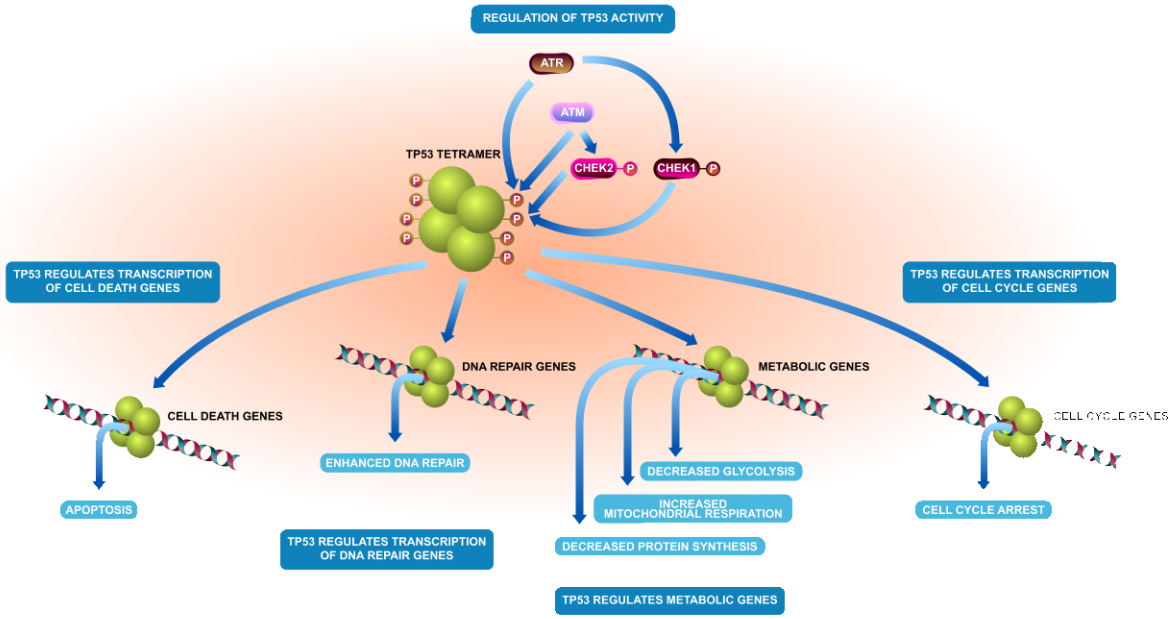
Transcriptional Regulation by TP53



Hwang, PM., Inga, A., Kang, JG., Orlic-Milacic, M., Wang, PY., Zaccara, S.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

15/09/2021

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. ↗

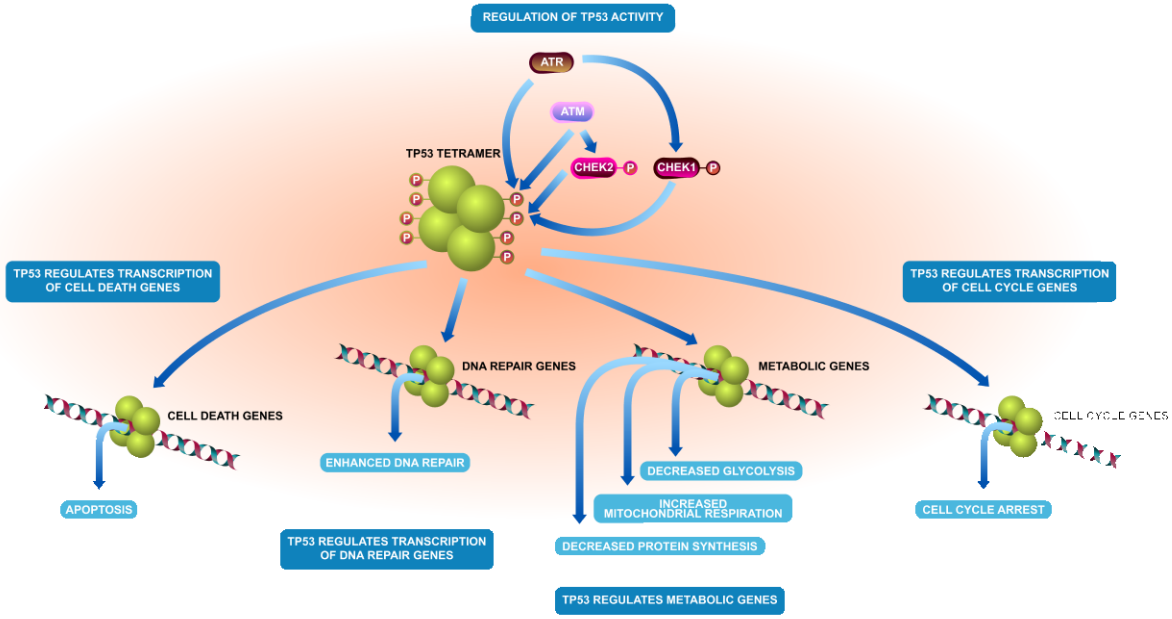
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Transcriptional Regulation by TP53 ↗

Stable identifier: R-HSA-3700989



The tumor suppressor TP53 (encoded by the gene p53) is a transcription factor. Under stress conditions, it recognizes specific responsive DNA elements and thus regulates the transcription of many genes involved in a variety of cellular processes, such as cellular metabolism, survival, senescence, apoptosis and DNA damage response. Because of its critical function, p53 is frequently mutated in around 50% of all malignant tumors. For a recent review, please refer to Vousden and Prives 2009 and Kruiswijk et al. 2015.

Literature references

Kruiswijk, F., Labuschagne, CF., Vousden, KH. (2015). p53 in survival, death and metabolic health: a lifeguard with a licence to kill. *Nat. Rev. Mol. Cell Biol., 16*, 393-405. ↗

Vousden, KH., Prives, C. (2009). Blinded by the Light: The Growing Complexity of p53. *Cell, 137*, 413-31. ↗

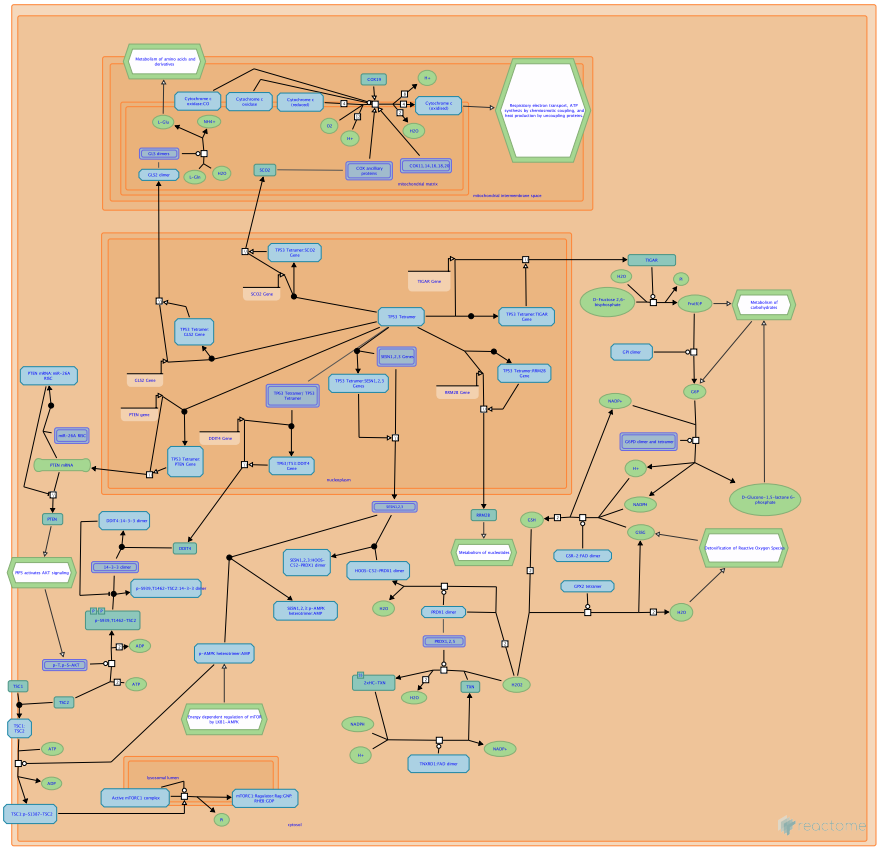
Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

TP53 Regulates Metabolic Genes ↗

Location: Transcriptional Regulation by TP53

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

Feng, Z., Levine, AJ. (2010). The regulation of energy metabolism and the IGF-1/mTOR pathways by the p53 protein. *Trends Cell Biol., 20*, 427-34. ↗

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

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

Kondoh, H., Lleonart, ME., Gil, J., Wang, J., Degan, P., Peters, G. et al. (2005). Glycolytic enzymes can modulate cellular life span. *Cancer Res., 65*, 177-85. ↗

Schwartzenberg-Bar-Yoseph, F., Armoni, M., Karnieli, E. (2004). The tumor suppressor p53 down-regulates glucose transporters GLUT1 and GLUT4 gene expression. *Cancer Res., 64*, 2627-33. ↗

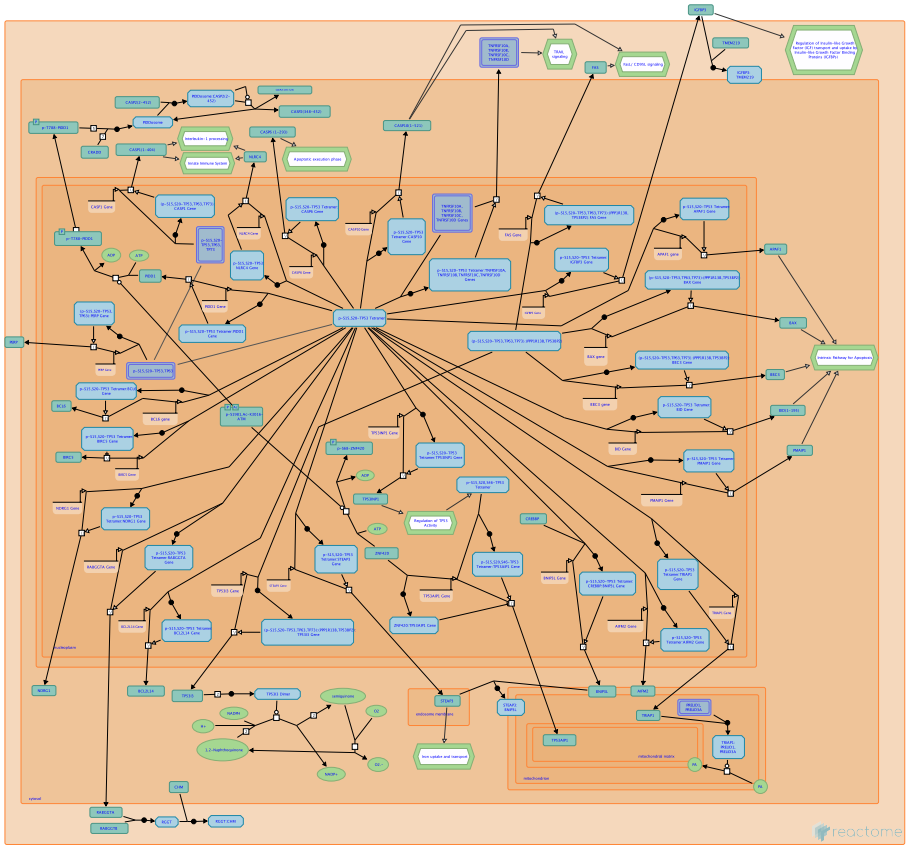
Editions

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 Regulates Transcription of Cell Death Genes ↗

Location: Transcriptional Regulation by TP53

Stable identifier: R-HSA-5633008



The tumor suppressor TP53 (p53) exerts its tumor suppressive role in part by regulating transcription of a number of genes involved in cell death, mainly apoptotic cell death. The majority of apoptotic genes that are transcriptional targets of TP53 promote apoptosis, but there are also several TP53 target genes that inhibit apoptosis, providing cells with an opportunity to attempt to repair the damage and/or recover from stress.

Pro-apoptotic transcriptional targets of TP53 involve TRAIL death receptors TNFRSF10A (DR4), TNFRSF10B (DR5), TNFRSF10C (DcR1) and TNFRSF10D (DcR2), as well as the FASL/CD95L death receptor FAS (CD95). TRAIL receptors and FAS induce pro-apoptotic signaling in response to external stimuli via extrinsic apoptosis pathway (Wu et al. 1997, Takimoto et al. 2000, Guan et al. 2001, Liu et al. 2004, Ruiz de Almodovar et al. 2004, Liu et al. 2005, Schilling et al. 2009, Wilson et al. 2013). IGFBP3 is a transcriptional target of TP53 that may serve as a ligand for a novel death receptor TMEM219 (Buckbinder et al. 1995, Ingermann et al. 2010).

TP53 regulates expression of a number of genes involved in the intrinsic apoptosis pathway, triggered by the cellular stress. Some of TP53 targets, such as BAX, BID, PMAIP1 (NOXA), BBC3 (PUMA) and probably BNIP3L, AIFM2, STEAP3, TRIAP1 and TP53AIP1, regulate the permeability of the mitochondrial membrane and/or cytochrome C release (Miyashita and Reed 1995, Oda et al. 2000, Samuels-Lev et al. 2001, Nakano and Vousden 2001, Sax et al. 2002, Passer et al. 2003, Bergamaschi et al. 2004, Li et al. 2004, Fei et al. 2004, Wu et al. 2004, Park and Nakamura 2005, Patel et al. 2008, Wang et al. 2012, Wilson et al. 2013). Other pro-apoptotic genes, either involved in the intrinsic apoptosis pathway, extrinsic apoptosis pathway or pyroptosis (inflammation-related cell death), which are transcriptionally regulated by TP53 are cytosolic caspase activators, such as APAF1, PIDD1, and NLRC4, and caspases themselves, such as

CASP1, CASP6 and CASP10 (Lin et al. 2000, Robles et al. 2001, Gupta et al. 2001, MacLachlan and El-Deiry 2002, Rikhof et al. 2003, Sadasivam et al. 2005, Brough and Rothwell 2007).

It is uncertain how exactly some of the pro-apoptotic TP53 targets, such as TP53I3 (PIG3), RABGGTA, BCL2L14, BCL6, NDRG1 and PERP contribute to apoptosis (Attardi et al. 2000, Guo et al. 2001, Samuels-Lev et al. 2001, Contente et al. 2002, Ihrie et al. 2003, Bergamaschi et al. 2004, Stein et al. 2004, Phan and Dalla-Favera 2004, Jen and Cheung 2005, Margalit et al. 2006, Zhang et al. 2007, Saito et al. 2009, Davies et al. 2009, Giam et al. 2012).

TP53 is stabilized in response to cellular stress by phosphorylation on at least serine residues S15 and S20. Since TP53 stabilization precedes the activation of cell death genes, the TP53 tetramer phosphorylated at S15 and S20 is shown as a regulator of pro-apoptotic/pro-cell death genes. Some pro-apoptotic TP53 target genes, such as TP53AIP1, require additional phosphorylation of TP53 at serine residue S46 (Oda et al. 2000, Taira et al. 2007). Phosphorylation of TP53 at S46 is regulated by another TP53 pro-apoptotic target, TP53INP1 (Okamura et al. 2001, Tomasini et al. 2003). Additional post-translational modifications of TP53 may be involved in transcriptional regulation of genes presented in this pathway and this information will be included as evidence becomes available.

Activation of some pro-apoptotic TP53 targets, such as BAX, FAS, BBC3 (PUMA) and TP53I3 (PIG3) requires the presence of the complex of TP53 and an ASPP protein, either PPP1R13B (ASPP1) or TP53BP2 (ASPP2) (Samuels-Lev et al. 2001, Bergamaschi et al. 2004, Patel et al. 2008, Wilson et al. 2013), indicating how the interaction with specific co-factors modulates the cellular response/outcome.

TP53 family members TP63 and or TP73 can also activate some of the pro-apoptotic TP53 targets, such as FAS, BAX, BBC3 (PUMA), TP53I3 (PIG3), CASP1 and PERP (Bergamaschi et al. 2004, Jain et al. 2005, Ihrie et al. 2005, Patel et al. 2008, Schilling et al. 2009, Celardo et al. 2013).

For a review of the role of TP53 in apoptosis and pro-apoptotic transcriptional targets of TP53, please refer to Riley et al. 2008, Murray-Zmijewski et al. 2008, Bieging et al. 2014, Kruiswijk et al. 2015.

Literature references

Wu, GS., Burns, TF., McDonald, ER., Jiang, W., Meng, R., Krantz, ID. et al. (1997). KILLER/DR5 is a DNA damage-inducible p53-regulated death receptor gene. *Nat. Genet., 17*, 141-3. ↗

Takimoto, R., el-Deiry, WS. (2000). Wild-type p53 transactivates the KILLER/DR5 gene through an intronic sequence-specific DNA-binding site. *Oncogene, 19*, 1735-43. ↗

Guan, B., Yue, P., Clayman, GL., Sun, SY. (2001). Evidence that the death receptor DR4 is a DNA damage-inducible, p53-regulated gene. *J. Cell. Physiol., 188*, 98-105. ↗

Liu, X., Yue, P., Khuri, FR., Sun, SY. (2004). p53 upregulates death receptor 4 expression through an intronic p53 binding site. *Cancer Res., 64*, 5078-83. ↗

Ruiz de Almodóvar, C., Ruiz-Ruiz, C., Rodríguez, A., Ortiz-Ferrón, G., Redondo, JM., López-Rivas, A. (2004). Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) decoy receptor TRAIL-R3 is up-regulated by p53 in breast tumor cells through a mechanism involving an intronic p53-binding site. *J. Biol. Chem., 279*, 4093-101. ↗

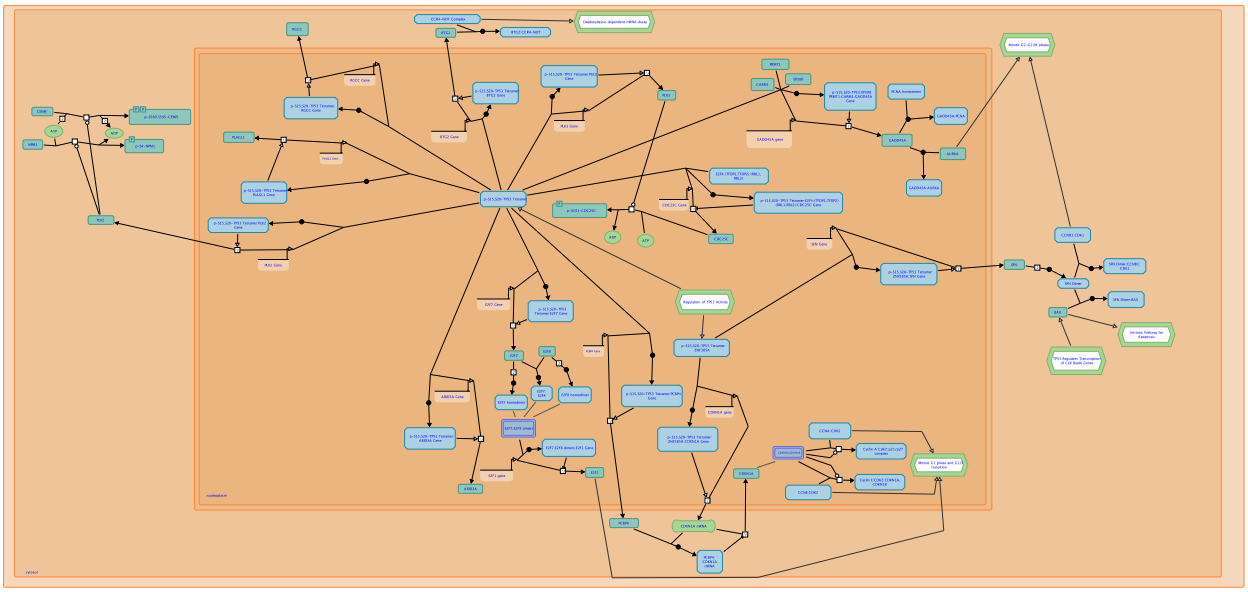
Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

TP53 Regulates Transcription of Cell Cycle Genes ↗

Location: Transcriptional Regulation by TP53

Stable identifier: R-HSA-6791312



Under a variety of stress conditions, TP53 (p53), stabilized by stress-induced phosphorylation at least on S15 and S20 serine residues, can induce the transcription of genes involved in cell cycle arrest. Cell cycle arrest provides cells an opportunity to repair the damage before division, thus preventing the transmission of genetic errors to daughter cells. In addition, it allows cells to attempt a recovery from the damage and survive, preventing premature cell death.

TP53 controls transcription of genes involved in both G1 and G2 cell cycle arrest. The most prominent TP53 target involved in G1 arrest is the inhibitor of cyclin-dependent kinases CDKN1A (p21). CDKN1A is one of the earliest genes induced by TP53 (El-Deiry et al. 1993). CDKN1A binds and inactivates CDK2 in complex with cyclin A (CCNA) or E (CCNE), thus preventing G1/S transition (Harper et al. 1993). Nevertheless, under prolonged stress, the cell destiny may be diverted towards an apoptotic outcome. For instance, in case of an irreversible damage, TP53 can induce transcription of an RNA binding protein PCBP4, which can bind and destabilize CDKN1A mRNA, thus alleviating G1 arrest and directing the affected cell towards G2 arrest and, possibly, apoptosis (Zhu and Chen 2000, Scoumanne et al. 2011). Expression of E2F7 is directly induced by TP53. E2F7 contributes to G1 cell cycle arrest by repressing transcription of E2F1, a transcription factor that promotes expression of many genes needed for G1/S transition (Aksoy et al. 2012, Carvajal et al. 2012). ARID3A is a direct transcriptional target of TP53 (Ma et al. 2003) that may promote G1 arrest by cooperating with TP53 in induction of CDKN1A transcription (Lestari et al. 2012). However, ARID3A may also promote G1/S transition by stimulating transcriptional activity of E2F1 (Suzuki et al. 1998, Peeper et al. 2002).

TP53 contributes to the establishment of G2 arrest by inducing transcription of GADD45A and SFN, and by inhibiting transcription of CDC25C. TP53 induces GADD45A transcription in cooperation with chromatin modifying enzymes EP300, PRMT1 and CARM1 (An et al. 2004). GADD45A binds Aurora kinase A (AURKA), inhibiting its catalytic activity and preventing AURKA-mediated G2/M transition (Shao et al. 2006, Sanchez et al. 2010). GADD45A also forms a complex with PCNA. PCNA is involved in both normal and repair DNA synthesis. The effect of GADD45 interaction with PCNA, if any, on S phase progression, G2 arrest and DNA repair is not known (Smith et al. 1994, Hall et al. 1995, Sanchez et al. 2010, Kim et al. 2013). SFN (14-3-3-sigma) is induced by TP53 (Hermeking et al. 1997) and contributes to G2 arrest by bind-

ing to the complex of CDK1 and CCNB1 (cyclin B1) and preventing its translocation to the nucleus. Phosphorylation of a number of nuclear proteins by the complex of CDK1 and CCNB1 is needed for G2/M transition (Chan et al. 1999). While promoting G2 arrest, SFN can simultaneously inhibit apoptosis by binding to BAX and preventing its translocation to mitochondria, a step involved in cytochrome C release (Samuel et al. 2001). TP53 binds the promoter of the CDC25C gene in cooperation with the transcriptional repressor E2F4 and represses CDC25C transcription, thus maintaining G2 arrest (St Clair et al. 2004, Benson et al. 2014).

Several direct transcriptional targets of TP53 are involved in cell cycle arrest but their mechanism of action is still unknown. BTG2 is induced by TP53, leading to cessation of cellular proliferation (Rouault et al. 1996, Duriez et al. 2002). BTG2 binds to the CCR4-NOT complex and promotes mRNA deadenylation activity of this complex. Interaction between BTG2 and CCR4-NOT is needed for the antiproliferative activity of BTG2, but the underlying mechanism has not been elucidated (Rouault et al. 1998, Mauxion et al. 2008, Horiuchi et al. 2009, Doidge et al. 2012, Ezzeddine et al. 2012). Two polo-like kinases, PLK2 and PLK3, are direct transcriptional targets of TP53. TP53-mediated induction of PLK2 may be important for prevention of mitotic catastrophe after spindle damage (Burns et al. 2003). PLK2 is involved in the regulation of centrosome duplication through phosphorylation of centrosome-related proteins CENPJ (Chang et al. 2010) and NPM1 (Krause and Hoffmann 2010). PLK2 is frequently transcriptionally silenced through promoter methylation in B-cell malignancies (Syed et al. 2006). Induction of PLK3 transcription by TP53 (Jen and Cheung 2005) may be important for coordination of M phase events through PLK3-mediated nuclear accumulation of CDC25C (Bahassi et al. 2004). RGCC is induced by TP53 and implicated in cell cycle regulation, possibly through its association with PLK1 (Saigusa et al. 2007). PLAGL1 (ZAC1) is a zinc finger protein directly transcriptionally induced by TP53 (Rozenfeld-Granot et al. 2002). PLAGL1 expression is frequently lost in cancer (Varrault et al. 1998) and PLAGL1 has been implicated in both cell cycle arrest and apoptosis (Spengler et al. 1997), but its mechanism of action remains unknown.

The zinc finger transcription factor ZNF385A (HZF) is a direct transcriptional target of TP53 that can form a complex with TP53 and facilitate TP53-mediated induction of CDKN1A and SFN (14-3-3 sigma) transcription (Das et al. 2007).

For a review of the role of TP53 in cell cycle arrest and cell cycle transcriptional targets of TP53, please refer to Riley et al. 2008, Murray-Zmijewski et al. 2008, Bieging et al. 2014, Kruiswijk et al. 2015.

Literature references

el-Deiry, WS., Tokino, T., Velculescu, VE., Levy, DB., Parsons, R., Trent, JM. et al. (1993). WAF1, a potential mediator of p53 tumor suppression. *Cell, 75*, 817-25. ↗

Harper, JW., Adami, GR., Wei, N., Keyomarsi, K., Elledge, SJ. (1993). The p21 Cdk-interacting protein Cip1 is a potent inhibitor of G1 cyclin-dependent kinases. *Cell, 75*, 805-16. ↗

Zhu, J., Chen, X. (2000). MCG10, a novel p53 target gene that encodes a KH domain RNA-binding protein, is capable of inducing apoptosis and cell cycle arrest in G(2)-M. *Mol. Cell. Biol., 20*, 5602-18. ↗

Scoumanne, A., Cho, SJ., Zhang, J., Chen, X. (2011). The cyclin-dependent kinase inhibitor p21 is regulated by RNA-binding protein PCBP4 via mRNA stability. *Nucleic Acids Res., 39*, 213-24. ↗

Aksoy, O., Chicas, A., Zeng, T., Zhao, Z., McCurrach, M., Wang, X. et al. (2012). The atypical E2F family member E2F7 couples the p53 and RB pathways during cellular senescence. *Genes Dev., 26*, 1546-57. ↗

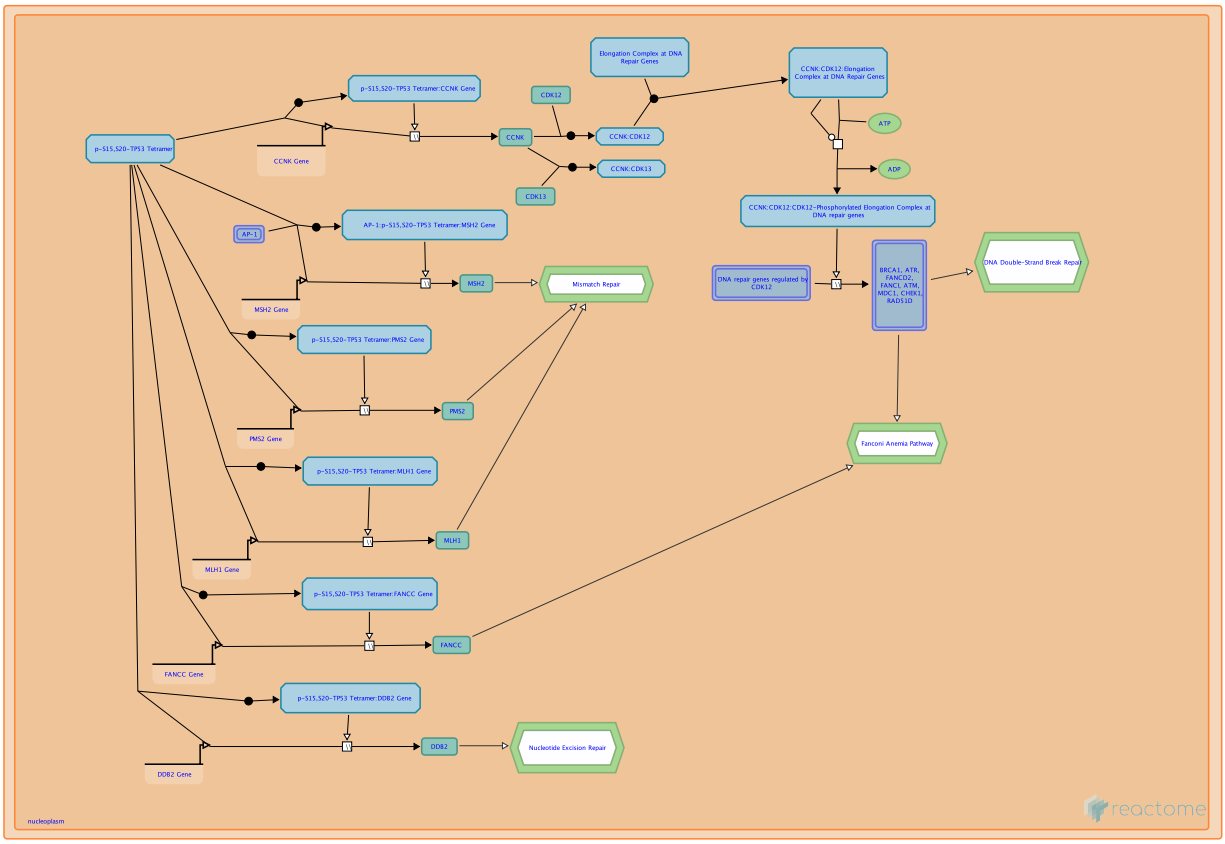
Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

TP53 Regulates Transcription of DNA Repair Genes ↗

Location: Transcriptional Regulation by TP53

Stable identifier: R-HSA-6796648



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

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

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

al. 2014, Bartkowiak and Greenleaf 2015, Ekumi et al. 2015).

Literature references

Scherer, SJ., Maier, SM., Seifert, M., Hanselmann, RG., Zang, KD., Müller-Hermelink, HK. et al. (2000). p53 and c-Jun functionally synergize in the regulation of the DNA repair gene hMSH2 in response to UV. *J. Biol. Chem., 275*, 37469-73. ↗

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

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

Tan, T., Chu, G. (2002). p53 Binds and activates the xeroderma pigmentosum DDB2 gene in humans but not mice. *Mol. Cell. Biol., 22*, 3247-54. ↗

Liebetrau, W., Budde, A., Savoia, A., Grummt, F., Hoehn, H. (1997). p53 activates Fanconi anemia group C gene expression. *Hum. Mol. Genet., 6*, 277-83. ↗

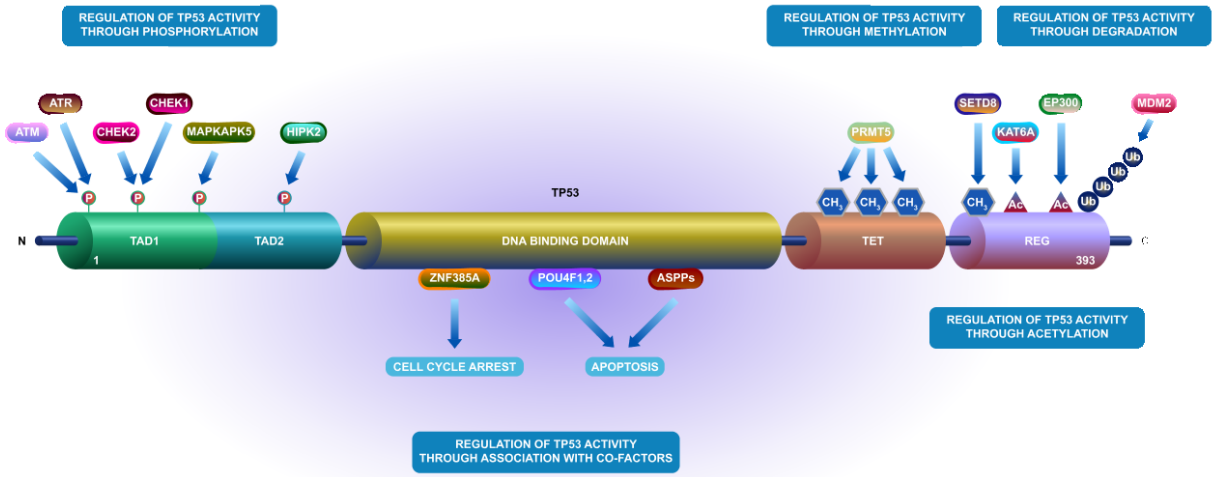
Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

Regulation of TP53 Activity ↗

Location: Transcriptional Regulation by TP53

Stable identifier: R-HSA-5633007



Protein stability and transcriptional activity of TP53 (p53) tumor suppressor are regulated by post-translational modifications that include ubiquitination, phosphorylation, acetylation, methylation, sumoylation and prolyl-isomerization (Kruse and Gu 2009, Meek and Anderson 2009, Santiago et al. 2013, Mantovani et al. 2015). In addition to post-translational modifications, the activity of TP53 is also regulated by binding of transcription co-factors.

In unstressed cells, TP53 protein levels are low due to MDM2-mediated ubiquitination of TP53, which triggers proteasome-mediated degradation. In response to stress, TP53 undergoes stabilizing phosphorylation, mainly at serine residues S15 and S20. Several different kinases can phosphorylate TP53 at these sites, but the main S15 kinases are considered to be ATM and ATR, while the main S20 kinases are considered to be CHEK2 and CHEK1. Additional phosphorylation of TP53 at serine residue S46 promotes transcription of pro-apoptotic, rather than cell cycle arrest genes.

Acetylation mainly has a positive impact on transcriptional activity of TP53, while methylation can both positively and negatively regulate TP53.

Some posttranslational modifications regulate interaction of TP53 with transcriptional co-factors, some of which are themselves transcriptional targets of TP53.

For review of the complex network of TP53 regulation, please refer to Kruse and Gu 2009, and Meek and Anderson 2009.

Literature references

Kruse, JP., Gu, W. (2009). Modes of p53 regulation. *Cell, 137*, 609-22. ↗

Meek, DW., Anderson, CW. (2009). Posttranslational modification of p53: cooperative integrators of function. *Cold Spring Harb Perspect Biol, 1*, a000950. ↗

Santiago, A., Li, D., Zhao, LY., Godsey, A., Liao, D. (2013). p53 SUMOylation promotes its nuclear export by facilitating its release from the nuclear export receptor CRM1. *Mol. Biol. Cell, 24*, 2739-52. ↗

Mantovani, F., Zannini, A., Rustighi, A., Del Sal, G. (2015). Interaction of p53 with prolyl isomerases: Healthy and unhealthy relationships. *Biochim. Biophys. Acta, 1850*, 2048-60. ↗

Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

Table of Contents