Regulation of TP53 Activity through Phosphorylation

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05/09/2020
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


Reactome database release: 73

This document contains 1 pathway and 26 reactions (see Table of Contents)
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 phosphorylated by the complex of casein kinase II (CK2) bound to the FACT complex, enhancing transcrip-
tional 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 TFIIID (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**


**Editions**

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ATM phosphorylates TP53 at S15

Location: Regulation of TP53 Activity through Phosphorylation

Stable identifier: R-HSA-5693609

Type: transition

Compartments: nucleoplasm

In response to DNA double strand breaks, serine at position 15 of the TP53 (p53) tumor suppressor protein is rapidly phosphorylated by the ATM kinase. This serves to stabilize the p53 protein. A rise in the levels of the p53 protein induces the expression of p21 cyclin-dependent kinase inhibitor. This prevents the normal progression from G1 to S phase, thus providing a check on replication of damaged DNA (Banin et al. 1998, Canman et al. 1998, Khanna et al. 1998).

Followed by: CHEK2 phosphorylates TP53, PLK3 phosphorylates TP53

Literature references


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ATR phosphorylates TP53

Location: Regulation of TP53 Activity through Phosphorylation

Stable identifier: R-HSA-6799332

Type: transition

Compartments: nucleoplasm

ATR, bound to DNA damage sites, phosphorylates TP53 (p53) at serine residue S15. S15 phosphorylation stabilizes TP53 by inhibiting the binding of TP53 to the ubiquitin ligase MDM2 (Tibbetts et al. 1999, Lakin et al. 1999).

Followed by: CHEK1 phosphorylates TP53, PLK3 phosphorylates TP53

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CHEK2 phosphorylates TP53

Location: Regulation of TP53 Activity through Phosphorylation

Stable identifier: R-HSA-69685

Type: transition

Compartments: nucleoplasm

CHEK2 (Chk2) phosphorylates TP53 (p53) at serine residue S20 (Hirao et al. 2000, Shieh et al. 2000, Chehab et al. 2000). Phosphorylation of TP53 at serine residue S20 is necessary for DNA damage-induced TP53 stabilization as it compromises the interaction of TP53 with the ubiquitin ligase MDM2 (Chehab et al. 1999, Chehab et al. 2000). S20 phosphorylation is also required for the induction of TP53-dependent transcripts in response to DNA damage (Hirao et al. 2000).

Preceded by: ATM phosphorylates TP53 at S15

Followed by: NOC2L binds TP53, DYRK2 phosphorylates TP53, CK2:FACT phosphorylates TP53, TP53INP1 and HIPK2 bind TP53

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https://www.reactome.org
CHEK1 phosphorylates TP53

**Location:** Regulation of TP53 Activity through Phosphorylation

**Stable identifier:** R-HSA-6799246

**Type:** transition

**Compartments:** nucleoplasm

CHEK1, activated by ATR-mediated phosphorylation, can phosphorylate TP53 at serine residue S20, resulting in the increased half-life of TP53 (Shieh et al. 2000).

**Preceded by:** ATR phosphorylates TP53

**Followed by:** NOC2L binds TP53, CK2:FACT phosphorylates TP53, TP53INP1 and HIPK2 bind TP53, DYRK2 phosphorylates TP53

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ATM phosphorylates DYRK2

Location: Regulation of TP53 Activity through Phosphorylation

Stable identifier: R-HSA-6798372

Type: transition

Compartments: nucleoplasm

Activated ATM kinase phosphorylates DYRK2 at threonine residue T106 (matching T33 in the shorter splicing isoform of DYRK2) and serine residue S442 (matching S369 in the shorter splicing isoform of DYRK2). ATM-mediated phosphorylation of DYRK2 prevents DYRK2 ubiquitination by MDM2 and the consequent DYRK2 degradation (Taira et al. 2010).

Followed by: DYRK2 phosphorylates TP53

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DYRK2 phosphorylates TP53 at serine residue S46 (Taira et al. 2007).

**Preceded by:** ATM phosphorylates DYRK2, CHEK2 phosphorylates TP53, CHEK1 phosphorylates TP53, PLK3 phosphorylates TP53

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https://www.reactome.org
MDM2 ubiquitinates DYRK2

**Location:** Regulation of TP53 Activity through Phosphorylation

**Stable identifier:** R-HSA-6798373

**Type:** transition

**Compartments:** nucleoplasm

MDM2 ubiquitinates DYRK2 in the nucleus, leading to proteasome-mediated degradation of DYRK2. This results in the removal of nuclear DYRK2 and exclusive localization of DYRK2 in the cytosol in the absence of DNA damage. ATM-mediated phosphorylation of DYRK2 prevents ubiquitination of DYRK2 by MDM2, leading to accumulation of nuclear DYRK2 (Taira et al. 2010).

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TP53INP1 and HIPK2 bind TP53

Location: Regulation of TP53 Activity through Phosphorylation

Stable identifier: R-HSA-3215251

Type: binding

Compartments: nucleoplasm

TP53INP1 (p53INP1) forms a complex with TP53 and its regulating kinase HIPK2 (Tomasini et al. 2003, Okamura et al. 2001). HIPK2 undergoes autophosphorylation in response to DNA damage, but the mechanism and the identity of autophosphorylation sites have not yet been fully elucidated (Bitomsky et al. 2013, Saul et al. 2013, Siepi et al. 2013). Autophosphorylation enables HIPK2 binding to PIN1. PIN1 likely facilitates a conformational change that enables HIPK2 to phosphorylate its targets, including TP53 (Bitomsky et al. 2013).

Preceded by: CHEK1 phosphorylates TP53, CHEK2 phosphorylates TP53, PLK3 phosphorylates TP53

Followed by: HIPK2 phosphorylates TP53

Literature references


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HIPK2 phosphorylates TP53

**Location:** Regulation of TP53 Activity through Phosphorylation

**Stable identifier:** R-HSA-6799409

**Type:** transition

**Compartments:** nucleoplasm


**Preceded by:** TP53INP1 and HIPK2 bind TP53

**Literature references**


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TP53 binds HIPK1

**Location:** Regulation of TP53 Activity through Phosphorylation

**Stable identifier:** R-HSA-6799431

**Type:** binding

**Compartments:** nucleoplasm

TP53 (p53) forms a complex with a protein kinase HIPK1 (Kondo et al. 2003, Rey et al. 2013). HIPK1 may phosphorylate TP53 on an unidentified serine residue (Kondo et al. 2003). Binding to HIPK1 has been implicated in the negative regulation of TP53 activity (Kondo et al. 2003), but HIPK1 overexpression has also been implicated in the positive regulation of TP53 activity (Rey et al. 2013).

**Literature references**


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TP53 binds STK11 and NUAK1

Location: Regulation of TP53 Activity through Phosphorylation

Stable identifier: R-HSA-6805035

Type: binding

Compartment: nucleoplasm

In the presence of STK11 (LTKB1), TP53 associates with NUAK1 (Zeng and Berger 2006, Hou et al. 2011).

Followed by: STK11 (LKB1) phosphorylates NUAK1

Literature references


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STK11 (LKB1) phosphorylates NUAK1

**Location:** Regulation of TP53 Activity through Phosphorylation

**Stable identifier:** R-HSA-3222006

**Type:** transition

**Compartments:** nucleoplasm

STK11 (LKB1) phosphorylates NUAK1 at threonine residue T211, resulting in NUAK1 activation (Hou et al. 2011).

**Preceded by:** TP53 binds STK11 and NUAK1

**Followed by:** NUAK1 phosphorylates TP53

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NUAK1 phosphorylates TP53

**Location:** Regulation of TP53 Activity through Phosphorylation

**Stable identifier:** R-HSA-3222020

**Type:** transition

**Compartments:** nucleoplasm

NUAK1, activated by STK11 (LKB1)-mediated phosphorylation on threonine residue T211, phosphorylates TP53 (p53) on serine residues S15 and S392, contributing to TP53-mediated transcriptional activation of the CDKN1A (p21) gene (Zeng and Berger 2006, Hou et al. 2011).

**Preceded by:** STK11 (LKB1) phosphorylates NUAK1

**Literature references**


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**CK2 binds FACT**

**Location:** Regulation of TP53 Activity through Phosphorylation

**Stable identifier:** R-HSA-6805061

**Type:** binding

**Compartments:** nucleoplasm

In response to UV radiation, the casein kinase II (CK2) complex associates with the FACT complex (Keller et al. 2001, Keller and Lu 2002).

**Followed by:** CK2:FACT phosphorylates TP53

**Literature references**


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Casein kinase II (CK2), associated with the FACT2 complex, phosphorylates TP53 (p53) at serine residue S392, enhancing transcriptional activity of TP53 in response to UV irradiation (Keller et al. 2001, Keller and Lu 2002).

**Preceded by:** CK2 binds FACT, CHEK1 phosphorylates TP53, CHEK2 phosphorylates TP53, PLK3 phosphorylates TP53

**Literature references**


AURKA phosphorylates TP53 (p53) on serine residue S315. This leads to destabilization of TP53 by enhancing MDM2 binding (Katayama et al. 2004). Based on Xenopus studies, AURKA-mediated phosphorylation of TP53 occurs in the presence of AURKA activator TPX2 (Pascreau et al. 2009).

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CDK2 phosphorylates TP53

**Location:** Regulation of TP53 Activity through Phosphorylation

**Stable identifier:** R-HSA-6805109

**Type:** transition

**Compartments:** nucleoplasm

CDK2, bound to CCNA (cyclin A), phosphorylates TP53 on serine residue S315 (Luciani et al. 2000).

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NOC2L binds TP53

**Location:** Regulation of TP53 Activity through Phosphorylation

**Stable identifier:** R-HSA-3222128

**Type:** binding

**Compartments:** nucleoplasm

NOC2L (NIR) is an inhibitor of histone acetyltransferases that associates with TP53 (p53). NOC2L binding represses TP53-mediated transcriptional activation at TP53 target genes. One possible mechanism is the prevention of activating histone acetylation at TP53 target genes (Hublitz et al. 2005).

**Preceded by:** CHEK1 phosphorylates TP53, CHEK2 phosphorylates TP53, PLK3 phosphorylates TP53

**Followed by:** AURKB binds TP53

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AURKB binds TP53

**Location:** Regulation of TP53 Activity through Phosphorylation

**Stable identifier:** R-HSA-6805122

**Type:** binding

**Compartments:** nucleoplasm

AURKB (Aurora kinase B) is recruited to TP53 (p53) through interaction with NOC2L (NIR) (Wu et al. 2011).

**Preceded by:** NOC2L binds TP53

**Followed by:** AURKB phosphorylates TP53

**Literature references**


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AURKB phosphorylates TP53

Location: Regulation of TP53 Activity through Phosphorylation

Stable identifier: R-HSA-6805126

Type: transition

Compartments: nucleoplasm

AURKB (Aurora kinase B) phosphorylates TP53 (p53) at serine residue S269 and threonine residue T284, which inhibits TP53 transcriptional activity (Wu et al. 2011).

Preceded by: AURKB binds TP53

Literature references


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CDK5 phosphorylates TP53

Location: Regulation of TP53 Activity through Phosphorylation

Stable identifier: R-HSA-6805276

Type: transition

Compartments: nucleoplasm

CDK5, in complex with cleaved CDK5R1 (p25), which ensures nuclear localization (Patrick et al. 1999, Lee et al. 2008), phosphorylates TP53 (p53) on serine residues S15, S33 and S46. CDK5-mediated phosphorylation of TP53 promotes transcription of pro-apoptotic genes and neuronal cell death (Zhang et al. 2002, Lee et al. 2007, Lee et al. 2008).

Literature references


Editions

2015-10-14 Authored, Edited Orlic-Milacic, M.
2016-02-04 Reviewed Inga, A., Zaccara, S.
PLK3 phosphorylates TP53

**Location:** Regulation of TP53 Activity through Phosphorylation

**Stable identifier:** R-HSA-6805285

**Type:** transition

**Compartments:** nucleoplasm

PLK3 contributes to stabilizing phosphorylation of TP53 on serine residue S20 (Xie, Wang et al. 2001, Xie, Wu et al. 2001).

**Preceded by:** AMPK phosphorylates TP53, ATM phosphorylates TP53 at S15, ATR phosphorylates TP53, TP53RK phosphorylates TP53

**Followed by:** NOC2L binds TP53, CK2:FACT phosphorylates TP53, DYRK2 phosphorylates TP53, TP53INP1 and HIPK2 bind TP53

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TAF1 phosphorylates TP53

**Location:** Regulation of TP53 Activity through Phosphorylation

**Stable identifier:** R-HSA-6805399

**Type:** transition

**Compartments:** nucleoplasm

TAF1, the largest subunit of the transcription initiation factor TFIIID complex, phosphorylates TP53 (p53) at threonine residue T55. TAF1-mediated phosphorylation of TP53 increases affinity of TP53 for the ubiquitin ligase MDM2, thus promoting TP53 degradation (Li et al. 2004).

**Literature references**


**Editions**

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MAPKAPK5 phosphorylates TP53

**Location:** Regulation of TP53 Activity through Phosphorylation

**Stable identifier:** R-HSA-3239014

**Type:** transition

**Compartments:** nucleoplasm

Activated MAPKAPK5 (PRAK) phosphorylates TP53 (p53) on serine residue S37, thereby activating it. MAPKAPK5-mediated phosphorylation of TP53 promotes growth arrest and senescence induced by onco-genic RAS, but is not needed for TP53-dependent growth arrest in response to DNA damage (Sun et al. 2007).

**Literature references**


**Editions**

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AMPK phosphorylates TP53

**Location:** Regulation of TP53 Activity through Phosphorylation

**Stable identifier:** R-HSA-6805470

**Type:** transition

**Compartments:** nucleoplasm

AMPK, activated in response to glucose deprivation, phosphorylates TP53 (p53) on serine residue S15, initiating AMPK-dependent cell cycle arrest (Jones et al. 2005). AMPK-dependent phosphorylation of TP73 (p73) appears to be involved in TP53 stabilization upon AMPK activation (Adamovich et al. 2014).

Followed by: PLK3 phosphorylates TP53

**Literature references**


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The atypical protein serine/threonine kinase TP53RK (TP53-regulating kinase), also known as PRPK (p53-related protein kinase), phosphorylates TP53 (p53) on serine residue S15 (Abe et al. 2001, Facchin et al. 2003).

Followed by: PLK3 phosphorylates TP53

Literature references


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