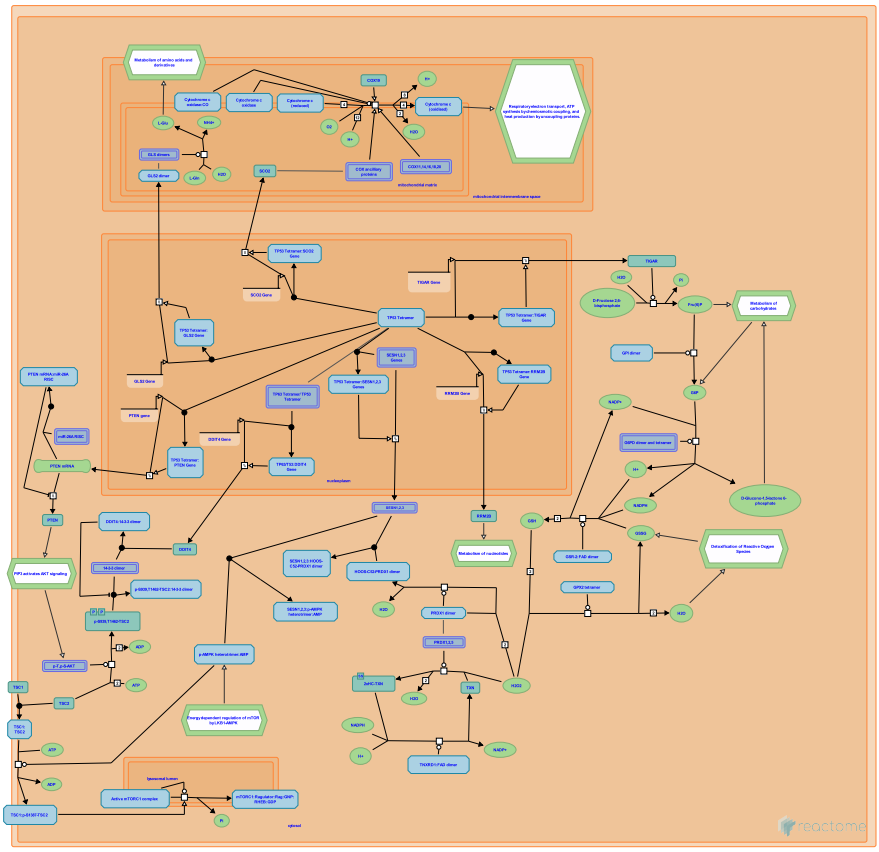
TP53 Regulates Metabolic Genes



Annibali, D., Barrientos, A., Carracedo, A., D'Eustachio, P., Greene, LA., Harris, RA., Hill, DP., Hwang, PM., Inga, A., Jassal, B., Jupe, S., Kang, JG., Katajisto, P., Kavdia, M., Kriplani, N., Leslie, N., Makela, T., Matthews, L., May, B., Nasi, S., Orlic-Milacic, M., Salmena, L., Schmidt, EE., Somers, J., Thorpe, L., Vastrik, I., Wang, PY., Wu, J., Yuzugullu, H., Zaccara, S., Zhao, JJ., Zwartkruis, FJ.

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05/05/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

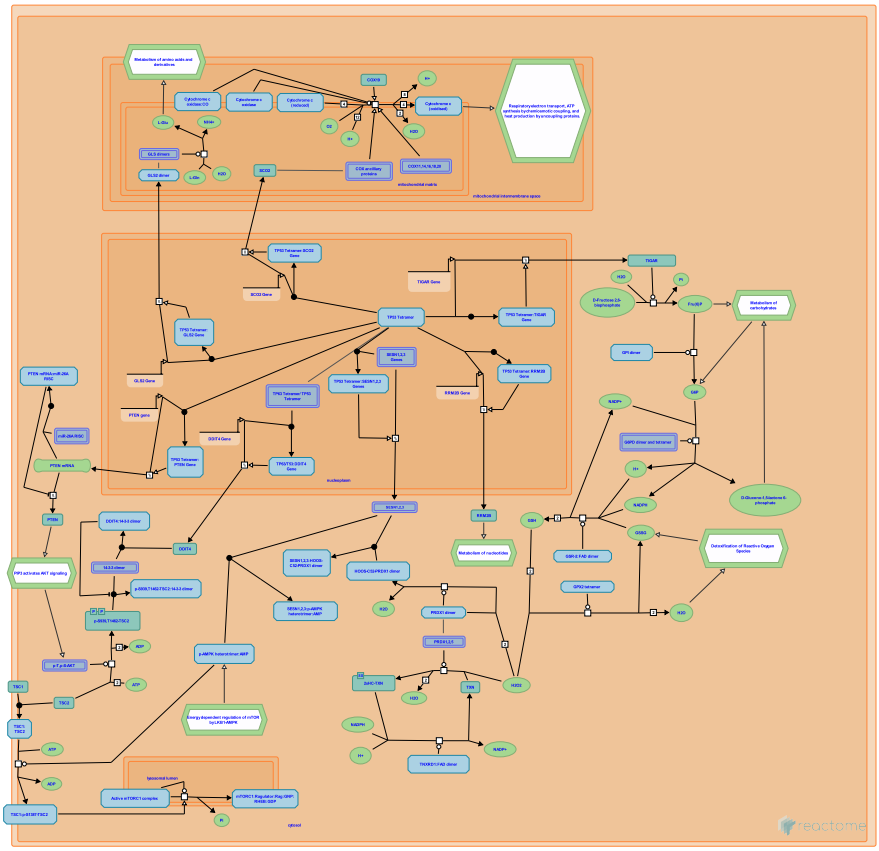
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 1 pathway and 34 reactions (see Table of Contents)

TP53 Regulates Metabolic Genes ↗

Stable identifier: R-HSA-5628897



While the p53 tumor suppressor protein (TP53) is known to inhibit cell growth by inducing apoptosis, senescence and cell cycle arrest, recent studies have found that p53 is also able to influence cell metabolism to prevent tumor development. TP53 regulates transcription of many genes involved in the metabolism of carbohydrates, nucleotides and amino acids, protein synthesis and aerobic respiration.

TP53 stimulates transcription of TIGAR, a D-fructose 2,6-bisphosphatase. TIGAR activity decreases glycolytic rate and lowers ROS (reactive oxygen species) levels in cells (Bensaad et al. 2006). TP53 may also negatively regulate the rate of glycolysis by inhibiting the expression of glucose transporters GLUT1, GLUT3 and GLUT4 (Kondoh et al. 2005, Schwartzenberg-Bar-Yoseph et al. 2004, Kawauchi et al. 2008).

TP53 negatively regulates several key points in PI3K/AKT signaling and downstream mTOR signaling, decreasing the rate of protein synthesis and, hence, cellular growth. TP53 directly stimulates transcription of the tumor suppressor PTEN, which acts to inhibit PI3K-mediated activation of AKT (Stambolic et al. 2001). TP53 stimulates transcription of sestrin genes, SESN1, SESN2, and SESN3 (Velasco-Miguel et al. 1999, Budanov et al. 2002, Brynczka et al. 2007). One of sestrin functions may be to reduce and reactivate overoxidized peroxiredoxin PRDX1, thereby reducing ROS levels (Budanov et al. 2004, Papadia et al. 2008, Essler et al. 2009). Another function of sestrins is to bind the activated AMPK complex and protect it from AKT-mediated inactivation. By enhancing AMPK activity, sestrins negatively regulate mTOR signaling (Budanov and Karin 2008, Cam et al. 2014). The expression of DDIT4 (REDD1), another negative regulator of mTOR signaling, is directly stimulated by TP63 and TP53. DDIT4 prevents AKT-mediated inactivation of TSC1:TSC2 complex, thus inhibiting mTOR cascade (Cam et al. 2014, Ellisen et al. 2002, DeYoung et al. 2008). TP53 may also be involved, directly or indirectly, in regulation of expression of other participants of PI3K/AKT/mTOR signaling, such as PIK3CA (Singh et al. 2002), TSC2 and AMPKB (Feng et al. 2007).

TP53 regulates mitochondrial metabolism through several routes. TP53 stimulates transcription of SCO2 gene, which encodes a mitochondrial cytochrome c oxidase assembly protein (Matoba et al. 2006). TP53 stimulates transcription of RRM2B gene, which encodes a subunit of the ribonucleotide reductase complex, responsible for the conversion of ribonucleotides to deoxyribonucleotides and essential for the maintenance of mitochondrial DNA content in the cell (Tanaka et al. 2000, Bourdon et al. 2007, Kulawiec et al. 2009). TP53 also transactivates mitochondrial transcription factor A (TFAM), a nuclear-encoded gene important for mitochondrial DNA (mtDNA) transcription and maintenance (Park et al. 2009). Finally, TP53 stimulates transcription of the mitochondrial

glutaminase GLS2, leading to increased mitochondrial respiration rate and reduced ROS levels (Hu et al. 2010).

The great majority of tumor cells generate energy through aerobic glycolysis, rather than the much more efficient aerobic mitochondrial respiration, and this metabolic change is known as the Warburg effect (Warburg 1956). Since the majority of tumor cells have impaired TP53 function, and TP53 regulates a number of genes involved in glycolysis and mitochondrial respiration, it is likely that TP53 inactivation plays an important role in the metabolic derangement of cancer cells such as the Warburg effect and the concomitant increased tumorigenicity (reviewed by Feng and Levine 2010). On the other hand, some mutations of TP53 in Li-Fraumeni syndrome may result in the retention of its wild-type metabolic activities while losing cell cycle and apoptosis functions (Wang et al. 2013). Consistent with such human data, some mutations of p53, unlike p53 null state, retain the ability to regulate energy metabolism while being inactive in regulating its classic gene targets involved in cell cycle, apoptosis and senescence. Retention of metabolic and antioxidant functions of p53 protects p53 mutant mice from early onset tumorigenesis (Li et al. 2012).

Literature references

Gelbert, L., Laidlaw, J., Talbott, R., Seizinger, B., Buckbinder, L., Jean, P. et al. (1999). PA26, a novel target of the p53 tumor suppressor and member of the GADD family of DNA damage and growth arrest inducible genes. *Oncogene, 18*, 127-37. ↗

Hwang, PM., Kang, JG., Patino, WD., Gavrilova, O., Boehm, M., Bunz, F. et al. (2006). p53 regulates mitochondrial respiration. *Science, 312*, 1650-3. ↗

Horak, P., Sgroi, D., Ellisen, LW., Sofer, A., DeYoung, MP. (2008). Hypoxia regulates TSC1/2-mTOR signaling and tumor suppression through REDD1-mediated 14-3-3 shuttling. *Genes Dev., 22*, 239-51. ↗

Zambetti, GP., Houghton, PJ., Bid, HK., Cam, H., Xiao, L., Cam, M. (2014). p53/TAp63 and AKT regulate mammalian target of rapamycin complex 1 (mTORC1) signaling through two independent parallel pathways in the presence of DNA damage. *J. Biol. Chem., 289*, 4083-94. ↗

Dehne, N., Brüne, B., Essler, S. (2009). Role of sestrin2 in peroxide signaling in macrophages. *FEBS Lett., 583*, 3531-5. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

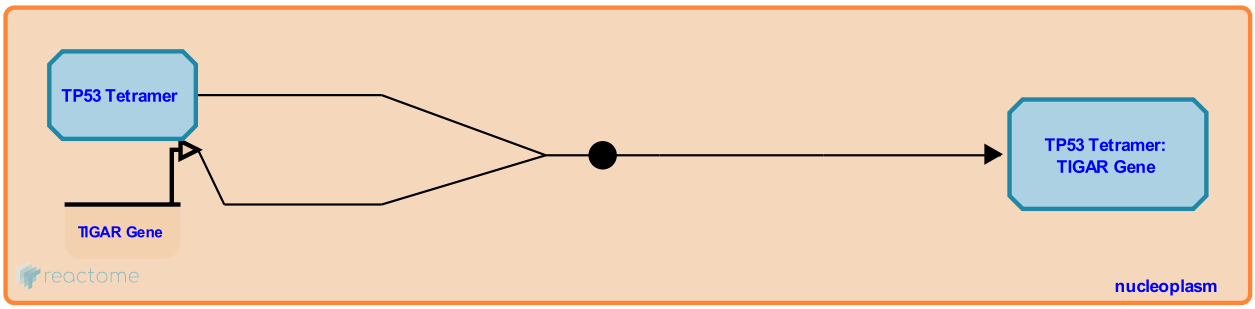
TP53 binds the TIGAR gene ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5628899

Type: binding

Compartments: nucleoplasm



TIGAR gene possesses two TP53 (p53) binding sites, one upstream of the first exon and another within the first intron. TP53 can bind both sites, with a higher affinity for the intronic site (Bensaad et al. 2006).

Followed by: TP53 stimulates TIGAR expression

Literature references

Vidal, MN., Bensaad, K., Selak, MA., Tsuruta, A., Nakano, K., Gottlieb, E. et al. (2006). TIGAR, a p53-inducible regulator of glycolysis and apoptosis. *Cell, 126*, 107-20. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

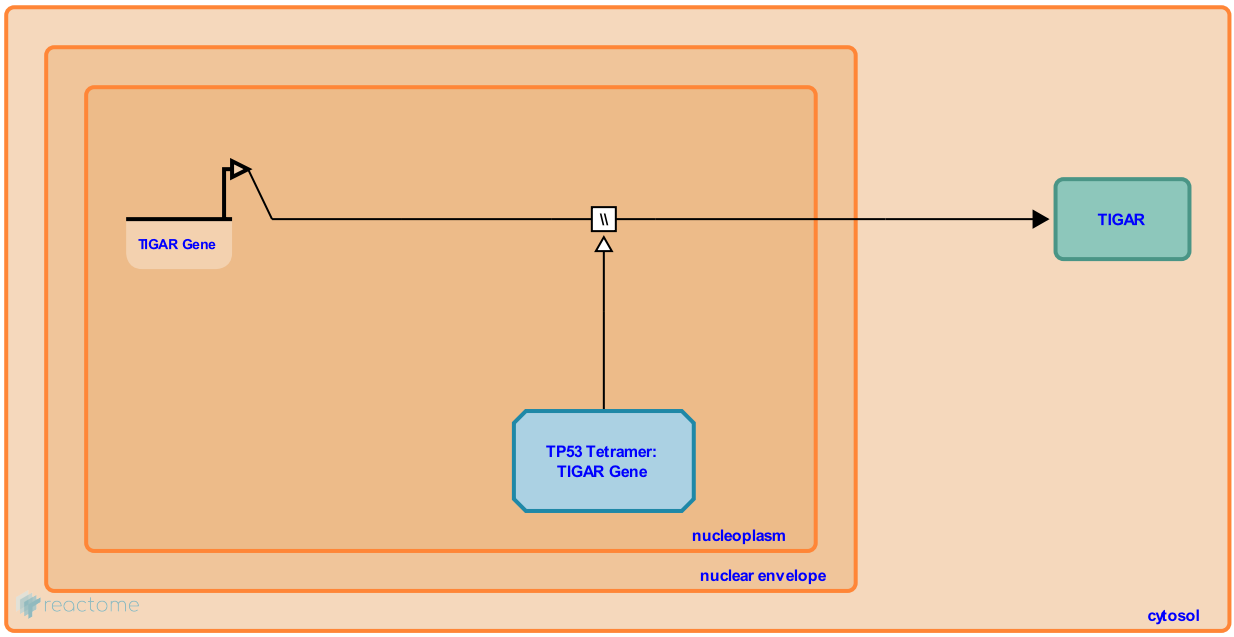
TP53 stimulates TIGAR expression ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5628901

Type: omitted

Compartments: nucleoplasm, cytosol



TIGAR was first identified as a TP53 target through high-throughput gene expression profiling (Jen and Cheung 2005). TP53 stimulates TIGAR transcription, although TIGAR can be regulated through TP53-independent mechanisms, including TP53 family members TP63 (p63) and TP73 (p73). TIGAR is induced by TP53 under low stress levels and decreases under high stress levels (Bensaad et al. 2006). TIGAR functions as a fructose-2,6-bisphosphatase, thereby lowering glycolytic flux and promoting antioxidant functions. By protecting cells from oxidative stress, TIGAR may mediate some of the tumor suppressor activity of p53 but could also contribute to tumorigenesis. (Bensaad, 2006, Lee et al. 2014).

Preceded by: TP53 binds the TIGAR gene

Followed by: TIGAR converts D-fructose-2,6-bisphosphate to D-fructose 6-phosphate

Literature references

Venkatanarayan, A., Raulji, P., Norton, W., Flores, ER. (2016). Novel therapeutic interventions for p53-altered tumors through manipulation of its family members, p63 and p73. *Cell Cycle, 15*, 164-71. ↗

Vidal, MN., Bensaad, K., Selak, MA., Tsuruta, A., Nakano, K., Gottlieb, E. et al. (2006). TIGAR, a p53-inducible regulator of glycolysis and apoptosis. *Cell, 126*, 107-20. ↗

Jen, KY., Cheung, VG. (2005). Identification of novel p53 target genes in ionizing radiation response. *Cancer Res., 65*, 7666-73. ↗

Cheung, EC., Vousden, KH., Lee, P. (2014). TIGAR, TIGAR, burning bright. *Cancer Metab, 2*, 1. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

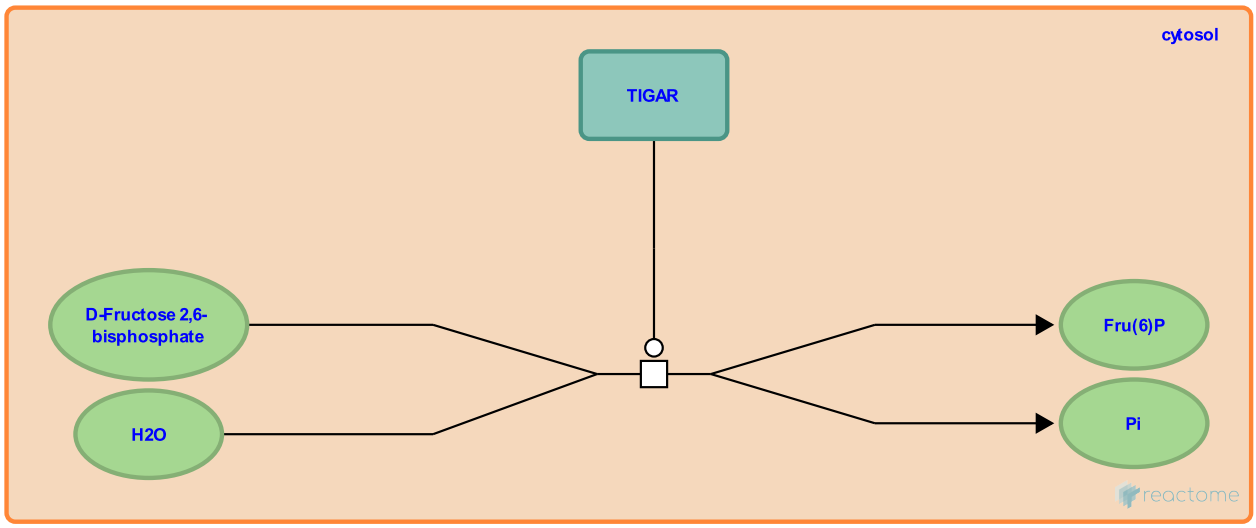
TIGAR converts D-fructose-2,6-bisphosphate to D-fructose 6-phosphate ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5628905

Type: transition

Compartments: cytosol



TIGAR shares similarity with PGMs (phosphoglycerate mutases), especially PFK2 (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase). TIGAR possesses only the bisphosphatase domain and converts D-fructose 2,6-bisphosphate into D-fructose 6-phosphate (Bensaad et al. 2006). Reduction of fructose 2,6-bisphosphate levels correlates with decrease in glycolytic rates, which makes cells more sensitive to apoptotic stimuli (Vander Heiden et al. 2001). Alternatively, fructose 6-phosphate can be isomerized to glucose 6-phosphate, which is diverted to the pentose phosphate pathway, which can have an anti-apoptotic effect (Boada et al. 2000, Perez et al. 2000). In the pentose phosphate pathway, oxidized glutathione is reduced, and this reduced glutathione can then be used by glutathione peroxidase to remove hydrogen peroxide, thereby protecting cells from the oxidative stress (Kletzien et al. 1994, Tian et al. 1999). Indeed, expression of TIGAR increases reduced glutathione to oxidized glutathione ratio and lowers ROS (reactive oxygen species) levels in cells (Bensaad et al. 2006, Lee et al. 2014).

Preceded by: TP53 stimulates TIGAR expression

Followed by: GPI dimer isomerizes Fru(6)P to G6P

Literature references

Braunstein, LD., Apse, K., Stanton, RC., Pang, J., Rose, M., Tian, X. et al. (1999). Importance of glucose-6-phosphate dehydrogenase activity in cell death. *Am. J. Physiol., 276*, C1121-31. ↗

Kletzien, RF., Harris, PK., Foellmi, LA. (1994). Glucose-6-phosphate dehydrogenase: a "housekeeping" enzyme subject to tissue-specific regulation by hormones, nutrients, and oxidant stress. *FASEB J., 8*, 174-81. ↗

Harris, MH., Plas, DR., Vander Heiden, MG., Thompson, CB., Fox, CJ., Rathmell, JC. (2001). Growth factors can influence cell growth and survival through effects on glucose metabolism. *Mol. Cell. Biol., 21*, 5899-912. ↗

Vidal, MN., Bensaad, K., Selak, MA., Tsuruta, A., Nakano, K., Gottlieb, E. et al. (2006). TIGAR, a p53-inducible regulator of glycolysis and apoptosis. *Cell, 126*, 107-20. ↗

Iaccarino, I., Cigliano, L., Martini, G., Filosa, S., Fico, A., Verde, P. et al. (2004). RETRACTED:Glucose-6-phosphate dehydrogenase plays a crucial role in protection from redox-stress-induced apoptosis. *Cell Death Differ., 11*, 823-31. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

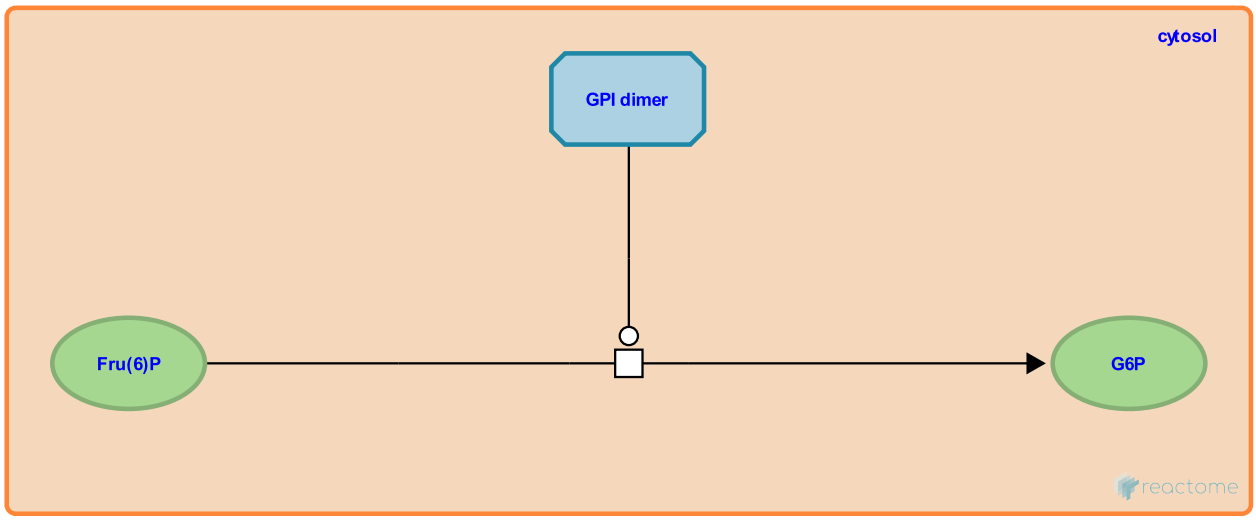
GPI dimer isomerizes Fru(6)P to G6P ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-70475

Type: transition

Compartments: cytosol



The reversible isomerization of Fru(6)P (fructose-6-phosphate) to form G6P (glucose-6-phosphate) is catalyzed by cytosolic GPI (phosphoglucose isomerase) dimer (Noltman 1972; Tsuboi et al. 1958; Xu and Beutler 1994).

Preceded by: TIGAR converts D-fructose-2,6-bisphosphate to D-fructose 6-phosphate

Followed by: alpha-D-glucose 6-phosphate + NADP+ => D-glucono-1,5-lactone 6-phosphate + NADPH + H+

Literature references

Beutler, E., Xu, W. (1994). The characterization of gene mutations for human glucose phosphate isomerase deficiency associated with chronic hemolytic anemia. *J Clin Invest, 94*, 2326-9. ↗

Tsuboi, KK., Hudson, PB., Estrada, J. (1958). Enzymes of the human erythrocyte. IV. Phosphoglucose isomerase, purification and properties. *J Biol Chem, 231*, 19-29. ↗

Boyer, PD. (1972). Aldose-ketose isomerases, The Enzymes, 3rd ed. *Academic Press*, 271-354.

Editions

2003-02-05	Authored	Schmidt, EE.
2008-09-10	Edited	D'Eustachio, P.
2008-09-10	Reviewed	Harris, RA.
2022-08-29	Revised	D'Eustachio, P.
2022-08-29	Reviewed	Hill, DP.

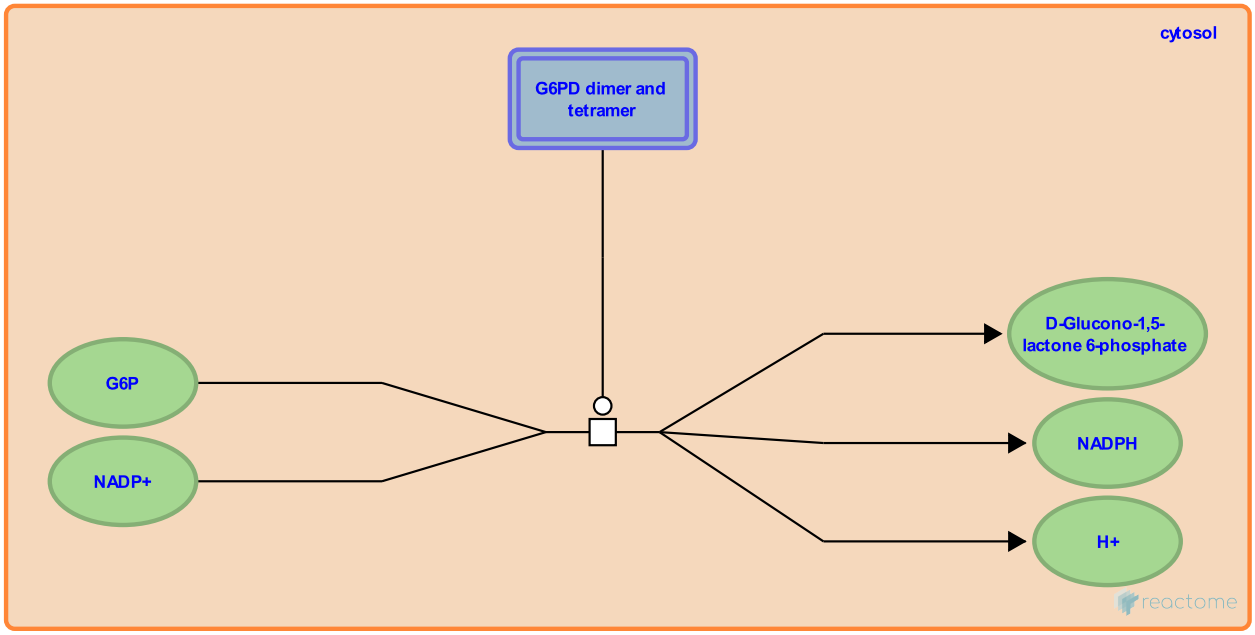
alpha-D-glucose 6-phosphate + NADP+ => D-glucono-1,5-lactone 6-phosphate + NADPH + H+ ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-70377

Type: transition

Compartments: cytosol



Cytosolic glucose-6-phosphate dehydrogenase (G6PD) catalyzes the reaction of glucose 6-phosphate and NADP+ to form D-glucono-1,5-lactone 6-phosphate and NADPH + H+. This constitutes the first committed step of the pentose phosphate pathway and it is critical to the maintenance of NAPDH pool and redox homeostasis. For this reason, anti-cancer therapies are making this step as a prominent target in cancer therapy (Zhang et al. 2014). The reaction is inhibited by high ADP/AMP concentration, and by high NAPDH concentration. Biochemical studies indicate that both G6PD dimers and tetramers are catalytically active and present under physiological conditions in vivo (Au et al. 2000). Mutations that reduce the catalytic efficiency of G6PD are remarkably common in human populations; these appear to have a protective effect against malaria (e.g., Luzzatto and Afolayan 1968).

Preceded by: GPI dimer isomerizes Fru(6)P to G6P

Followed by: glutathione (oxidized) + NADPH + H+ => 2 glutathione (reduced) + NADP+

Literature references

Zhu, Y., Zhang, C., Zhang, Z., Qin, S. (2014). Glucose-6-phosphate dehydrogenase: a biomarker and potential therapeutic target for cancer. *Anticancer Agents Med Chem, 14*, 280-9. ↗

Lam, VM., Adams, MJ., Au, SW., Gover, S. (2000). Human glucose-6-phosphate dehydrogenase: the crystal structure reveals a structural NADP(+) molecule and provides insights into enzyme deficiency. *Structure, 8*, 293-303. ↗

Luzzatto, L., Afolayan, A. (1968). Enzymic properties of different types of human erythrocyte glucose-6-phosphate dehydrogenase, with characterization of two new genetic variants. *J Clin Invest, 47*, 1833-42. ↗

Editions

2003-06-25	Authored	D'Eustachio, P.
2010-01-25	Edited, Revised	D'Eustachio, P.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

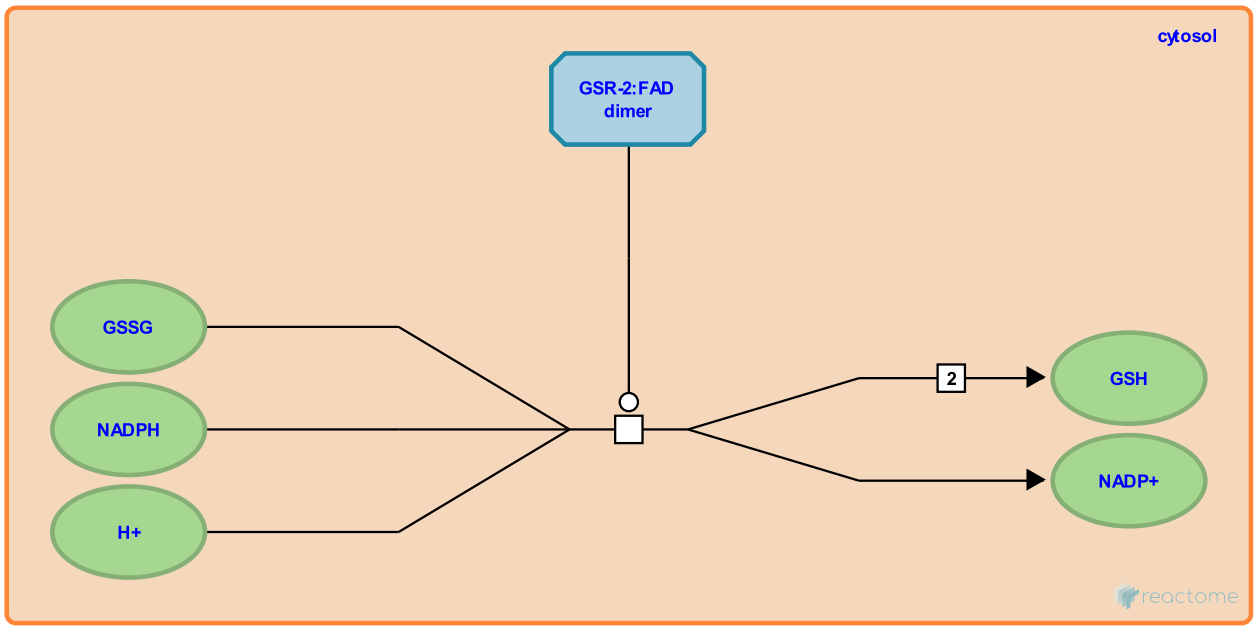
glutathione (oxidized) + NADPH + H+ => 2 glutathione (reduced) + NADP+ ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-71682

Type: transition

Compartments: cytosol



Cytosolic glutathione reductase catalyzes the reaction of glutathione (oxidized) and NADPH + H+ to form two molecules of glutathione (reduced) and NADP+ (Scott et al. 1963, Loos et al. 1976). Deficiency of glutathione reductase can cause hemolytic anemia.

Preceded by: alpha-D-glucose 6-phosphate + NADP+ => D-glucono-1,5-lactone 6-phosphate + NADPH + H+

Literature references

Roos, D., Houwerzijl, J., Weening, R., Loos, H. (1976). Familial deficiency of glutathione reductase in human blood cells. *Blood, 48*, 53-62. ↗

EKSTRAND, V., SCOTT, EM., DUNCAN, IW. (1963). PURIFICATION AND PROPERTIES OF GLUTATHIONE REDUCTASE OF HUMAN ERYTHROCYTES. *J. Biol. Chem., 238*, 3928-33. ↗

Editions

2004-03-17	Authored, Edited	D'Eustachio, P.
2005-04-29	Edited	Vastrik, I.
2010-02-06	Revised	D'Eustachio, P.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

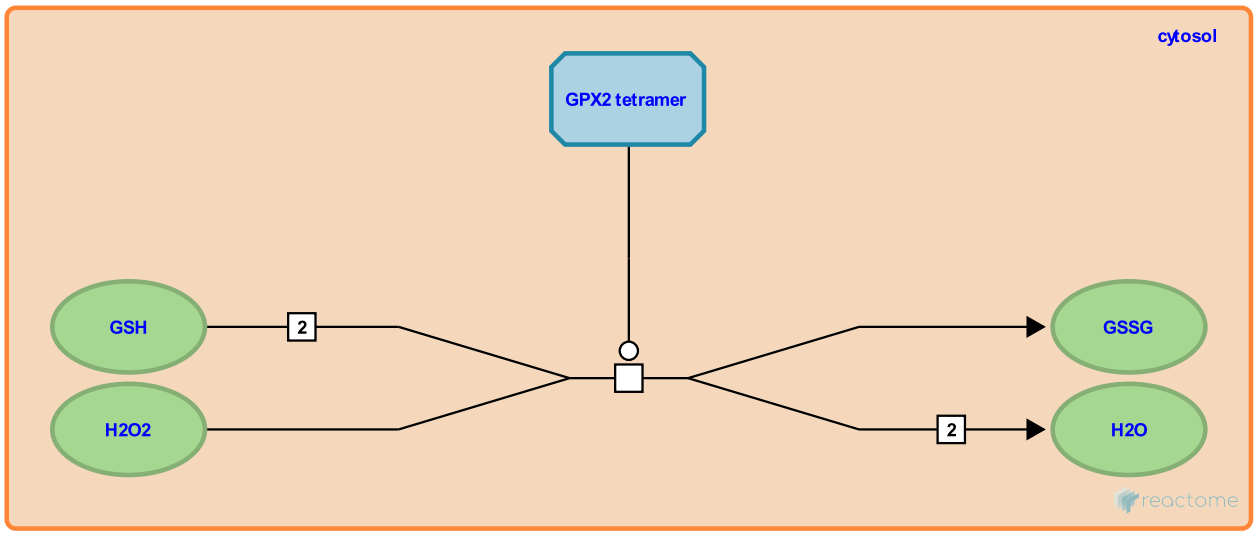
GPX2 catalyzes 2 glutathione, reduced + H2O2 => glutathione, oxidized + 2 H2O ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-3341277

Type: transition

Compartments: cytosol



GPX2 (located in the gastrointestinal tract, also called GSHPx-GI, GPX-GI, and GI-GPx), like glutathione peroxidase 1 (GPX1, ubiquitous), reduces one molecule of hydrogen peroxide (H2O2) with two molecules of glutathione to yield one molecule of oxidized glutathione (glutathione disulfide, GSSG) and two molecules of water (Chu et al. 1998).

Literature references

Esworthy, RS., Chu, FF., Doroshow, JH. (1993). Expression, characterization, and tissue distribution of a new cellular selenium-dependent glutathione peroxidase, GSHPx-GI. *J Biol Chem, 268*, 2571-6. ↗

Editions

2013-05-09	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

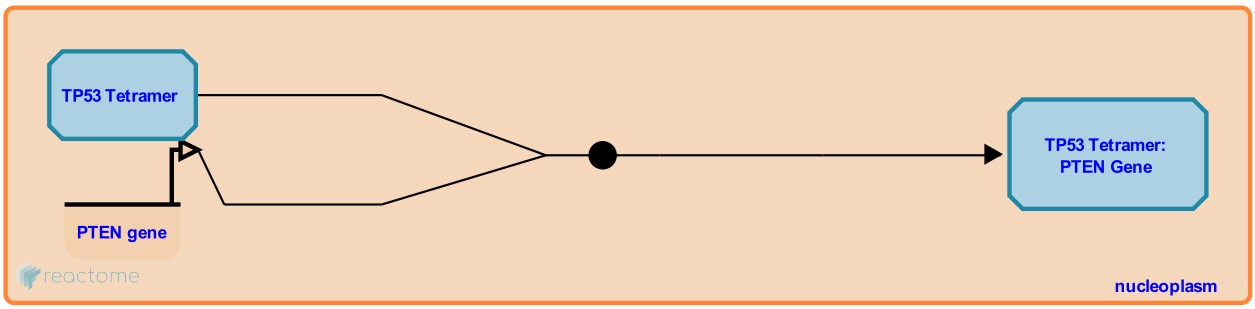
TP53 binds the PTEN promoter ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5632939

Type: binding

Compartments: nucleoplasm



PTEN (phosphatase and tensin homolog deleted in chromosome 10) is a tumor suppressor gene that is deleted or mutated in a variety of human cancers. TP53 (p53) binds to the p53-binding site at the PTEN promoter level (Stambolic et al. 2001).

Literature references

Stambolic, V., Sas, D., Benchimol, S., Snow, B., Jang, Y., MacPherson, D. et al. (2001). Regulation of PTEN transcription by p53. *Mol. Cell, 8*, 317-25. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.
2016-08-11	Reviewed	Carracedo, A., Salmena, L.
2016-09-30	Reviewed	Leslie, N., Kriplani, N.

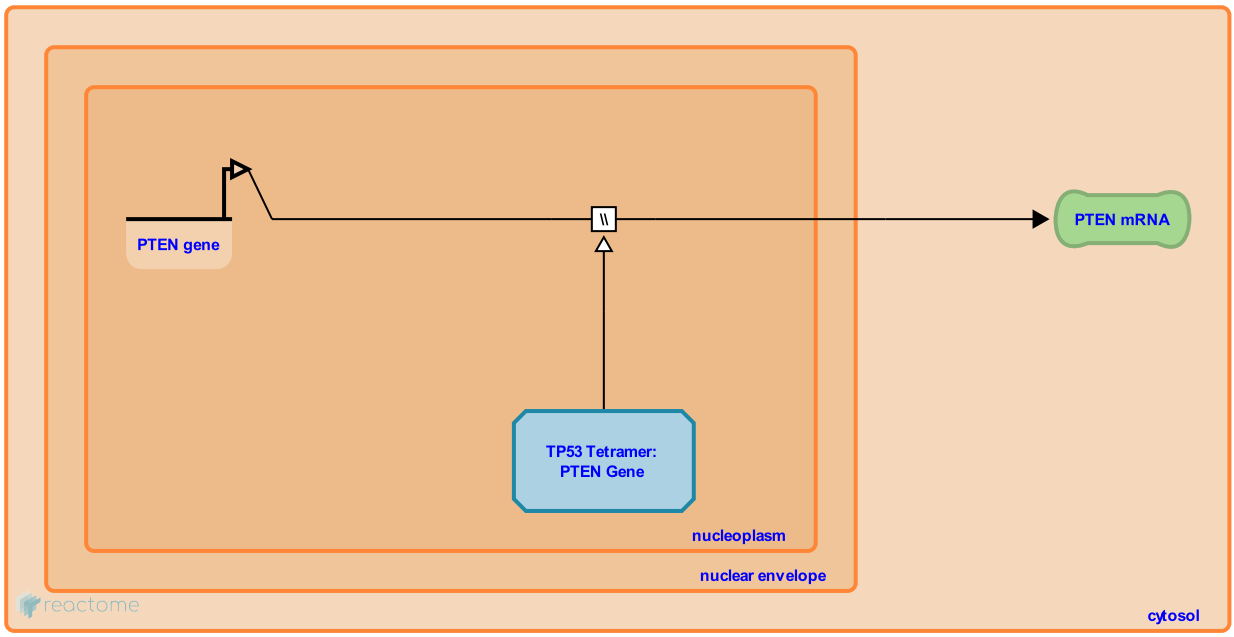
PTEN gene transcription is stimulated by TP53 ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5632993

Type: omitted

Compartments: nucleoplasm, cytosol



PTEN (phosphatase and tensin homolog deleted in chromosome 10) is a tumor suppressor gene that is deleted or mutated in a variety of human cancers. TP53 (p53) stimulates PTEN transcription (Stambolic et al. 2000, Singh et al. 2002). PTEN, acting as a negative regulator of PI3K/AKT signaling, affects cell survival, cell cycling, proliferation and migration. PTEN regulates TP53 stability by inhibiting AKT-mediated activation of TP53 ubiquitin ligase MDM2, and thus enhances TP53 transcriptional activity and its own transcriptional activation by TP53. Beside their cross-regulation, PTEN and TP53 can interact and cooperate to regulate survival or apoptotic phenomena (Stambolic et al. 2000, Singh et al. 2002, Nakanishi et al. 2014).
In response to UV induced DNA damage, PTEN transcription is stimulated by binding of the transcription factor EGR1 to the promoter region of PTEN (Virolle et al. 2001).
PTEN transcription is also stimulated by binding of the activated nuclear receptor PPARG (PPARgamma) to peroxisome proliferator response elements (PPREs) in the promoter of the PTEN gene (Patel et al. 2001), binding of the ATF2 transcription factor, activated by stress kinases of the p38 MAPK family, to ATF response elements in the PTEN gene promoter (Shen et al. 2006) and by the transcription factor MAF1 (Li et al. 2016).
NR2E1 (TLX) associated with transcription repressors binds the evolutionarily conserved TLX consensus site in the PTEN promoter. NR2E1 inhibits PTEN transcription by associating with various transcriptional repressors, probably in a cell type or tissue specific manner. PTEN transcription is inhibited when NR2E1 forms a complex with ATN1 (atrophin-1) (Zhang et al. 2006, Yokoyama et al. 2008), KDM1A (LSD1) histone methyltransferase containing CoREST complex (Yokoyama et al. 2008), or histone deacetylases HDAC3, HDAC5 or HDAC7 (Sun et al. 2007).
Binding of the transcriptional repressor SNAI1 (Snail1) to the PTEN promoter represses PTEN transcription. SNAI1-mediated repression of PTEN transcription may require phosphorylation of SNAI1 on serine residue S246. Binding of SNAI1 to the PTEN promoter increases in response to ionizing radiation and is implicated in SNAI1-mediated resistance to gamma-radiation induced apoptosis (Escriva et al. 2008). Binding of another Slug/Snail family member SNAI2 (SLUG) to the PTEN gene promoter also represses PTEN transcription (Uygur et al. 2015).
Binding of JUN to the AP-1 element in the PTEN gene promoter (Hettinger et al. 2007) inhibits PTEN transcription. JUN partner FOS is not needed for JUN-mediated downregulation of PTEN (Vasudevan et al. 2007).
Binding of the transcription factor SALL4 to the PTEN gene promoter (Yang et al. 2008) and SALL4-medaited recruitment of the transcriptional repressor complex NuRD (Lu et al. 2009, Gao et al. 2013), containing histone deacetylases HDAC1 and HDAC2, inhibits the PTEN gene transcription. SALL4-mediated recruitment of DNA methyltransferases (DNMTs) is also implicated in transcriptional repression of PTEN (Yang et al. 2012).
Binding of the transcription factor MECOM (EVI1) to the PTEN gene promoter and MECOM-mediated recruitment of polycomb repressor complexes containing BMI1 (supposedly PRC1.4), and EZH2 (PRC2) leads to repression of PTEN transcription (Song et al. 2009, Yoshimi et al. 2011).

Followed by: miR-26A microRNAs bind PTEN mRNA

Literature references

O-Charoenrat, P., Walsh, C., Reddy, PG., Chou, TC., Ngai, I., Dao, S. et al. (2002). p53 regulates cell survival by inhibiting PIK3CA in squamous cell carcinomas. *Genes Dev., 16*, 984-93. ↗

Matsuda, S., Kitagishi, Y., Nakanishi, A., Ogura, Y. (2014). The tumor suppressor PTEN interacts with p53 in hereditary cancer (Review). *Int. J. Oncol., 44*, 1813-9. ↗

Stambolic, V., Sas, D., Benchimol, S., Snow, B., Jang, Y., MacPherson, D. et al. (2001). Regulation of PTEN transcription by p53. *Mol. Cell, 8*, 317-25. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A.
2016-02-04	Revised	Orlic-Milacic, M.
2016-02-04	Reviewed	Zaccara, S.

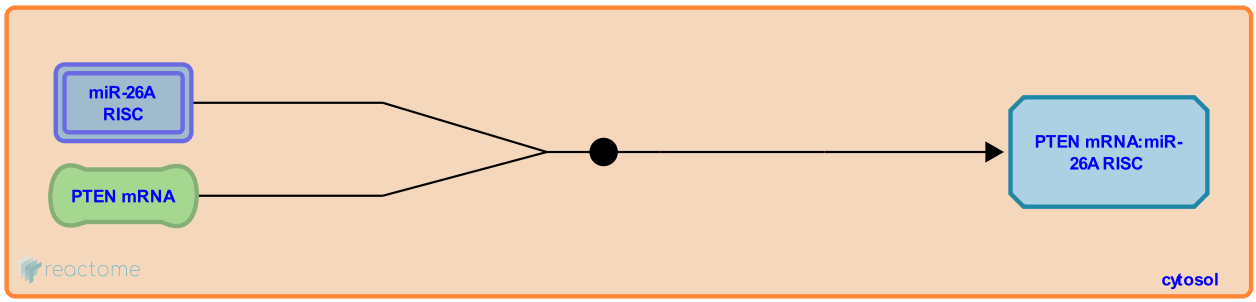
miR-26A microRNAs bind PTEN mRNA ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-2318752

Type: binding

Compartments: cytosol



MIR26A microRNAs, miR-26A1 and miR-26A2, transcribed from genes on chromosome 3 and 12, respectively, bind PTEN mRNA (Huse et al. 2009).

The MIR26A2 locus is frequently amplified in glioma tumors that retain one wild-type PTEN allele. The resulting miR-26A2 overexpression leads to down-regulation of PTEN protein level. Overexpression of miR-26A2 was shown to enhance tumorigenesis and negatively correlates with the loss of heterozygosity at the PTEN locus in a mouse PTEN +/- glioma model, based on monoallelic PTEN loss (Huse et al. 2009, Kim et al. 2010).

Preceded by: PTEN gene transcription is stimulated by TP53

Followed by: PTEN mRNA translation negatively regulated by microRNAs

Literature references

Park, PJ., Johnson, MD., Jiang, X., Kim, H., Huang, W., Pennicooke, B. (2010). Integrative genome analysis reveals an oncomir/oncogene cluster regulating glioblastoma survivorship. *Proc. Natl. Acad. Sci. U.S.A., 107*, 2183-8. ↗

Rouhanifard, SH., le Sage, C., Hambardzumyan, D., Brennan, C., Holland, EC., Sohn-Lee, C. et al. (2009). The PTEN-regulating microRNA miR-26a is amplified in high-grade glioma and facilitates gliomagenesis in vivo. *Genes Dev., 23*, 1327-37. ↗

Editions

2012-07-18	Authored	Orlic-Milacic, M.
2012-08-03	Edited	Matthews, L.
2012-08-13	Reviewed	Zhao, JJ., Yuzugullu, H., Thorpe, L.
2016-08-11	Reviewed	Carracedo, A., Salmena, L.
2016-09-30	Reviewed	Leslie, N., Kriplani, N.

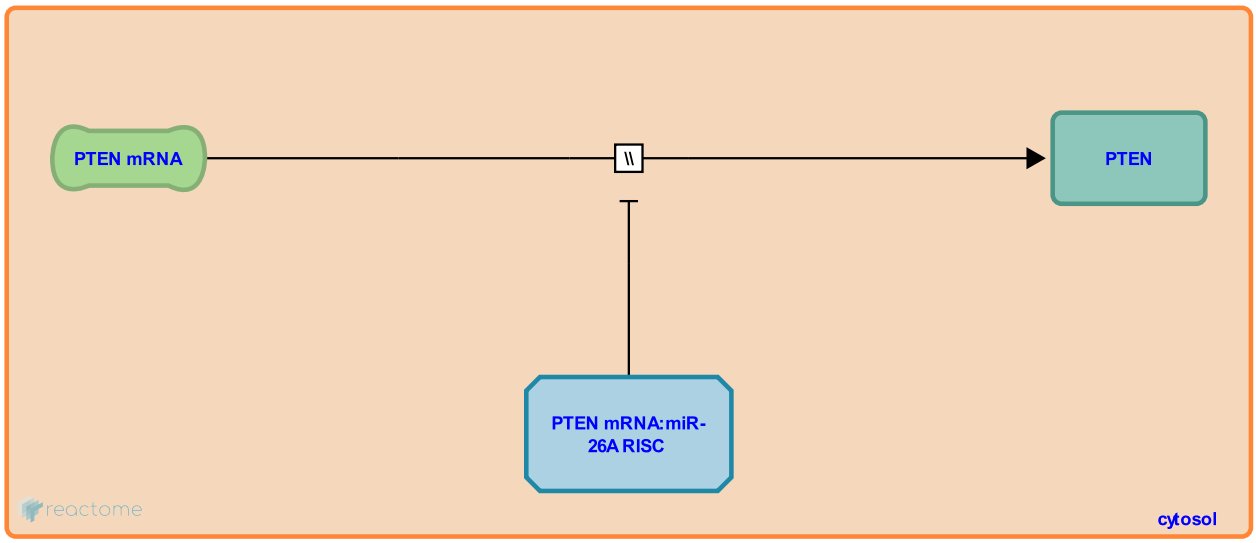
PTEN mRNA translation negatively regulated by microRNAs ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-2321904

Type: omitted

Compartments: cytosol



PTEN protein synthesis is negatively regulated by microRNAs miR-26A1 and miR-26A2, which recruit the RISC complex to PTEN mRNA. Overexpression of miR-26A2, caused by genomic amplification of MIR26A2 locus on chromosome 12, is frequently observed in human brain glioma tumors possessing one wild-type PTEN allele, and is thought to contribute to tumor progression by repressing PTEN protein expression from the remaining allele (Huse et al. 2009). Other microRNAs, which may also be altered in cancer, such as miR-17, miR-19a, miR-19b, miR-20a, miR-20b, miR-21, miR-22, miR-25, miR-93, miR-106a, miR-106b, miR 205, and miR 214, also bind PTEN mRNA and inhibit its translation into protein (Meng et al. 2007, Xiao et al. 2008, Yang et al. 2008, Kim et al. 2010, Poliseno, Salmena, Riccardi et al. 2010, Zhang et al. 2010, Tay et al. 2011, Qu et al. 2012, Cai et al. 2013).

Preceded by: miR-26A microRNAs bind PTEN mRNA

Literature references

Rouhanifard, SH., le Sage, C., Hambardzumyan, D., Brennan, C., Holland, EC., Sohn-Lee, C. et al. (2009). The PTEN-regulating microRNA miR-26a is amplified in high-grade glioma and facilitates gliomagenesis in vivo. *Genes Dev., 23*, 1327-37. ↗

Editions

2012-07-18	Authored	Orlic-Milacic, M.
2012-08-03	Edited	Matthews, L.
2012-08-13	Reviewed	Zhao, JJ., Yuzugullu, H., Thorpe, L.

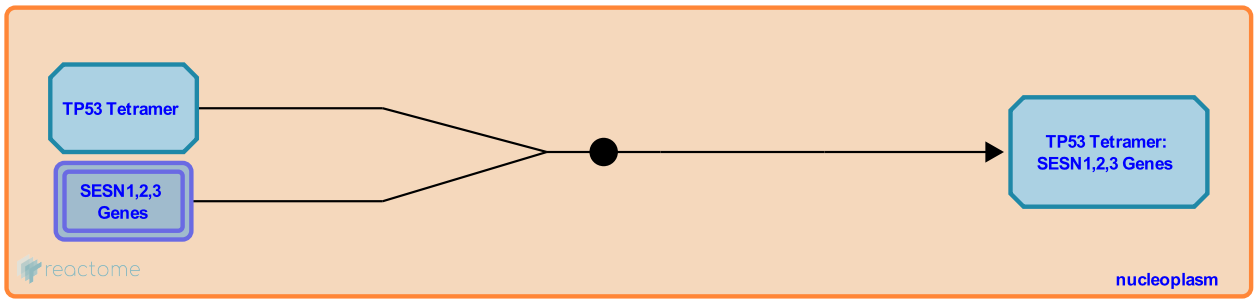
TP53 binds regulatory elements of SESN1,2,3 genes ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5629187

Type: binding

Compartments: nucleoplasm



TP53 (p53) binds to the p53 response element in the intron 2 of SESN1 gene and stimulates transcription of SESN1 transcripts SESN1-1 and SESN1-3, also known as PA26 T2 and PA26 T3 (Velasco-Miguel et al. 1999). Recently, TP53 binding to SESN2 gene regulatory elements has been identified by ChIPseq (Menendez et al. 2013), and SESN2 gene expression was previously shown to be responsive to TP53 (Budanov et al. 2002). Rat ortholog of SESN3 was shown to possess p53 binding sites in the promoter region, but direct binding of TP53 to regulatory elements of human SESN3 has not been examined (Brynczka et al. 2007).

Followed by: TP53 stimulates expression of SESN1,2,3 genes

Literature references

Menendez, D., Anderson, CW., Nguyen, TA., Mathew, VJ., Jothi, R., Freudenberg, JM. et al. (2013). Diverse stresses dramatically alter genome-wide p53 binding and transactivation landscape in human cancer cells. *Nucleic Acids Res., 41*, 7286-301. ↗

Gelbert, L., Laidlaw, J., Talbott, R., Seizinger, B., Buckbinder, L., Jean, P. et al. (1999). PA26, a novel target of the p53 tumor suppressor and member of the GADD family of DNA damage and growth arrest inducible genes. *Oncogene, 18*, 127-37. ↗

Labhart, P., Brynczka, C., Merrick, BA. (2007). NGF-mediated transcriptional targets of p53 in PC12 neuronal differentiation. *BMC Genomics, 8*, 139. ↗

Feinstein, E., Gudkov, AV., Chajut, A., Kamer, I., Kalinski, H., Fishman, A. et al. (2002). Identification of a novel stress-responsive gene Hi95 involved in regulation of cell viability. *Oncogene, 21*, 6017-31. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

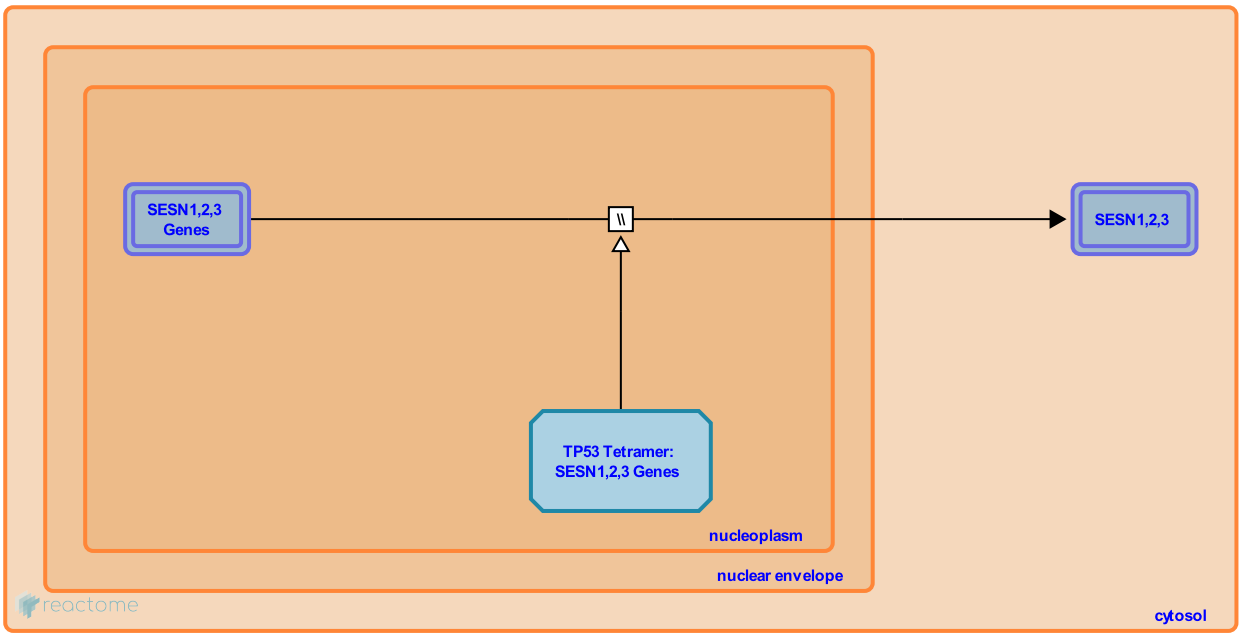
TP53 stimulates expression of SESN1,2,3 genes ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5629189

Type: omitted

Compartments: nucleoplasm



Sestrins (SESN) are a small family of stress-sensitive gene that are conserved across several species. Mammals express three different SESN family members characterized as SESN1-3. Sestrin genes, SESN1, SESN2 and SESN3, are upregulated in response to TP53-mediated transcriptional regulation. SESN1 and SESN2 were classified as members of the growth arrest and DNA damage (GADD) gene family that can regulate cell growth and viability under different cellular pressures. In particular, p53 negatively modulates the mTOR pahtway via SESN1 and SESN2 upregulation (Feng 2010). SESN3 was identified shortly after SESN2 through in silico analysis and was found to be a target of the forkhead transcription factor (FOXO) family. A specific TP53 binding site on the human SESN3 promoter has not been identified yet, but was found in the rat ortholog (Velasco-Miguel et al. 1999, Budanov et al. 2002, Brynczka et al. 2007).

Preceded by: TP53 binds regulatory elements of SESN1,2,3 genes

Followed by: SESN1,2,3 bind AMPK, SESN1,2,3 bind overoxidized PRDX1

Literature references

Gelbert, L., Laidlaw, J., Talbott, R., Seizinger, B., Buckbinder, L., Jean, P. et al. (1999). PA26, a novel target of the p53 tumor suppressor and member of the GADD family of DNA damage and growth arrest inducible genes. *Oncogene, 18*, 127-37. ↗

Feng, Z. (2010). p53 regulation of the IGF-1/AKT/mTOR pathways and the endosomal compartment. *Cold Spring Harb Perspect Biol, 2*, a001057. ↗

Labhart, P., Brynczka, C., Merrick, BA. (2007). NGF-mediated transcriptional targets of p53 in PC12 neuronal differentiation. *BMC Genomics, 8*, 139. ↗

Feinstein, E., Gudkov, AV., Chajut, A., Kamer, I., Kalinski, H., Fishman, A. et al. (2002). Identification of a novel stress-responsive gene Hi95 involved in regulation of cell viability. *Oncogene, 21*, 6017-31. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

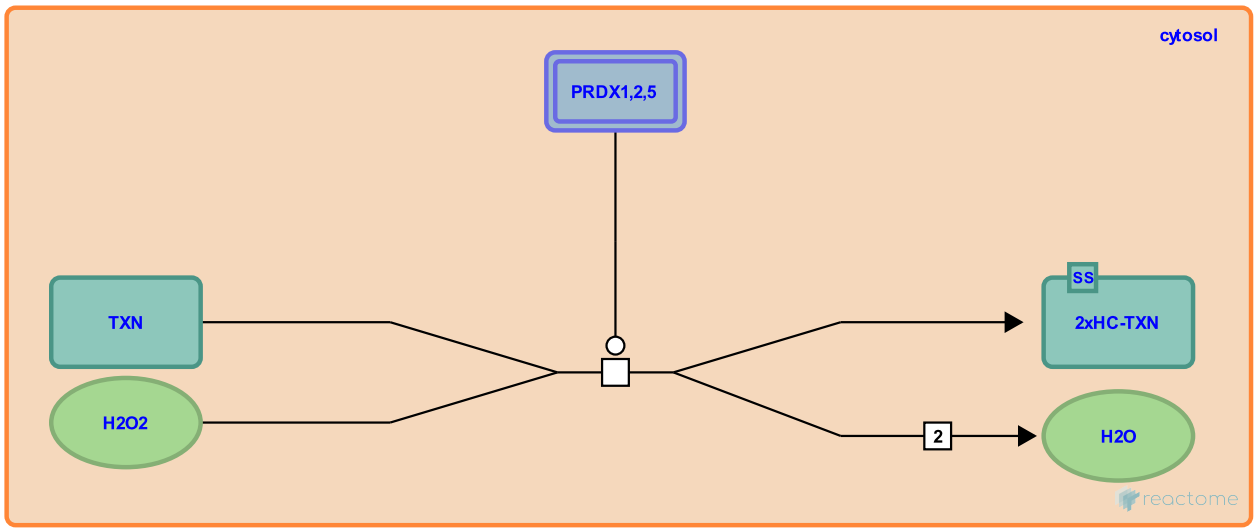
PRDX1,2,5 catalyze TXN reduced + H2O2 => TXN oxidized + 2H2O ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-3341343

Type: transition

Compartments: cytosol



Peroxiredoxin 1 (PRDX1), PRDX2, and PRDX5 in the cytosol reduce hydrogen peroxide (H2O2) with thioredoxin yielding oxidized thioredoxin and water (Yamashita et al. 1999, Lee et al. 2007, Nagy et al. 2011).

Preceded by: thioredoxin, oxidized + NADPH + H+ => thioredoxin, reduced + NADP+

Followed by: PRDX1 overoxidizes

Literature references

Radom, L., Hampton, MB., O'Reilly, RJ., Karton, A., Nagy, P., Pace, P. et al. (2011). Model for the exceptional reactivity of peroxiredoxins 2 and 3 with hydrogen peroxide: a kinetic and computational study. *J. Biol. Chem., 286*, 18048-55. ↗

Subramani, S., London, R., Avraham, S., Rogers, RA., Van Veldhoven, PP., Avraham, H. et al. (1999). Characterization of human and murine PMP20 peroxisomal proteins that exhibit antioxidant activity in vitro. *J. Biol. Chem., 274*, 29897-904. ↗

Riddell, J., Park, JH., Park, YM., Ip, C., Lee, W., Ghosh, D. et al. (2007). Human peroxiredoxin 1 and 2 are not duplicate proteins: the unique presence of CYS83 in Prx1 underscores the structural and functional differences between Prx1 and Prx2. *J. Biol. Chem., 282*, 22011-22. ↗

Editions

2013-05-05	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

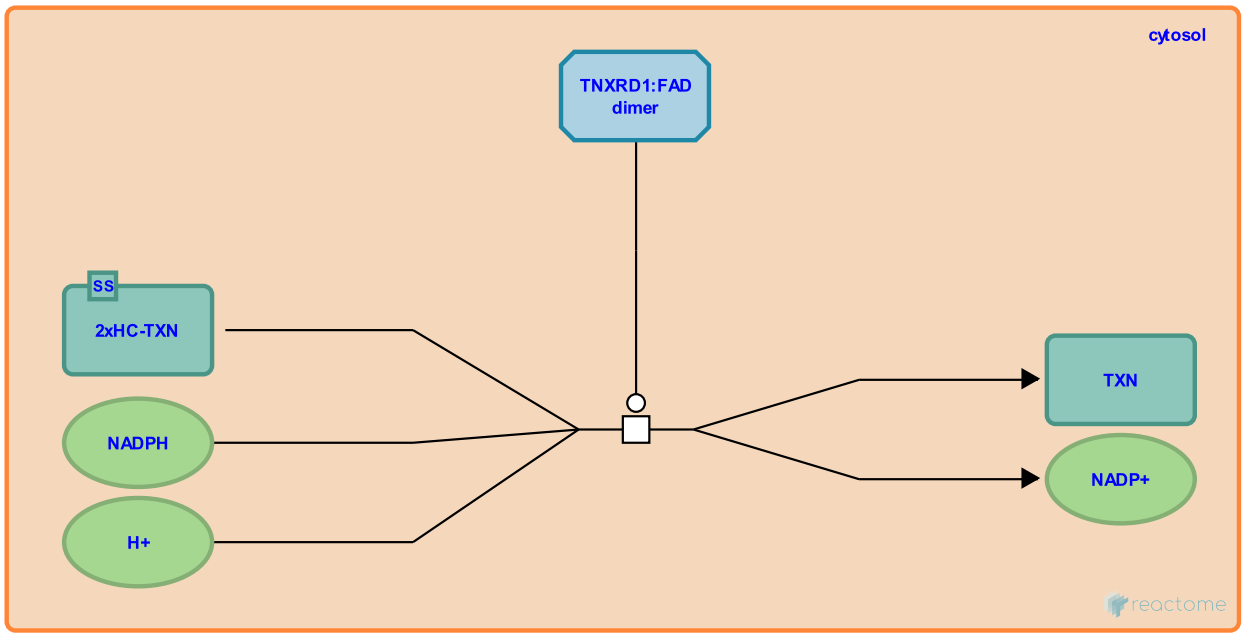
thioredoxin, oxidized + NADPH + H+ => thioredoxin, reduced + NADP+ ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-73646

Type: transition

Compartments: cytosol



Cytosolic thioredoxin reductase catalyzes the reaction of thioredoxin, oxidized and NADPH + H+ to form thioredoxin, reduced and NADP+ (Urig et al. 2006).

Followed by: PRDX1 overoxidizes, PRDX1,2,5 catalyze TXN reduced + H2O2 => TXN oxidized + 2H2O

Literature references

Lieske, J., Urig, S., Irmler, A., Fritz-Wolf, K., Becker, K. (2006). Truncated mutants of human thioredoxin reductase 1 do not exhibit glutathione reductase activity. *FEBS Lett, 580*, 3595-600. ↗

Editions

2003-06-17	Authored, Edited	Jassal, B.
2010-02-06	Edited, Revised	D'Eustachio, P.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

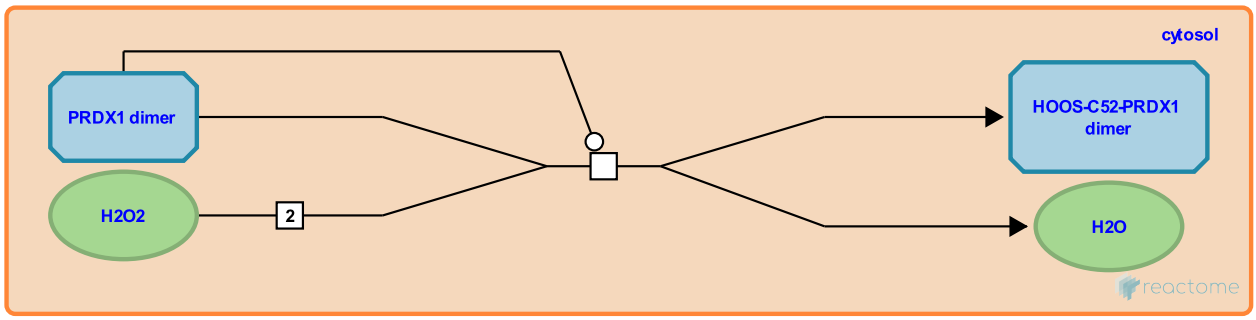
PRDX1 overoxidizes ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5631885

Type: transition

Compartments: cytosol



The activity of eukaryotic PRDX1 gradually decreases with time, which is due to the overoxidation of the catalytic cysteine C52. Normally, oxidized cysteine C52-SOH is generated as a catalytic intermediate, which is subsequently reduced by thioredoxin. Occasionally, further oxidation happens, generating C52-SOOH , where the catalytic cysteine is converted to cysteine-sulfinic acid. This over-oxidation cannot be reversed by thioredoxin (Yang et al. 2002, Budanov et al. 2004). Bacterial peroxiredoxin AhpC does not undergo over-oxidation due to structural difference (Wood et al. 2003).

Preceded by: thioredoxin, oxidized + NADPH + H+ => thioredoxin, reduced + NADP+, PRDX1,2,5 catalyze TXN reduced + H2O2 => TXN oxidized + 2H2O

Followed by: SESN1,2,3 bind overoxidized PRDX1

Literature references

Woo, HA., Kim, K., Yang, KS., Kang, SW., Chae, HZ., Hwang, SC. et al. (2002). Inactivation of human peroxiredoxin I during catalysis as the result of the oxidation of the catalytic site cysteine to cysteine-sulfinic acid. *J. Biol. Chem., 277*, 38029-36. ↗

Wood, ZA., Poole, LB., Karplus, PA. (2003). Peroxiredoxin evolution and the regulation of hydrogen peroxide signaling. *Science, 300*, 650-3. ↗

Feinstein, E., Budanov, AV., Chumakov, PM., Koonin, EV., Sablina, AA. (2004). Regeneration of peroxiredoxins by p53-regulated sestrins, homologs of bacterial AhpD. *Science, 304*, 596-600. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

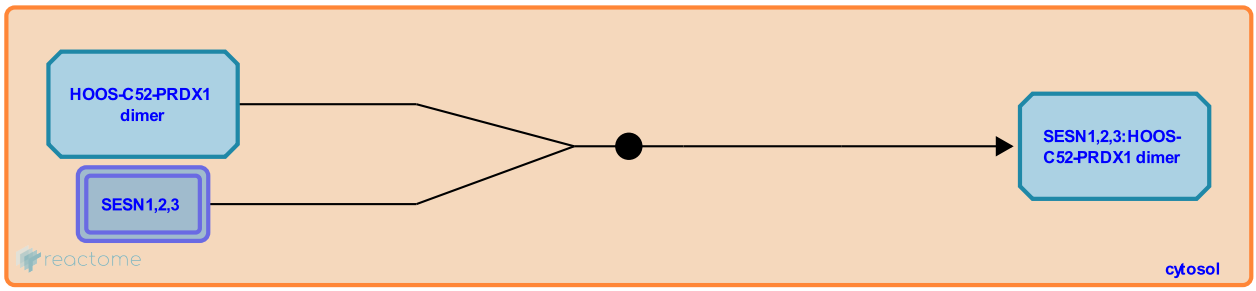
SESN1,2,3 bind overoxidized PRDX1 ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5631903

Type: binding

Compartments: cytosol



Sestrins (SESN1, SESN2 and likely SESN3) bind overoxidized PRDX1, in which the catalytic cysteine C52 has been converted to cysteine-sulfinic acid. Among all peroxiredoxins, PRDX1 is the most abundant member of the PRDX family. The major function is to protect cells against reactive oxygen species (ROS), thus impacting on cell proliferation and survival (Gong et al. 2015). While several reports state that sestrins reduce overoxidized PRDX1 to the catalytically active homodimer (Budanov et al. 2004, Papadia et al. 2008, Essler et al. 2009), there are conflicting reports claiming that sestrins do not possess cysteine sulfinyl reductase activity (Woo et al. 2009).

Preceded by: PRDX1 overoxidizes, TP53 stimulates expression of SESN1,2,3 genes

Literature references

Zhang, M., Gong, F., Liu, H., Hou, G. (2015). Peroxiredoxin 1 promotes tumorigenesis through regulating the activity of mTOR/p70S6K pathway in esophageal squamous cell carcinoma. *Med. Oncol., 32*, 455. ↗

Feinstein, E., Budanov, AV., Chumakov, PM., Koonin, EV., Sablina, AA. (2004). Regeneration of peroxiredoxins by p53-regulated sestrins, homologs of bacterial AhpD. *Science, 304*, 596-600. ↗

Woo, HA., Bae, SH., Park, S., Rhee, SG. (2009). Sestrin 2 is not a reductase for cysteine sulfinic acid of peroxiredoxins . *Antioxid. Redox Signal., 11*, 739-45. ↗

Corriveau, R., Stefovska, V., Hardingham, GE., Hansen, HH., Dakin, KA., McKenzie, G. et al. (2008). Synaptic NMDA receptor activity boosts intrinsic antioxidant defenses. *Nat. Neurosci., 11*, 476-87. ↗

Dehne, N., Brüne, B., Essler, S. (2009). Role of sestrin2 in peroxide signaling in macrophages. *FEBS Lett., 583*, 3531-5. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

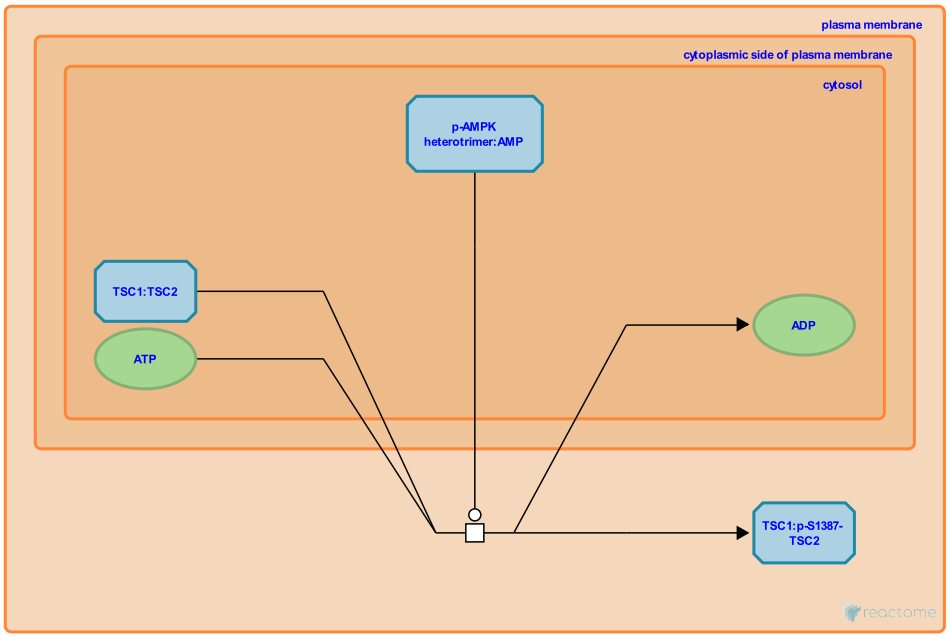
p-AMPK phosphorylates TSC1:TSC2 ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-380927

Type: transition

Compartments: plasma membrane, cytosol



Activated AMPK (phosphorylated on the alpha subunit and with AMP bound) phosphorylates TSC2 (also known as tuberin) on Ser-1387, thereby activating the GTPase activating protein (GAP) activity of the Tuberous Sclerosis Complex (TSC). The TSC tumor suppressor is a critical upstream inhibitor of the mTORC1 complex. TSC is a GTPase-activating protein that stimulates the intrinsic GTPase activity of the small G-protein Rheb. This inactivates Rheb by stimulating its GTPase activity. The GDP-bound form of Rheb looses the ability to activate the kinase activity of the mTORC1 complex (Sancak et al. 2007). Loss of TSC1 or TSC2 leads to hyperactivation of mTORC1.

Phosphorylation of TSC1 and TSC2 serves as an integration point for a wide variety of environmental signals that regulate mTORC1 (Sabatini 2006). Mitogen-activated kinases including Akt, Erk, and Rsk directly phosphorylate TSC2, leading to its inactivation by an unknown mechanism. Another Akt substrate, PRAS40, was recently shown to bind and inhibit the mTORC1 complex. Upon phosphorylation by Akt, PRAS40 no longer inhibits mTORC1 (Sancak et al. 2007; Vander Haar et al. 2007).

Preceded by: Formation of TSC1:TSC2 complex

Literature references

Inoki, K., Guan, KL., Zhu, T. (2003). TSC2 mediates cellular energy response to control cell growth and survival. *Cell, 115*, 577-90. ↗

Editions

2008-11-19	Edited	Jassal, B.
2008-11-19	Authored	Wu, J., Katajisto, P., Makela, T.
2015-04-08	Revised	Jupe, S.
2015-05-14	Reviewed	Zwartkruis, FJ.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

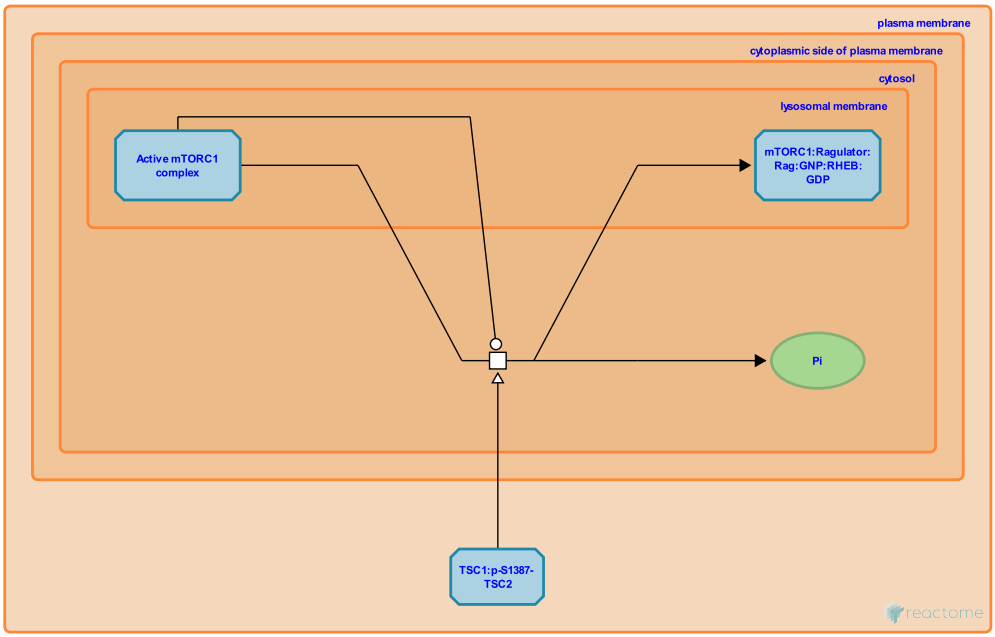
RHEB in mTORC1:RHEB:GTP hydrolyses GTP ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-380979

Type: transition

Compartments: cytosol, lysosomal membrane



TSC2 (in the TSC complex) functions as a GTPase-activating protein and stimulates the intrinsic GTPase activity of the small G-protein Rheb. This results in the conversion of Rheb:GTP to Rheb:GDP. GDP-bound Rheb is unable to activate mTOR (Inoki et al. 2003, Tee et al. 2003). It is not demonstrated that RHEB hydrolyzes GTP when present in the mTORC1 complex; given the low affinity of RHEB for mTOR, it may dissociate from the mTORC1 complex before TSC2 stimulates hydrolysis of GTP; TSC2 may not have access to critical residues of RHEB when present inside mTORC1.

Literature references

Tee, AR., Manning, BD., Cantley, LC., Blenis, J., Roux, PP. (2003). Tuberous sclerosis complex gene products, Tuberin and Hamartin, control mTOR signaling by acting as a GTPase-activating protein complex toward Rheb. *Curr Biol, 13*, 1259-68. ↗

Inoki, K., Guan, KL., Li, Y., Xu, T. (2003). Rheb GTPase is a direct target of TSC2 GAP activity and regulates mTOR signaling. *Genes Dev, 17*, 1829-34. ↗

Editions

2008-11-19	Edited	Jassal, B.
2008-11-19	Authored	Wu, J., Katajisto, P., Makela, T.
2015-04-08	Revised	Jupe, S.
2015-05-14	Reviewed	Zwartkruis, FJ.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

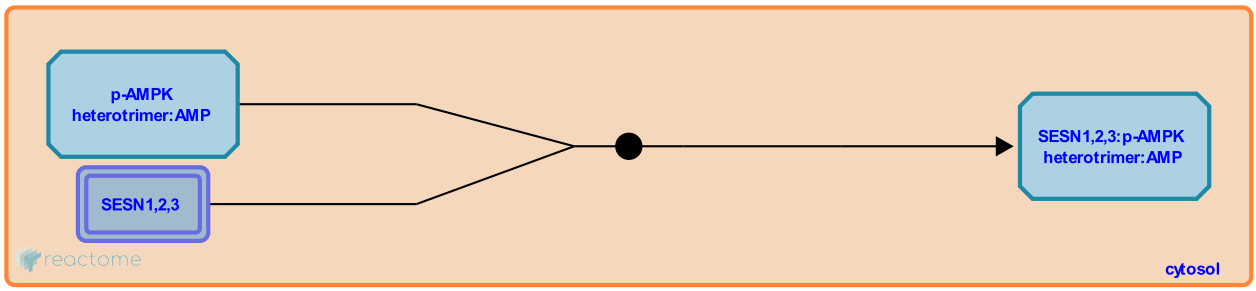
SESN1,2,3 bind AMPK ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5631941

Type: binding

Compartments: cytosol



SESN1, SESN2 and possibly SESN3 are able to bind the AMPK complex and increase its catalytic activity. The exact mechanism has not been elucidated, but recent studies suggest that sestrin-bound AMPK is resistant to inactivation through AKT-induced dephosphorylation (Budanov and Karin 2008, Sanli et al. 2012, Cam et al. 2014).

Preceded by: TP53 stimulates expression of SESN1,2,3 genes

Literature references

Tsakiridis, T., Linher-Melville, K., Singh, G., Sanli, T. (2012). Sestrin2 modulates AMPK subunit expression and its response to ionizing radiation in breast cancer cells. *PLoS ONE, 7*, e32035. ↗

Zambetti, GP., Houghton, PJ., Bid, HK., Cam, H., Xiao, L., Cam, M. (2014). p53/TAp63 and AKT regulate mammalian target of rapamycin complex 1 (mTORC1) signaling through two independent parallel pathways in the presence of DNA damage. *J. Biol. Chem., 289*, 4083-94. ↗

Budanov, AV., Karin, M. (2008). p53 target genes sestrin1 and sestrin2 connect genotoxic stress and mTOR signaling. *Cell, 134*, 451-60. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

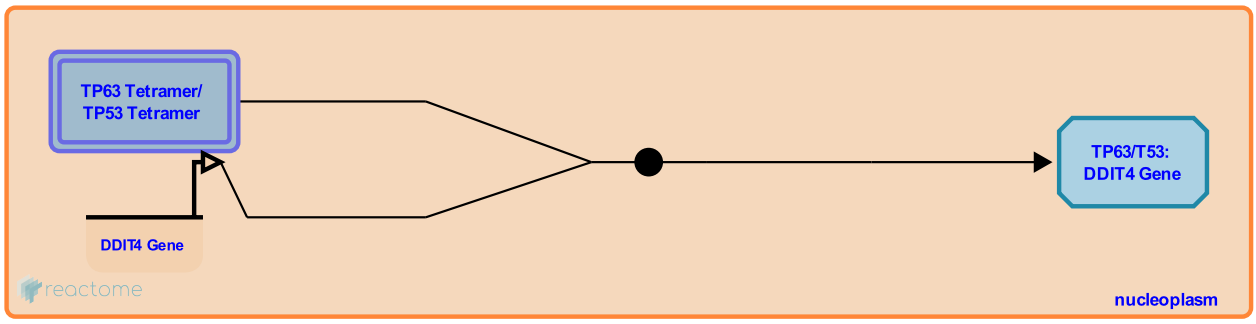
TP63/TP53 bind the DDIT4 gene promoter ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5632393

Type: binding

Compartments: nucleoplasm



DDIT4 (REDD1) gene has a p53 response element immediately upstream of the transcription start site, and this p53 response element is able to bind both TP63 and TP53 transcription factors (Ellisen et al. 2002).

Followed by: TP63/TP53 stimulates transcription of DDIT4 gene

Literature references

Yang, A., Oliner, JD., Minda, K., Ellisen, LW., Haber, DA., McKeon, F. et al. (2002). REDD1, a developmentally regulated transcriptional target of p63 and p53, links p63 to regulation of reactive oxygen species. *Mol. Cell, 10*, 995-1005. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

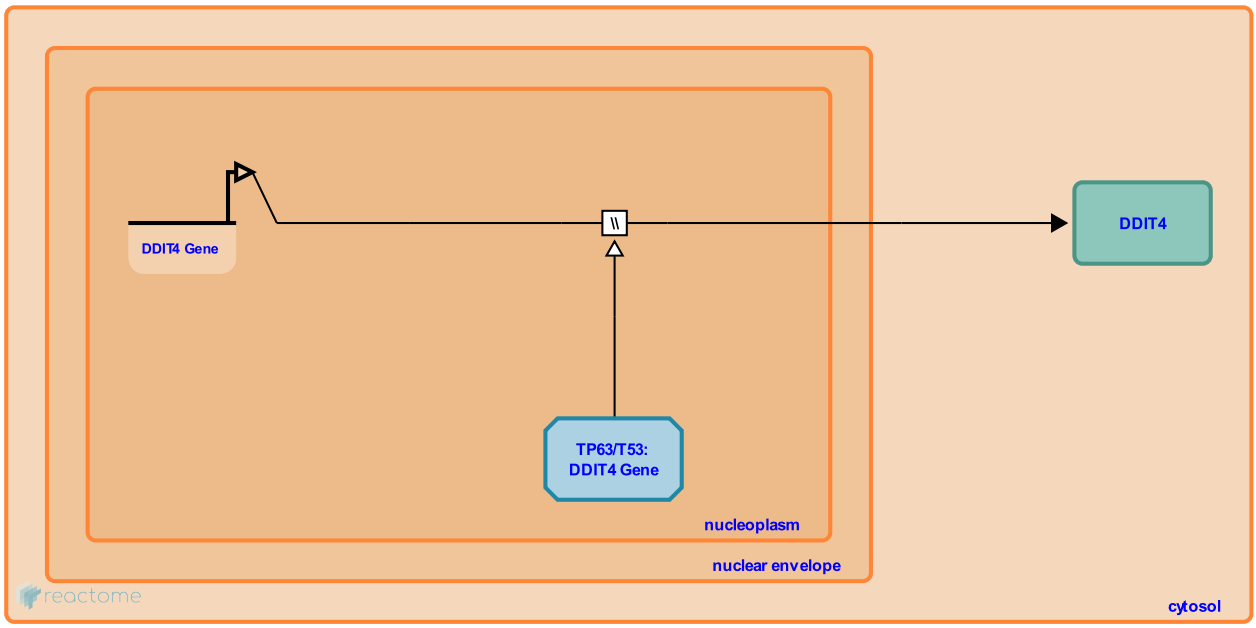
TP63/TP53 stimulates transcription of DDIT4 gene ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5632386

Type: omitted

Compartments: nucleoplasm, cytosol



Transcription of DDIT4 (REDD1) gene is stimulated by TP63, both during mouse embryonal development and under conditions of genotoxic and oxidative stress. TP53 stimulates DDIT4 transcription after TP53 activation by ionizing radiation, but it seems that TP63 is the main activator of DDIT4 transcription under stress conditions (Ellisen et al. 2002).

Preceded by: TP63/TP53 bind the DDIT4 gene promoter

Followed by: DDIT4 binds 14-3-3 dimer

Literature references

Yang, A., Oliner, JD., Minda, K., Ellisen, LW., Haber, DA., McKeon, F. et al. (2002). REDD1, a developmentally regulated transcriptional target of p63 and p53, links p63 to regulation of reactive oxygen species. *Mol. Cell, 10*, 995-1005. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

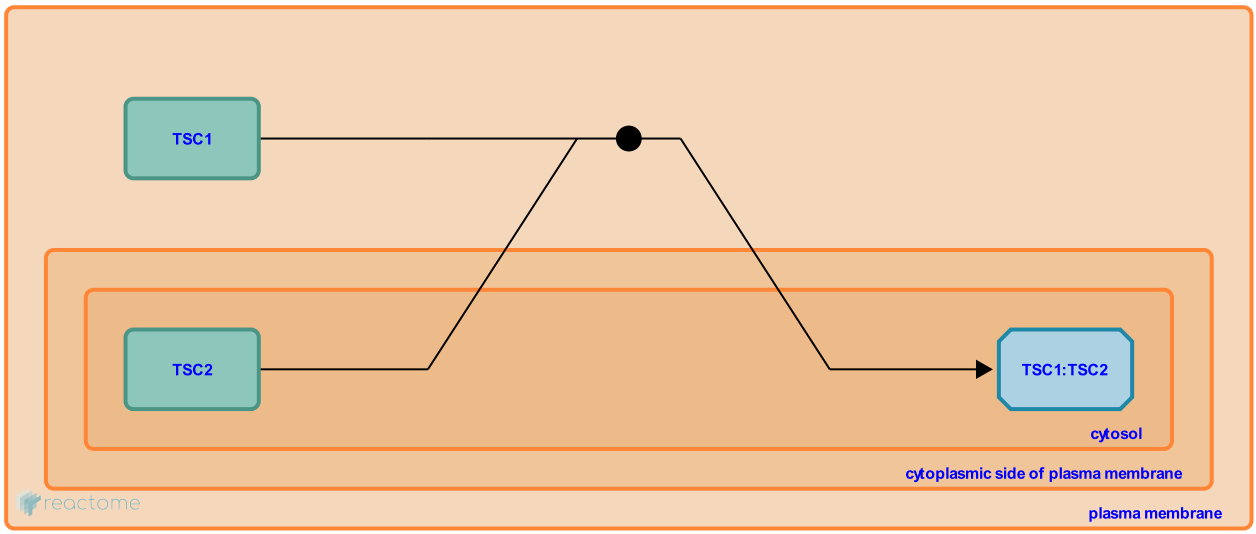
Formation of TSC1:TSC2 complex ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-165179

Type: binding

Compartments: plasma membrane, cytosol



A membrane-associated TSC1 (hamartin) binds TSC2 (tuberin) and recruits it to the plasma membrane where it can exert its function as a GAP (GTPase activating protein) for the small GTPase RHEB (Cai et al. 2006).

Followed by: p-AMPK phosphorylates TSC1:TSC2

Literature references

Kim, J., Guo, R., Walker, CL., Shen, J., Kiguchi, K., Cai, SL. et al. (2006). Activity of TSC2 is inhibited by AKT-mediated phosphorylation and membrane partitioning. *J. Cell Biol., 173*, 279-89. ↗

White, MF., Fisher, TL. (2004). Signaling pathways: the benefits of good communication. *Curr Biol, 14*, R1005-7. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

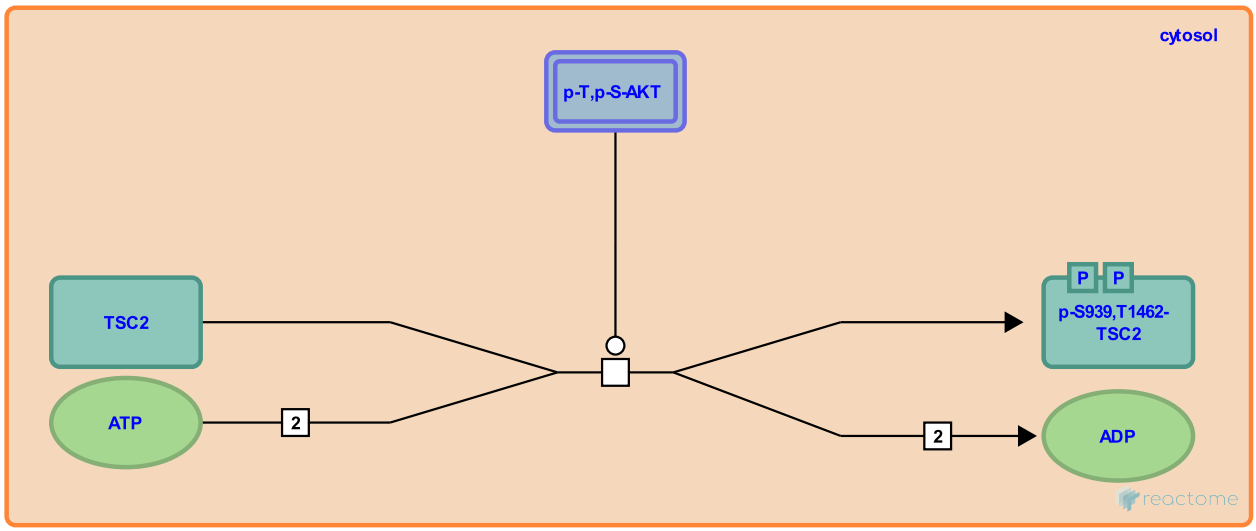
AKT phosphorylates TSC2, inhibiting it ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-198609

Type: transition

Compartments: cytosol



AKT phosphorylates and inhibits TSC2 (tuberin), a suppressor of the TOR kinase pathway, which senses nutrient levels in the environment. TSC2 forms a protein complex with TSC1 and this complex acts as a GAP (GTPase activating protein) for the RHEB G-protein. RHEB, in turn, activates the TOR kinase. Thus, an active AKT1 activates the TOR kinase, both of which are positive signals for cell growth (an increase in cell mass) and division.
The TOR kinase regulates two major processes: translation of selected mRNAs in the cell and autophagy. In the presence of high nutrient levels TOR is active and phosphorylates the 4EBP protein releasing the eukaryotic initiation factor 4E (eIF4E), which is essential for cap-dependent initiation of translation and promoting growth of the cell (PMID: 15314020). TOR also phosphorylates the S6 kinase, which is implicated in ribosome biogenesis as well as in the modification of the S6 ribosomal protein. AKT can also activate mTOR by another mechanism, involving phosphorylation of PRAS40, an inhibitor of mTOR activity.

Followed by: p-S939,T1462-TSC2 binding to 14-3-3 dimer is negatively regulated by DDIT4

Literature references

Inoki, K., Guan, KL., Li, Y., Wu, J., Zhu, T. (2002). TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. *Nat Cell Biol, 4*, 648-57. ↗

Tee, AR., Logsdon, MN., Manning, BD., Blenis, J., Cantley, LC. (2002). Identification of the tuberous sclerosis complex-2 tumor suppressor gene product tuberin as a target of the phosphoinositide 3-kinase/akt pathway. *Mol Cell, 10*, 151-62. ↗

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.
2014-12-23	Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

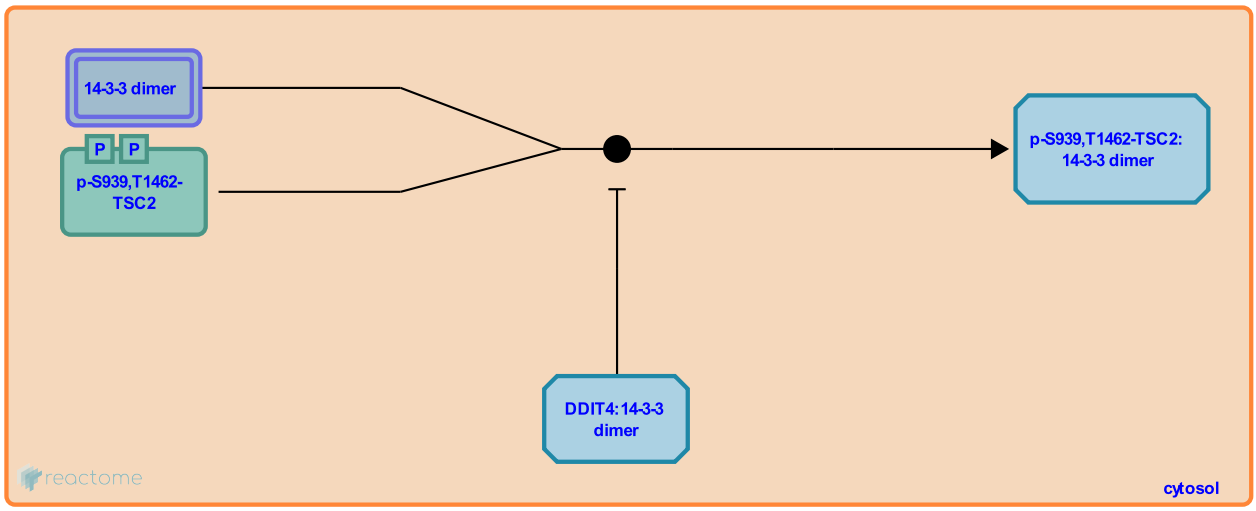
p-S939,T1462-TSC2 binding to 14-3-3 dimer is negatively regulated by DDIT4 ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5632732

Type: binding

Compartments: cytosol



Phosphorylation of TSC2 by AKT enables association of TSC2 with 14-3-3 proteins YWHAB (14-3-3 protein beta/alpha), YWHAQ (14-3-3 protein theta), YWHAG (14-3-3 protein gamma), YWHAH (14-3-3 protein eta), YWHAE (14-3-3 protein epsilon), YWHAZ (14-3-3 protein zeta/delta) or SFN (14-3-3 protein sigma) (Liu et al. 2002). Binding to 14-3-3 proteins sequesters TSC2 to the cytosol and prevents its association with TSC1 (Cai et al. 2006).

Preceded by: AKT phosphorylates TSC2, inhibiting it

Literature references

Liu, MY., Walker, CL., Bedford, MT., Cai, S., Espejo, A. (2002). 14-3-3 interacts with the tumor suppressor tuberin at Akt phosphorylation site(s). *Cancer Res., 62*, 6475-80. ↗

Kim, J., Guo, R., Walker, CL., Shen, J., Kiguchi, K., Cai, SL. et al. (2006). Activity of TSC2 is inhibited by AKT-mediated phosphorylation and membrane partitioning. *J. Cell Biol., 173*, 279-89. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

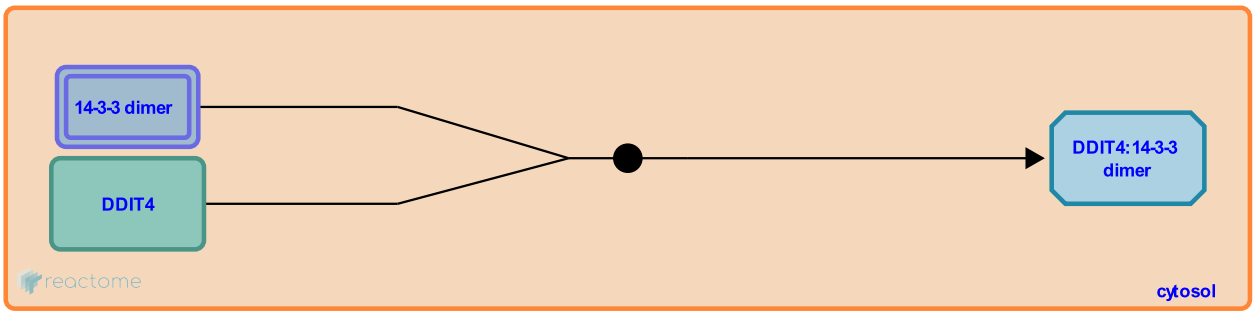
DDIT4 binds 14-3-3 dimer ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5632738

Type: binding

Compartments: cytosol



DDIT4 (REDD1) binds 14-3-3 proteins through a conserved 14-3-3 binding motif Arg-X-X-X-Ser/Thr-X-Pro (DeYoung et al. 2008). Binding of DDIT4 to 14-3-3 proteins competes with 14-3-3 binding to TSC2 and thus prevents AKT-mediated inactivation of TSC2 (Cam et al. 2014).

Preceded by: TP63/TP53 stimulates transcription of DDIT4 gene

Literature references

Zambetti, GP., Houghton, PJ., Bid, HK., Cam, H., Xiao, L., Cam, M. (2014). p53/TAp63 and AKT regulate mammalian target of rapamycin complex 1 (mTORC1) signaling through two independent parallel pathways in the presence of DNA damage. *J. Biol. Chem., 289*, 4083-94. ↗

Horak, P., Sgroi, D., Ellisen, LW., Sofer, A., DeYoung, MP. (2008). Hypoxia regulates TSC1/2-mTOR signaling and tumor suppression through REDD1-mediated 14-3-3 shuttling. *Genes Dev., 22*, 239-51. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

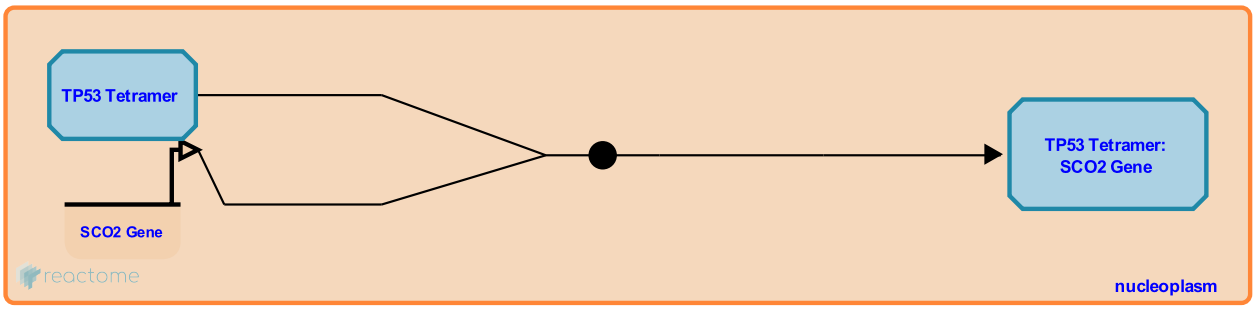
TP53 binds the SCO2 gene ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5632759

Type: binding

Compartments: nucleoplasm



TP53 (p53) binds the p53 response element in the intron 1 of SCO2 (Synthesis of Cytochrome c Oxidase 2) gene (Matoba et al. 2006). The binding of TP53 on SCO2 gene was verified in a genome wide chromatin immunoprecipitation study (Wei et al. 2006). Tp53 was also found to bind to the promoter region in mouse Sco2 gene to stimulate its expression in response to physical exercise (Qi et al. 2011).

Followed by: TP53 stimulates SCO2 gene transcription

Literature references

Hwang, PM., Kang, JG., Patino, WD., Gavrilova, O., Boehm, M., Bunz, F. et al. (2006). p53 regulates mitochondrial respiration. *Science, 312*, 1650-3. ↗

Ng, HH., Lim, B., Chew, JL., Ng, P., Liu, ET., Wei, CL. et al. (2006). A global map of p53 transcription-factor binding sites in the human genome. *Cell, 124*, 207-19. ↗

Ding, S., Qi, Z., Ji, L., Su, Y., He, Q., He, J. et al. (2011). Physical exercise regulates p53 activity targeting SCO2 and increases mitochondrial COX biogenesis in cardiac muscle with age. *PLoS ONE, 6*, e21140. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

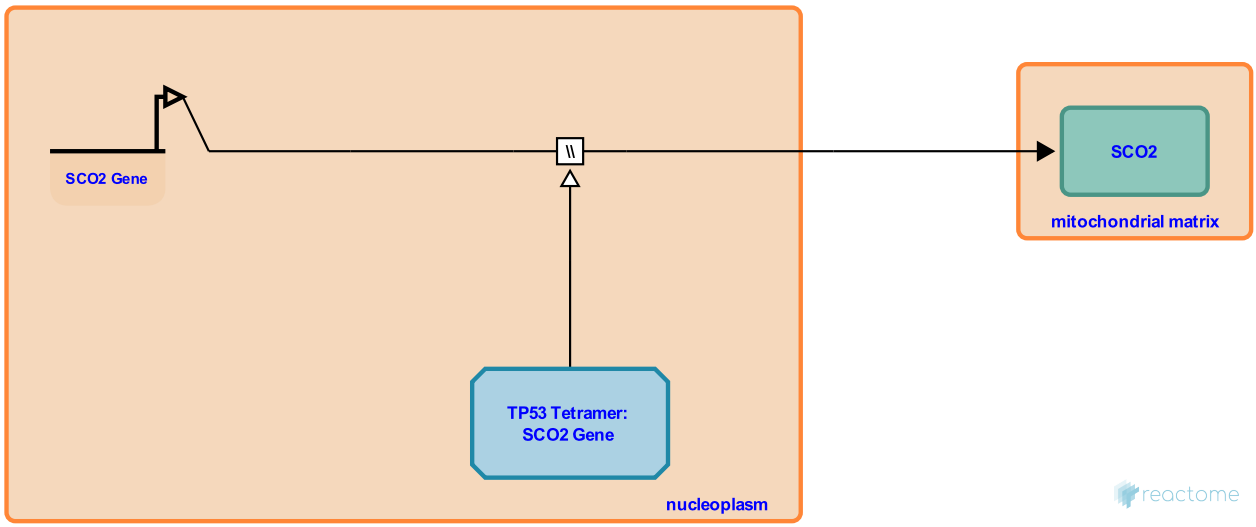
TP53 stimulates SCO2 gene transcription ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5632766

Type: omitted

Compartments: nucleoplasm, mitochondrial matrix



TP53 (p53) directly stimulates transcription of the SCO2 gene. SCO2, synthesis of cytochrome c oxidase 2, is a copper-binding assembly protein for the mitochondrial COX (cytochrome C oxidase) complex which enables aerobic respiration. When SCO2 levels are reduced, as occurs in TP53 deficient cells, the glycolysis becomes the main energy source for the cell. The TP53-mediated regulation of SCO2 and other mitochondrial biogenesis genes provides a possible explanation for the Warburg effect (Warburg 1956) observed in some cancer cells (Matoba et al. 2006).

Preceded by: TP53 binds the SCO2 gene

Literature references

WARBURG, O. (1956). On the origin of cancer cells. *Science, 123*, 309-14. ↗

Hwang, PM., Kang, JG., Patino, WD., Gavrilova, O., Boehm, M., Bunz, F. et al. (2006). p53 regulates mitochondrial respiration. *Science, 312*, 1650-3. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

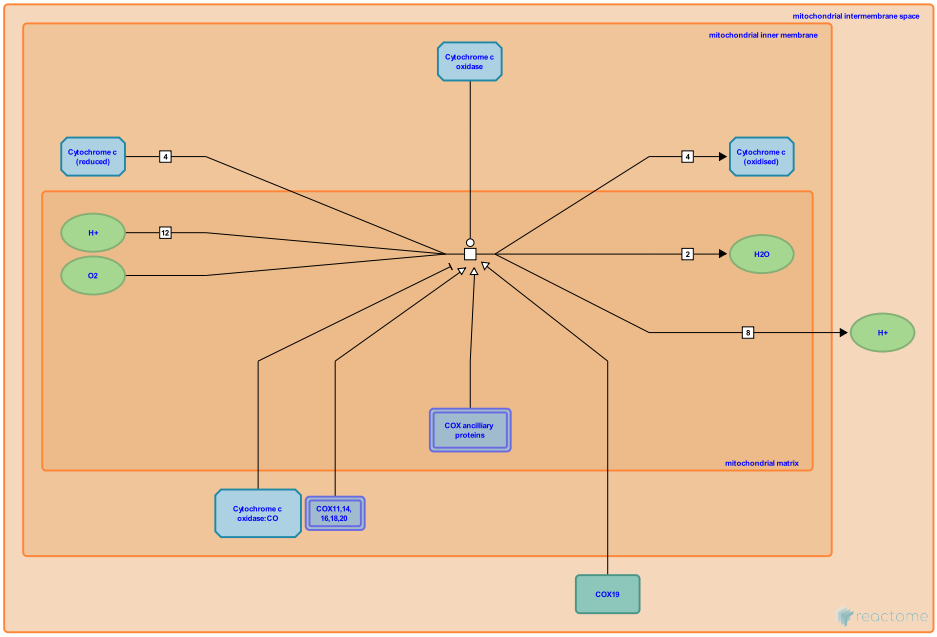
Electron transfer from reduced cytochrome c to molecular oxygen ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-163214

Type: transition

Compartments: mitochondrial matrix, mitochondrial intermembrane space, mitochondrial inner membrane



Complex IV (COX, cytochrome c oxidase) contains the hemeprotein cytochrome a and a3. It also contains copper atoms which undergo a transition from Cu+ to Cu2+ during the transfer of electrons through the complex to molecular oxygen. A bimetallic centre containing a copper atom and a heme-linked iron protein binds oxygen after 4 electrons have been picked up. Water, the final product of oxygen reduction, is then released. Oxygen is the final electron acceptor in the respiratory chain. The overall reaction can be summed as

4Cyt c (red.) + 12H+ (in) + O2 = 4Cyt c (ox.) + 2H2O + 8H+ (out)

Four protons are taken up from the matrix side of the membrane to form the water (scalar protons). Wikstrom (1977) suggests 4 protons are additionally transferred out from the matrix to the intermembrane space.

COX ancillary proteins mediate membrane insertion, catalytic core processing, copper transport and insertion into core subunits and heme A biosynthesis (Stilburek et al. 2006, Fontanesi et al. 2006, Soto et al. 2012). To date, all Mendelian disorders presenting COX deficiency have been assigned to mutations in ancillary factors, with the exception of an infantile encephalomyopathy caused by a defective COX6B1 and an exocrine pancreatic insufficiency caused by a defective COX4I2 gene (Soto et al. 2012). Balsa et al have shown that NDUFA4, formerly considered to be a constituent of NADH dehydrogenase (Complex I), is instead a component of the cytochrome c oxidase (CIV) (Balsa et al. 2012). Patients with NDUFA4 mutations display COX deficiencies (Pitceathly et al. 2013).

Carbon monoxide (CO) readily inhibits oxygen consumption by mitochondrial cytochrome oxidase. This inhibition is responsible for much of its toxicity when it is applied externally to the body. However, CO has been implicated in normal cellular signalling, especially in anti-inflammatory effects. The addition of antioxidants or inhibition of complex III of the electron transport chain by antimycin A attenuates the inhibitory effects of CO on lipopolysaccharide (LPS)-induced NLRP3 formation and TNF-alpha secretion, and blocked CO-induced p38 MAPK phosphorylation. These effects may be mediated via inhibition of cytochrome c oxidase and its generation of mitochondrial reactive oxygen species (Alonso et al, 2003; Zuckerbraun et al, 2007; Cooper and Brown, 2008; Jung et al, 2014; Ishigami et al, 2017).

Literature references

Schultz, BE., Chan, SI. (2001). Structures and proton-pumping strategies of mitochondrial respiratory. *Annu Rev Biophys Biomol Struct, 30*, 23-65. ↗

Soto, IC., Horn, D., Barrientos, A., Fontanesi, F. (2006). Assembly of mitochondrial cytochrome c-oxidase, a complicated and highly regulated cellular process. *Am. J. Physiol., Cell Physiol., 291*, C1129-47. ↗

Hurles, ME., Rahman, S., Taanman, JW., Woodward, CE., Sweeney, MG., Foley, AR. et al. (2013). NDUFA4 mutations underlie dysfunction of a cytochrome c oxidase subunit linked to human neurological disease. *Cell Rep, 3*, 1795-805. ↗

Calvo, E., Balsa, E., Marco, R., Szklarczyk, R., Enríquez, JA., Landázuri, MO. et al. (2012). NDUFA4 is a subunit of complex IV of the mammalian electron transport chain. *Cell Metab., 16*, 378-86. ↗

Wikstrom, MK. (1977). Proton pump coupled to cytochrome c oxidase in mitochondria. *Nature, 266*, 271-3. ↗

Editions

2005-04-25	Edited	Jassal, B.
2005-06-28	Authored	Jassal, B.
2014-09-02	Revised	Barrientos, A.
2015-02-11	Revised	Jassal, B.
2016-02-04	Reviewed	Inga, A., Zaccara, S.
2021-01-23	Reviewed	Somers, J.

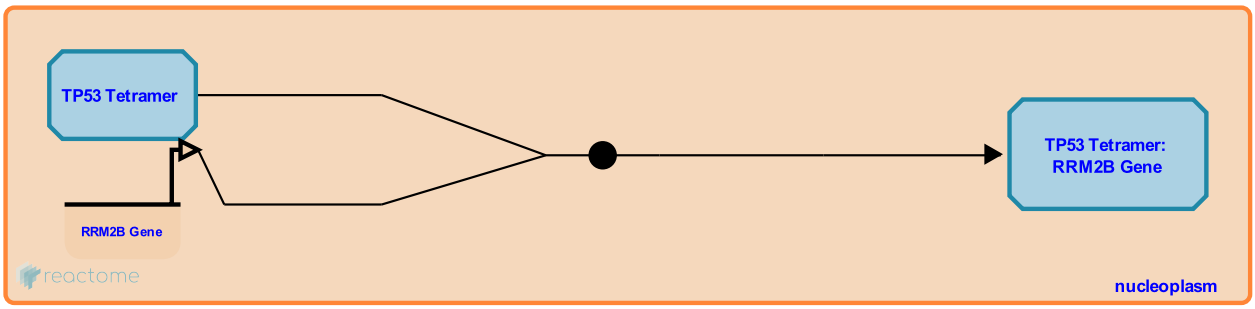
TP53 binds the RRM2B gene ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5632887

Type: binding

Compartments: nucleoplasm



TP53 (p53) binds the p53-binding site in the first intron of RRM2B (p53R2) gene, which encodes a subunit of the ribonucleotide reductase complex (Tanaka et al. 2000). RRM2B is also regulated by TP73 (p73), a p53 family member (Nakano et al. 2000).

Followed by: TP53 stimulates transcription of RRM2B gene

Literature references

Arakawa, H., Nakamura, Y., Matsui, K., Takei, Y., Shiraishi, K., Fukuda, S. et al. (2000). A ribonucleotide reductase gene involved in a p53-dependent cell-cycle checkpoint for DNA damage. *Nature, 404*, 42-49. ↗

Ashcroft, M., Nakano, K., Vousden, KH., Bálint, E. (2000). A ribonucleotide reductase gene is a transcriptional target of p53 and p73. *Oncogene, 19*, 4283-9. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

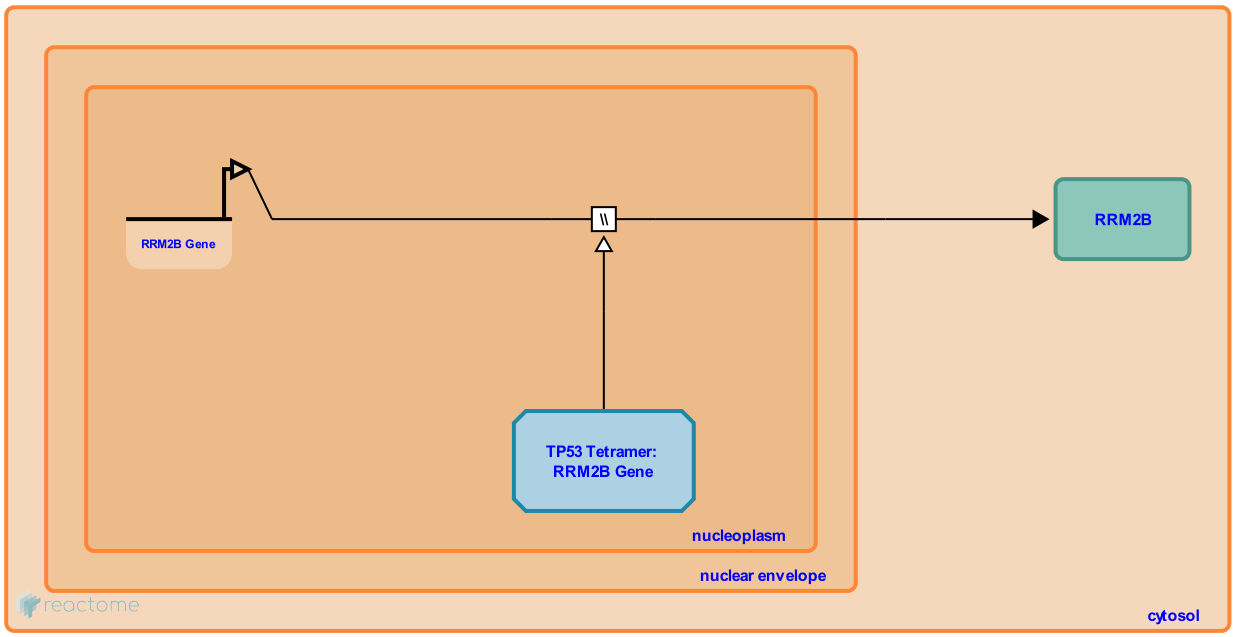
TP53 stimulates transcription of RRM2B gene ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5632892

Type: omitted

Compartments: nucleoplasm



TP53 (p53) directly stimulates transcription of RRM2B gene (p53R2), which encodes a critical subunit of the ribonucleotide reductase complex (Tanaka et al. 2000), responsible for de novo conversion of ribonucleotides (NTPs) to deoxyribonucleotides (dNTPs). This regulation provides a direct mechanism through which TP53 contributes to DNA synthesis/repair. Mutations in RRM2B gene cause severe mitochondrial DNA depletion (Bourdon et al. 2007, Kulawiec et al. 2009).

Preceded by: TP53 binds the RRM2B gene

Literature references

Arakawa, H., Nakamura, Y., Matsui, K., Takei, Y., Shiraishi, K., Fukuda, S. et al. (2000). A ribonucleotide reductase gene involved in a p53-dependent cell-cycle checkpoint for DNA damage. *Nature, 404*, 42-49. ↗

Arakawa, H., Munnich, A., Aubert, S., Serre, V., Chrétien, D., Rötig, A. et al. (2007). Mutation of RRM2B, encoding p53-controlled ribonucleotide reductase (p53R2), causes severe mitochondrial DNA depletion. *Nat. Genet., 39*, 776-80. ↗

Kulawiec, M., Ayyasamy, V., Singh, KK. (2009). p53 regulates mtDNA copy number and mitocheckpoint pathway. *J Carcinog, 8*, 8. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

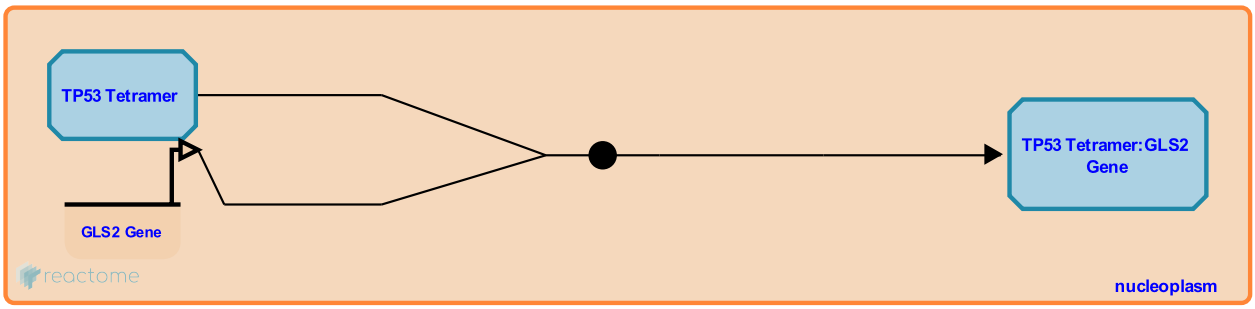
TP53 binds the GLS2 promoter ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5632914

Type: binding

Compartments: nucleoplasm



The mitochondrial glutaminase GLS2 gene possesses two putative p53-binding sites in its promoter and one putative p53 binding site in the first intron. TP53 was demonstrated to bind to p53-response elements in the promoter but not intron 1 of GLS2 (Hu et al. 2010, Suzuki et al. 2010).

Followed by: TP53 stimulates GLS2 transcription

Literature references

Zhang, C., Hu, W., Sun, Y., Wu, R., Levine, A., Feng, Z. (2010). Glutaminase 2, a novel p53 target gene regulating energy metabolism and antioxidant function. *Proc. Natl. Acad. Sci. U.S.A., 107*, 7455-60. ↗

Hosokawa, H., Poyurovsky, MV., Nagano, H., Mayama, T., Tanaka, T., Prives, C. et al. (2010). Phosphate-activated glutaminase (GLS2), a p53-inducible regulator of glutamine metabolism and reactive oxygen species. *Proc. Natl. Acad. Sci. U.S.A., 107*, 7461-6. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

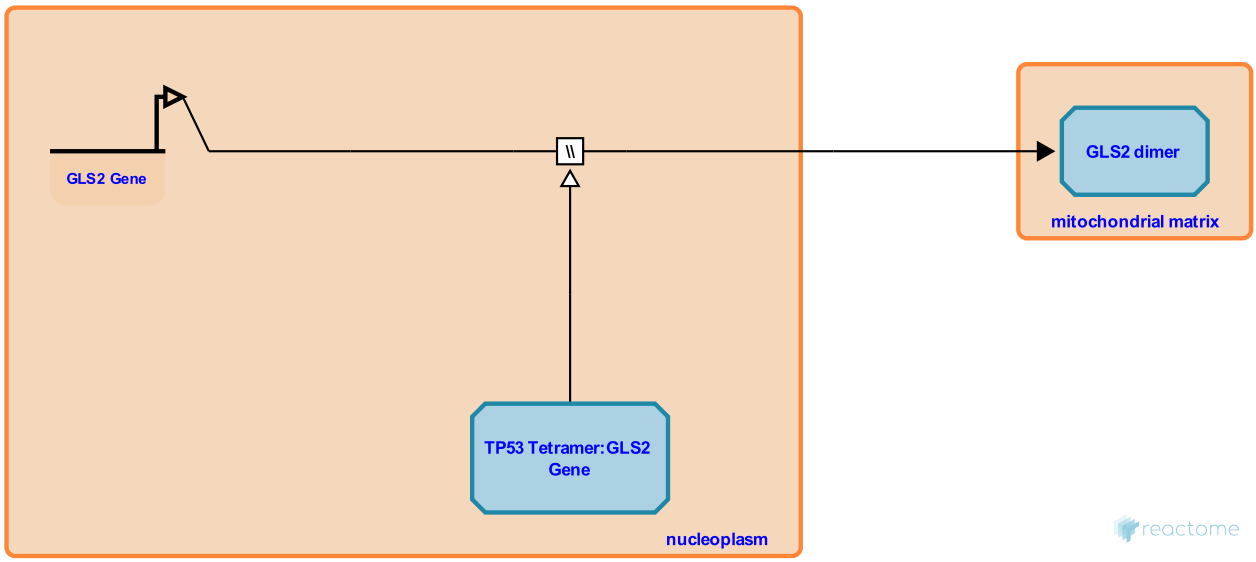
TP53 stimulates GLS2 transcription ↗

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-5632924

Type: omitted

Compartments: nucleoplasm, mitochondrial matrix



TP53 (p53) directly stimulates transcription of mitochondrial glutaminase GLS2 under non-stress and stress conditions. Increased GLS2 levels lead to increased production of glutamate and alpha-ketoglutarate, increased mitochondrial respiration rate, and reduced ROS (reactive oxygen species) load through enhanced glutathione reduction (Hu et al. 2010).

Elevated GLS2 was associated with lower levels of intracellular ROS and a decrease in DNA oxidation. GLS2 knockdown resulted in higher ROS levels and was associated with stimulation of p53-induced cell death (Suzuki et al. 2010).

Preceded by: TP53 binds the GLS2 promoter

Followed by: glutamine + H2O => glutamate + NH4+ [GLS]

Literature references

Zhang, C., Hu, W., Sun, Y., Wu, R., Levine, A., Feng, Z. (2010). Glutaminase 2, a novel p53 target gene regulating energy metabolism and antioxidant function. *Proc. Natl. Acad. Sci. U.S.A., 107*, 7455-60. ↗

Hosokawa, H., Poyurovsky, MV., Nagano, H., Mayama, T., Tanaka, T., Prives, C. et al. (2010). Phosphate-activated glutaminase (GLS2), a p53-inducible regulator of glutamine metabolism and reactive oxygen species. *Proc. Natl. Acad. Sci. U.S.A., 107*, 7461-6. ↗

Editions

2014-12-23	Authored, Edited	Orlic-Milacic, M.
2014-12-30	Reviewed	Hwang, PM., Kang, JG., Wang, PY.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

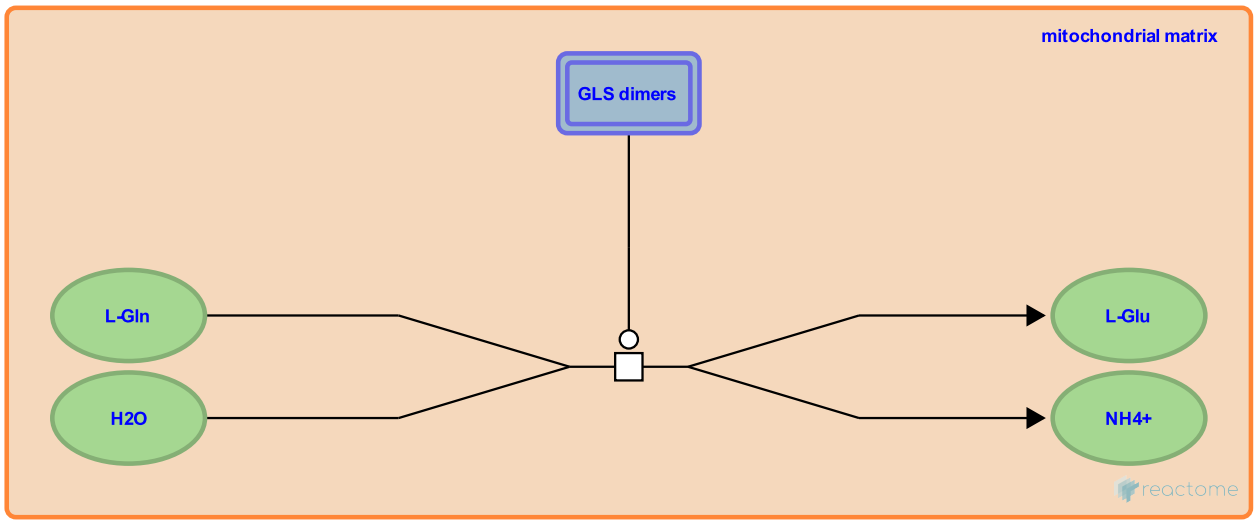
glutamine + H2O => glutamate + NH4+ [GLS]

Location: TP53 Regulates Metabolic Genes

Stable identifier: R-HSA-70609

Type: transition

Compartments: mitochondrial matrix



Mitochondrial glutaminase (GLS) catalyzes the hydrolysis of glutamine to yield glutamate and ammonia. Two GLS enzymes have been identified, one abundantly expressed in the liver (GLS - Elgadi et al. 1999) and one abundantly expressed in kidney (GLS2 - Gomez-Fabre et al. 2000). Their biochemical properties are similar. The enzymes are inferred to function as dimers based on unpublished crystallographic data for GLS (PDB 3CZD) and studies of glutaminase enzyme purified from Ehrlich Ascites cells (Quesada et al. 1988).

Preceded by: TP53 stimulates GLS2 transcription

Literature references

Aledo, JC., Alonso, FJ., Gomez-Fabre, PM., Nunez De Castro, I., Marquez, J., Campos, JA. et al. (2000). Molecular cloning, sequencing and expression studies of the human breast cancer cell glutaminase. *Biochem J, 345*, 365-75.

Medina, MA., Nunez De Castro, I., Marquez, J., Quesada, AR., Sánchez-Jiménez, F., Perez-Rodriguez, J. (1988). Purification of phosphate-dependent glutaminase from isolated mitochondria of Ehrlich ascites-tumour cells. *Biochem J, 255*, 1031-5.

Souba, WW., Elgadi, KM., Qian, M., Meguid, RA., Abcouwer, SF. (1999). Cloning and analysis of unique human glutaminase isoforms generated by tissue-specific alternative splicing. *Physiol Genomics, 1*, 51-62.

Editions

2003-05-04	Authored	D'Eustachio, P.
2010-04-30	Edited	D'Eustachio, P.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

Table of Contents