Regulation of TP53 Activity

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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.

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Literature references


Reactome database release: 82

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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.

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TP53 (p53) tumor suppressor protein is a transcription factor that functions as a homotetramer (Jeffrey et al. 1995). The protein levels of TP53 are low in unstressed cells due to MDM2-mediated ubiquitination that triggers proteasome-mediated degradation of TP53 (Wu et al. 1993). The E3 ubiquitin ligase MDM2 functions as a homodimer/homo-oligomer or a heterodimer/hetero-oligomer with MDM4 (MDMX) (Lin- ares et al. 2003, Toledo and Wahl 2007, Cheng et al. 2011, Wade et al. 2013).

Activating phosphorylation of TP53 at serine residues S15 and S20 in response to genotoxic stress disrupts TP53 interaction with MDM2. In contrast to MDM2, E3 ubiquitin ligases RNF34 (CARP1) and RFFL (CARP2) can ubiquitinate phosphorylated TP53 (Yang et al. 2007). Binding of MDM2 to TP53 is also inhibited by the tumor suppressor p14-ARF, transcribed from the CDKN2A gene in response to oncogenic signaling or oxidative stress (Zhang et al. 1998, Parisi et al. 2002, Voncken et al. 2005). Ubiquitin-dependant degradation of TP53 can also be promoted by PIRH2 (Leng et al. 2003) and COP1 (Dornan et al. 2004) ubiquitin ligases. HAUSP (USP7) can deubiquitinate TP53, contributing to TP53 stabilization (Li et al. 2002).


**Literature references**


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Regulation of TP53 Activity through Phosphorylation

Phosphorylation of TP53 (p53) at the N-terminal serine residues S15 and S20 plays a critical role in protein stabilization as phosphorylation at these sites interferes with binding of the ubiquitin ligase MDM2 to TP53. Several different kinases can phosphorylate TP53 at S15 and S20. In response to double strand DNA breaks, S15 is phosphorylated by ATM (Banin et al. 1998, Canman et al. 1998, Khanna et al. 1998), and S20 by CHEK2 (Chehab et al. 1999, Chehab et al. 2000, Hirao et al. 2000). DNA damage or other types of genotoxic stress, such as stalled replication forks, can trigger ATR-mediated phosphorylation of TP53 at S15 (Lakin et al. 1999, Tibbetts et al. 1999) and CHEK1-mediated phosphorylation of TP53 at S20 (Shieh et al. 2000). In response to various types of cell stress, NUAK1 (Hou et al. 2011), CDK5 (Zhang et al. 2002, Lee et al. 2007, Lee et al. 2008), AMPK (Jones et al. 2005) and TP53RK (Abe et al. 2001, Facchin et al. 2003) can phosphorylate TP53 at S15, while PLK3 (Xie, Wang et al. 2001, Xie, Wu et al. 2001) can phosphorylate TP53 at S20.

Phosphorylation of TP53 at serine residue S46 promotes transcription of TP53-regulated apoptotic genes rather than cell cycle arrest genes. Several kinases can phosphorylate S46 of TP53, including ATM-activated DYRK2, which, like TP53, is targeted for degradation by MDM2 (Taira et al. 2007, Taira et al. 2010). TP53 is also phosphorylated at S46 by HIPK2 in the presence of the TP53 transcriptional target TP53INP1 (D'Orazi et al. 2002, Hofmann et al. 2002, Tomasini et al. 2003). CDK5, in addition to phosphorylating TP53 at S15, also phosphorylates it at S33 and S46, which promotes neuronal cell death (Lee et al. 2007).

MAPKAPK5 (PRAK) phosphorylates TP53 at serine residue S37, promoting cell cycle arrest and cellular senescence in response to oncogenic RAS signaling (Sun et al. 2007).

NUAK1 phosphorylates TP53 at S15 and S392, and phosphorylation at S392 may contribute to TP53-mediated transcriptional activation of cell cycle arrest genes (Hou et al. 2011). S392 of TP53 is also phos-
phorylated by the complex of casein kinase II (CK2) bound to the FACT complex, enhancing transcriptional activity of TP53 in response to UV irradiation (Keller et al. 2001, Keller and Lu 2002).

The activity of TP53 is inhibited by phosphorylation at serine residue S315, which enhances MDM2 binding and degradation of TP53. S315 of TP53 is phosphorylated by Aurora kinase A (AURKA) (Katayama et al. 2004) and CDK2 (Luciani et al. 2000). Interaction with MDM2 and the consequent TP53 degradation is also increased by phosphorylation of TP53 threonine residue T55 by the transcription initiation factor complex TFIID (Li et al. 2004).

Aurora kinase B (AURKB) has been shown to phosphorylate TP53 at serine residue S269 and threonine residue T284, which is possibly facilitated by the binding of the NIR co-repressor. AURKB-mediated phosphorylation was reported to inhibit TP53 transcriptional activity through an unknown mechanism (Wu et al. 2011). A putative direct interaction between TP53 and AURKB has also been described and linked to TP53 phosphorylation and S183, T211 and S215 and TP53 degradation (Gully et al. 2012).

**Literature references**


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Association of TP53 (p53) with various transcriptional co-factors can promote, inhibit or provide specificity towards either transcription of cell cycle arrest genes or transcription of cell death genes. Binding of the zinc finger protein ZNF385A (HZF), which is a transcriptional target of TP53, stimulates transcription of cell cycle arrest genes, such as CDKN1A (Das et al. 2007). Binding of POU4F1 (BRN3A) to TP53 also stimulates transcription of cell cycle arrest genes while inhibiting transcription of pro-apoptotic genes (Budhram-Mahadeo et al. 1999, Hudson et al. 2005).

Binding of ASPP family proteins PPP1R13B (ASPP1) or TP53BP2 (ASPP2) to TP53 stimulates transcription of pro-apoptotic TP53 targets (Samuels-Lev et al. 2001, Bergamaschi et al. 2004). Binding of the ASPP family member PPP1R13L (iASSP) inhibits TP53-mediated activation of pro-apoptotic genes probably by interfering with binding of stimulatory ASPPs to TP53 (Bergamaschi et al. 2003). Transcription of pro-apoptotic genes is also stimulated by binding of TP53 to POU4F2 (BRN3B) (Budhram-Mahadeo et al. 2006, Budhram-Mahadeo et al. 2014) or to hCAS/CSE1L (Tanaka et al. 2007).

Binding of co-factors to TP53 can also affect protein stability. For example, PHF20 binds to TP53 dimethylated on lysine residues K370 and K382 by unidentified protein lysine methyltransferase(s) and interferes with MDM2 binding, resulting in prolonged TP53 half-life (Cui et al. 2012). Long noncoding RNAs can contribute to p53-dependent transcriptional responses (Huarte et al. 2010). For a general review on this topic, see Espinosa 2008, Beckerman and Prives 2010, Murray-Zmijewski et al. 2008, An et al. 2004 and Barsotti and Prives 2010.

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TP53 (p53) undergoes methylation on several lysine and arginine residues, which modulates its transcriptional activity.


TP53 transcriptional activity is repressed by SMYD2-mediated methylation of TP53 at lysine residue K370 (Huang et al. 2006). Dimethylation of TP53 at lysine residue K373 by the complex of methyltransferases EHMT1 and EHMT2 also represses TP53-mediated transcription (Huang et al. 2010). The chromatin compaction factor L3MBTL1 binds TP53 monomethylated at lysine K382 by SETD8 (SET8) and, probably through changing local chromatin architecture, represses transcription of TP53 targets (West et al. 2010). The histone lysine-specific demethylase LSD1 interacts with TP53 and represses p53-mediated transcriptional activation (Huang et al. 2007). PRMT1 and CARM1 can also modulate p53 functions in a cooperative manner (An et al. 2004).

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Transcriptional activity of TP53 is positively regulated by acetylation of several of its lysine residues. BRD7 binds TP53 and promotes acetylation of TP53 lysine residue K382 by acetyltransferase EP300 (p300). Acetylation of K382 enhances TP53 binding to target promoters, including CDKN1A (p21), MDM2, SERPINE1, TIGAR, TNFRSF10C and NDRG1 (Bensaad et al. 2010, Burrows et al. 2010. Drost et al. 2010). The histone acetyltransferase KAT6A, in the presence of PML, also acetylates TP53 at K382, and, in addition, acetylates K120 of TP53. KAT6A-mediated acetylation increases transcriptional activation of CDKN1A by TP53 (Rokudai et al. 2013). Acetylation of K382 can be reversed by the action of the NuRD complex, containing the TP53-binding MTA2 subunit, resulting in inhibition of TP53 transcriptional activity (Luo et al. 2000). Acetylation of lysine K120 in the DNA binding domain of TP53 by the MYST family acetyltransferases KAT8 (hMOF) and KAT5 (TIP60) can modulate the decision between cell cycle arrest and apoptosis (Sykes et al. 2006, Tang et al. 2006). Studies with acetylation-defective knock-in mutant mice indicate that lysine acetylation in the p53 DNA binding domain acts in part by uncoupling transactivation and transrepression of gene targets, while retaining ability to modulate energy metabolism and production of reactive oxygen species (ROS) and influencing ferroptosis (Li et al. 2012, Jiang et al. 2015).

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