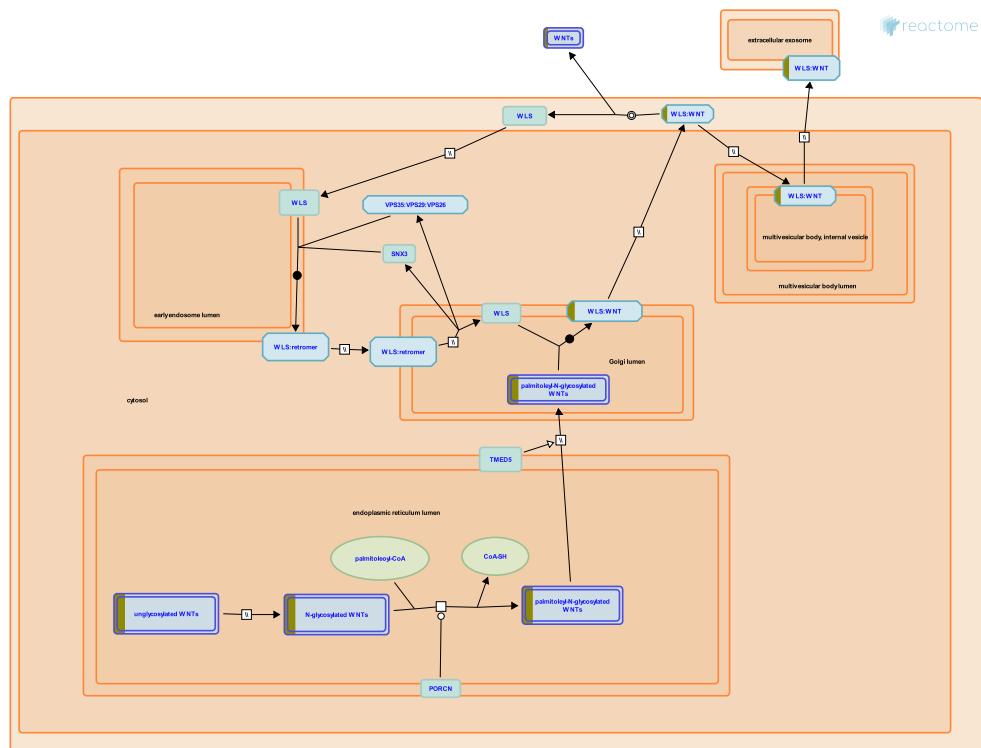
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Date	Action	Author
2018-12-03	Created	Orlic-Milacic M
2018-12-24	Authored	Orlic-Milacic M
2019-04-23	Reviewed	Bennett DC
2019-05-07	Edited	Orlic-Milacic M
2019-06-03	Reviewed	Nathan V, Hayward NK
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
CDKN2A	P42771

21. WNT ligand biogenesis and trafficking (R-HSA-3238698)



19 WNT proteins have been identified in human cells. The WNTs are members of a conserved metazoan family of secreted morphogens that activate several signaling pathways in the responding cell: the canonical (beta-catenin) WNT signaling cascade and several non-canonical pathways, including the planar cell polarity (PCP), the regulation of intracellular calcium signaling and activation of JNK kinases. WNT proteins exist in a gradient outside the secreting cell and are able to act over both short and long ranges to promote proliferation, changes in cell migration and polarity and tissue homeostasis, among others (reviewed in Saito-Diaz et al, 2012; Willert and Nusse, 2012).

The WNTs are ~40kDa proteins with 23 conserved cysteine residues in the N-terminal that may form intramolecular disulphide bonds. They also contain an N-terminal signal sequence and a number of N-linked glycosylation sites (Janda et al, 2012). In addition to being glycosylated, WNTs are also lipid-modified in the endoplasmic reticulum by a WNT-specific O-acyl-transferase, Porcupine (PORCN), contributing to their characteristic hydrophobicity. PORCN-dependent palmitoylation is required for the secretion of WNT as well as its signaling activity, as either depletion of PORCN or mutation of the conserved serine acylation site results in the intracellular accumulation of WNT ligand (Takada et al, 2006; Barrott et al, 2011; Biechele et al, 2011; reviewed in Willert and Nusse, 2012).

Secretion of WNT requires a number of other dedicated factors including the sorting receptor Wntless (WLS) (also known as Evi, Sprinter, and GPR177), which binds WNT and escorts it to the cell surface (Banziger et al, 2006; Bartscherer et al, 2006; Goodman et al, 2006). A WNT-specific retromer containing SNX3 is subsequently required for the recycling of WLS back to the Golgi (reviewed in Herr et al, 2012; Johannes and Wunder, 2011). Once at the cell surface, WNT makes extensive contacts with components of the extracellular matrix such as heparan sulphate proteoglycans (HSPGs) and may be bound by any of a number of regulatory proteins, including WIFs and SFRPs. The diffusion of the WNT ligand may be aided by its packing either into WNT multimers, exosomes or onto lipoprotein particles to shield the hydrophobic lipid adducts from the aqueous extracellular environment (Gross et al, 2012; Luga et al, 2012, Korkut et al, 2009; reviewed in Willert and Nusse, 2012).

References

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- Barrow JR, Barrott JJ, Murtaugh LC, Smith AP & Cash GM (2011). Deletion of mouse Porcn blocks Wnt ligand secretion and reveals an ectodermal etiology of human focal dermal hypoplasia/Goltz syndrome. *Proc. Natl. Acad. Sci. U.S.A.*, 108, 12752-7. [\[View\]](#)
- Herr P, Hausmann G & Basler K (2012). WNT secretion and signalling in human disease. *Trends Mol Med*, 18, 483-93. [\[View\]](#)
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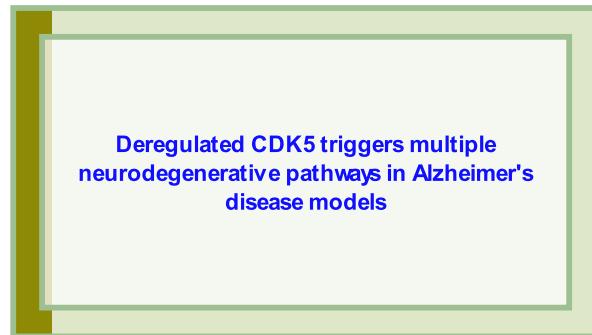
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Date	Action	Author
2013-03-27	Created	Rothfels K
2013-04-06	Authored	Rothfels K
2013-04-12	Edited	Matthews L
2013-05-24	Reviewed	Boutros M
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id
WNT4	O96014, P56705

22. Neurodegenerative Diseases ([R-HSA-8863678](#))



 reactome

Diseases: neurodegenerative disease.

Neurodegenerative diseases manifest as the progressive dysfunction and loss of neurons, which is frequently accompanied by formation of misfolded protein deposits in the brain. Classification of neurodegenerative diseases is based on clinical symptoms, which depend on the anatomical region affected by neuronal dysfunction, the identity of misfolded proteins and cellular and subcellular pathology.

In Alzheimerâ€™s disease (AD), beta-amyloid protein (APP) deposits form in the extracellular space, where they can make plaques, while abnormally phosphorylated tau protein (MAPT) accumulates in neuronal cells.

Beside AD, neuronal and/or glial inclusions of hyperphosphorylated tau are also found in Pick disease (PiD), neurofibrillary tangle-dementia (NFT), primary age-related tauopathy (PART), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD) and globular glial tauopathies (GGT).

In prion disease, such as Creutzfeldt-Jakob disease, deposits of PrP protein are formed mostly in the extracellular and presynaptic space. PrP deposits in neuronal cell bodies are mainly confined to endosomes and lysosomes, which is attributed to neuronal uptake of pathological proteins and intercellular prion spreading.

In Parkinson disease (PD) and dementia with Lewy bodies (DLB), deposits of alpha-synuclein (SNCA) are formed in the cytoplasm of neuronal cell bodies and neurites. In multiple system atrophy (MSA), deposits of alpha-synuclein form in the cytoplasm of glial cells (Papp-Lantos bodies).

Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) are characterized by ubiquitin-positive cytoplasmic inclusions of TAR DNA-binding protein 43 (TARDBP, commonly known as TDP-43), a protein that normally localizes to the nucleus. Pathological TDP-43 inclusions have been associated with the TDP-43 gene mutations, as well as mutations in several other genes, including C9orf72, GRN, VCP, SQSTM1, DCTN1 and OPTN. TDP-43 inclusions have also been reported in AD, DLB, hippocampal sclerosis (HS) and chronic traumatic encephalopathy.

FUS protein-positive inclusion bodies are found in familial ALS, caused by mutations in the FUS gene, as well as in a small subgroup of FTLD-related diseases. FUS-positive inclusions may be accompanied by FET protein-positive inclusions.

For a detailed review of molecular pathology of neurodegenerative diseases, please refer to Kovacs 2016.

Within this broad domain, the process by which APP-triggered deregulation of CDK5 (cyclin-dependent kinase 5) triggers multiple neurodegenerative pathways associated with Alzheimer's disease has been annotated.

References

Kovacs GG (2016). Molecular Pathological Classification of Neurodegenerative Diseases: Turning towards Precision Medicine. *Int J Mol Sci*, 17. [\[View\]](#)

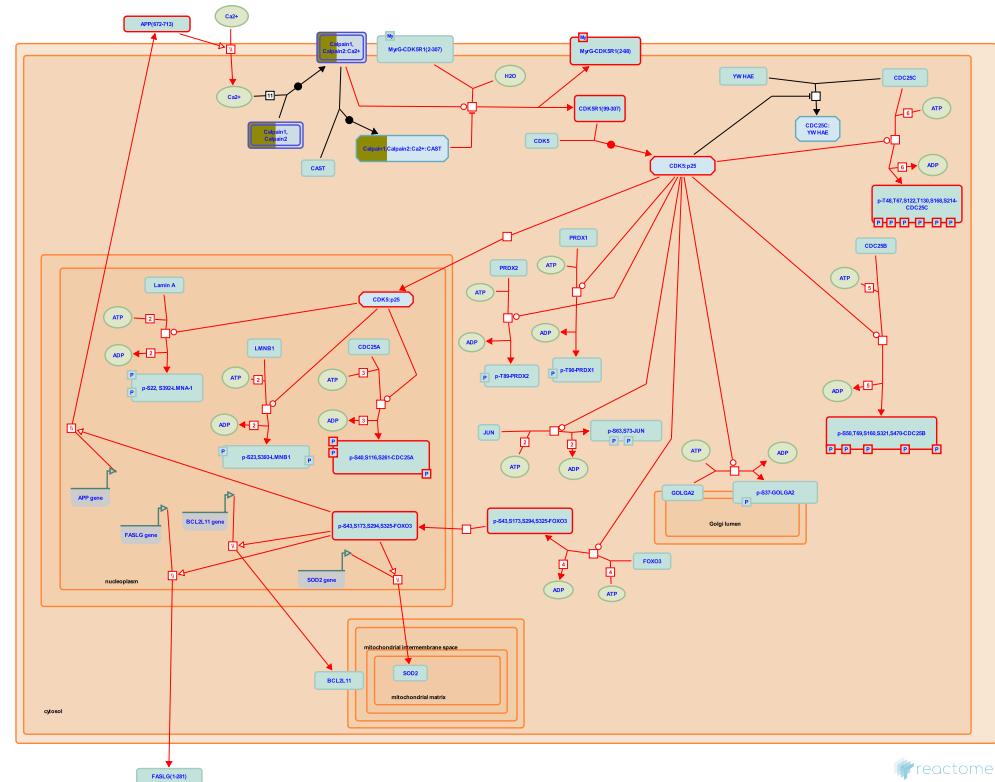
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Date	Action	Author
2016-03-10	Created	Orlic-Milacic M
2016-08-18	Reviewed	D'Eustachio P
2016-08-19	Authored	Orlic-Milacic M
2016-08-20	Modified	Orlic-Milacic M
2016-08-20	Edited	Orlic-Milacic M

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

Input	UniProt Id
CAPNS1	P04632, Q96L46

23. Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models (R-HSA-8862803)



Diseases: Alzheimer's disease.

Post-mitotic neurons do not have an active cell cycle. However, deregulation of Cyclin Dependent Kinase-5 (CDK5) activity in these neurons can aberrantly activate various components of cell cycle leading to neuronal death (Chang et al. 2012). Random activation of cell cycle proteins has been shown to play a key role in the pathogenesis of several neurodegenerative disorders (Yang et al. 2003, Lopes et al. 2009). CDK5 is not activated by the canonical cyclins, but binds to its own specific partners, CDK5R1 and CDK5R2 (aka p35 and p39, respectively) (Tsai et al. 1994, Tang et al. 1995). Expression of p35 is nearly ubiquitous, whereas p39 is largely expressed in the central nervous system. A variety of neurotoxic insults such as beta-amyloid (A-beta), ischemia, excitotoxicity and oxidative stress disrupt the intracellular calcium homeostasis in neurons, thereby leading to the activation of calpain, which cleaves p35 into p25 and p10 (Lee et al. 2000). p25 has a six-fold longer half-life compared to p35 and lacks the membrane anchoring signal, which results in its constitutive activation and mislocalization of the CDK5:p25 complex to the cytoplasm and the nucleus. There, CDK5:p25 is able to access and phosphorylate a variety of atypical targets, triggering a cascade of neurotoxic pathways that culminate in neuronal death. One such neurotoxic pathway involves CDK5-mediated random activation of cell cycle proteins which culminate in neuronal death. Exposure of primary cortical neurons to oligomeric beta-amyloid (1-42) hyper-activates CDK5 due to p25 formation, which in turn phosphorylates CDC25A, CDC25B and CDC25C. CDK5 phosphorylates CDC25A at S40, S116 and S261; CDC25B at S50, T69, S160, S321 and S470; and CDC25C at T48, T67, S122, T130, S168 and S214. CDK5-mediated phosphorylation of CDC25A, CDC25B and CDC25C not only increases their phosphatase activities but also facilitates their release from 14-3-3 inhibitory binding. CDC25A, CDC25B and CDC25C in turn activate CDK1, CDK2 and CDK4 kinases causing neuronal death. Consistent with this mechanism, higher CDC25A, CDC25B and CDC25C activities were observed in human Alzheimer's disease (AD) clinical samples, as compared to age-matched controls. Inhibition of CDC25 isoforms confers neuroprotection to beta-amyloid toxicity, which underscores the contribution of this pathway to AD pathogenesis

References

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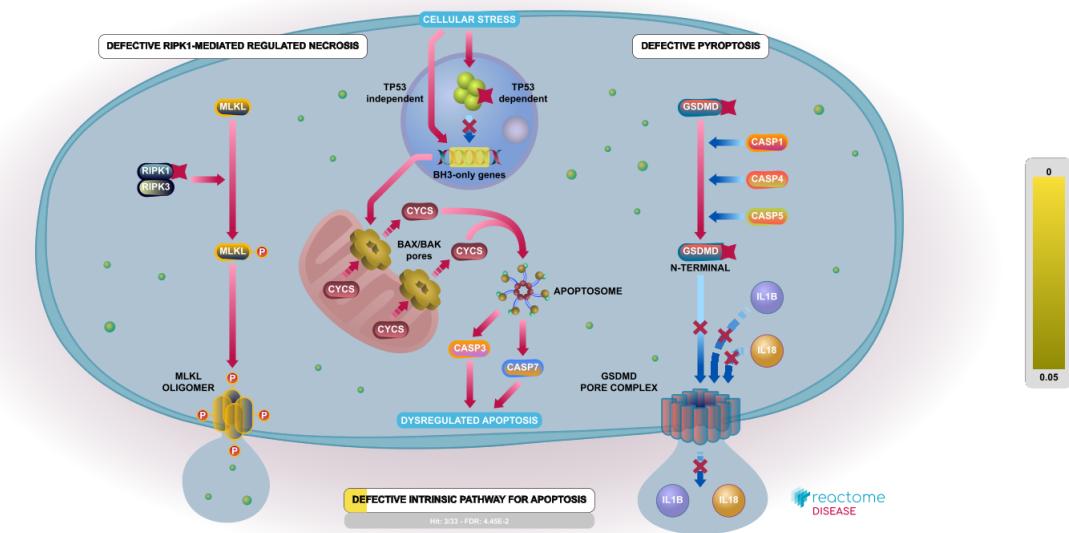
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Date	Action	Author
2016-02-23	Authored	Shah K
2016-03-02	Created	Orlic-Milacic M
2016-05-10	Edited	Orlic-Milacic M
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
CAPNS1	P04632, Q96L46

24. Diseases of programmed cell death (R-HSA-9645723)



Diseases: neurodegenerative disease, cancer.

Programmed cell death is frequently impaired in cancer and is thought to significantly contribute to resistance to chemotherapy. Mutations and perturbations in expression of different proteins involved in programmed cell death, such as TP53 (p53), BH3-only family proteins, caspases and their regulators enable malignant cells to evade apoptosis (Ghavami et al. 2009, Chao et al. 2011, Wong 2011, Fernald and Kurokawa 2013, Ichim and Tait 2016).

References

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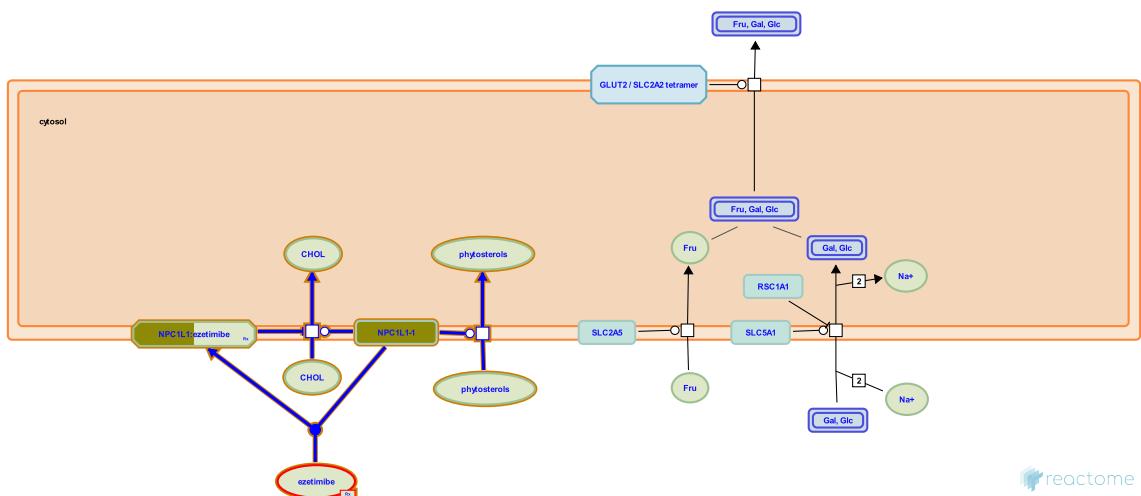
Date	Action	Author
2019-05-17	Created	Orlic-Milacic M
2021-08-16	Modified	Matthews L

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

Input	UniProt Id	Input	UniProt Id
CAPNS1	P04632, Q96L46	CDKN2A	Q8N726

Input	UniProt Id	Input	UniProt Id
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25. Intestinal lipid absorption (R-HSA-8963678)



reactome

Niemann-Pick C1 Like 1 (NPC1L1) protein in enterocytes is critical for intestinal cholesterol and phytosterol absorption, and is the target of the drug ezetimibe (Davis et al. 2004).

References

Iyer SP, Altmann SW, Detmers PA, Lam MH, Maguire M, Yao X, ... Zhu LJ (2004). Niemann-Pick C1 Like 1 (NPC1L1) is the intestinal phytosterol and cholesterol transporter and a key modulator of whole-body cholesterol homeostasis. *J. Biol. Chem.*, 279, 33586-92. [View](#)

Edit history

Date	Action	Author
2008-05-12	Authored	D'Eustachio P
2008-06-13	Reviewed	Jassal B
2017-02-10	Edited	D'Eustachio P
2017-02-10	Created	D'Eustachio P
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id
NPC1L1	Q9UHC9-2

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.

49 of the submitted entities were found, mapping to 66 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ANK2	Q8WXI3	AP2A2	O94973-3	CAPN\$1	P04632, Q96L46
CBX6	O95503	CDC14B	O60729	CDKN2A	P42771, P42772, Q8N726
CECR1	Q9NZK5	DDC	P20711	DGKQ	P52824
EPB41L3	Q9Y2J2	FASN	P49327	FBXW4	P57775
FBXW7	Q969H0-1, Q969H0-4	GCG	P01275	GNB2	P62879
GPC6	Q9Y625	GRIA3	P42263	KCNH2	Q12809
KLHL3	Q9UH77	LSAMP	Q13449	MED19	A0JLT2
MLL4	O14686, Q9UMN6	MLXIPL	Q9NP71	MMP15	P51511
NPC1L1	Q9UHC9-2	NPHP4	O75161	PCSK2	P16519
PDCD7	Q8N8D1	PDK4	Q16654	PI4KA	P42356
PKD1	P98161	PLXNA3	P51805	POLG	P27958
RGL3	Q3MIN7	RNF144A	P50876	RPS4Y1	P22090, Q8TD47
RRP36	Q96EU6	SCARB1	Q8WTV0-2	SLC6A19	Q695T7
SMPD1	P17405	SPG7	Q9UQ90	SSRP1	Q08945
TUBGCP6	Q96RT7	TXNIP	Q9H3M7	UBOX5	O94941
USH1C	Q9Y6N9	UTY	O14607	WDR59	Q6PJI9
WNT4	O96014, P56705				

Input	Ensembl Id	Input	Ensembl Id
CDKN2A	ENSG00000147889, ENST00000304494, ENST00000579755	FASN	ENSG00000169710
GCG	ENSG00000115263	WNT4	ENSG00000162552

7. Identifiers not found

These 23 identifiers were not found neither mapped to any entity in Reactome.

C11orf41	C19orf63	C4orf44	CCDC84	CMIP	FEV	FOXRED1	GPR64
H6PD	KIAA1244	KIAA1324	LOC100130899	PCNXL3	SEPN1	SNX29	SPEF2
SSBP3	STK36	TMEM41A	TPRG1L	UBE4B	WDFY2	ZFR2	