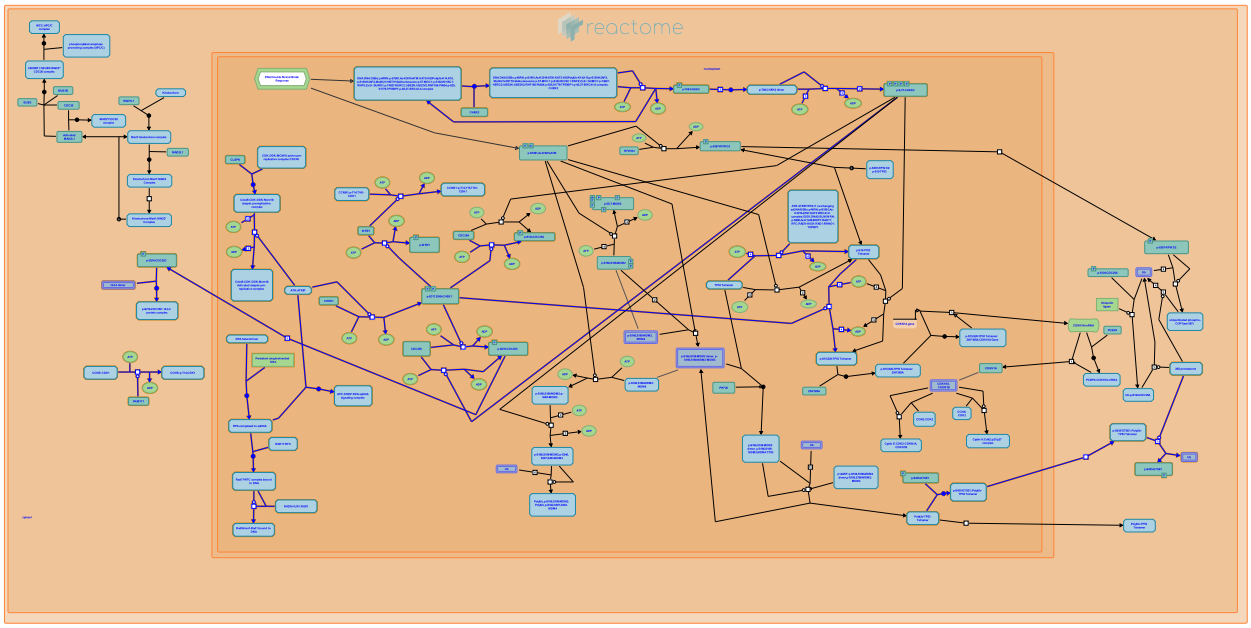
G2/M Checkpoints



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26/04/2024

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. ↗

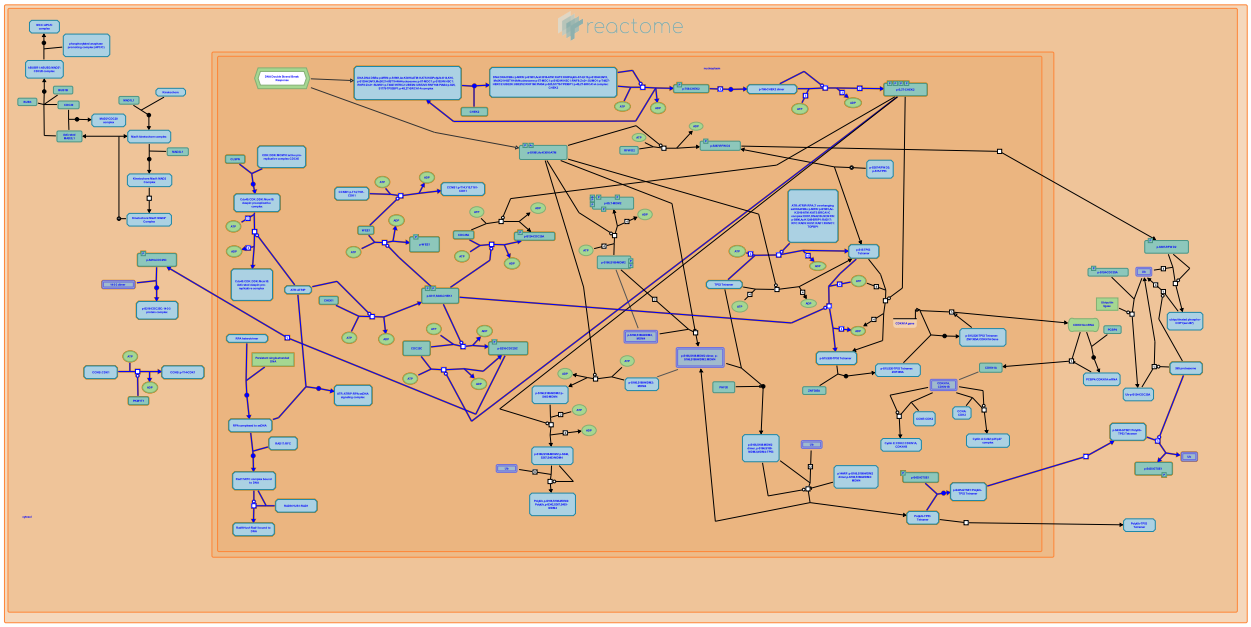
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

G2/M Checkpoints ↗

Stable identifier: R-HSA-69481



G2/M checkpoints include the checks for damaged DNA, unreplicated DNA, and checks that ensure that the genome is replicated once and only once per cell cycle. If cells pass these checkpoints, they follow normal transition to the M phase. However, if any of these checkpoints fail, mitotic entry is prevented by specific G2/M checkpoint events.

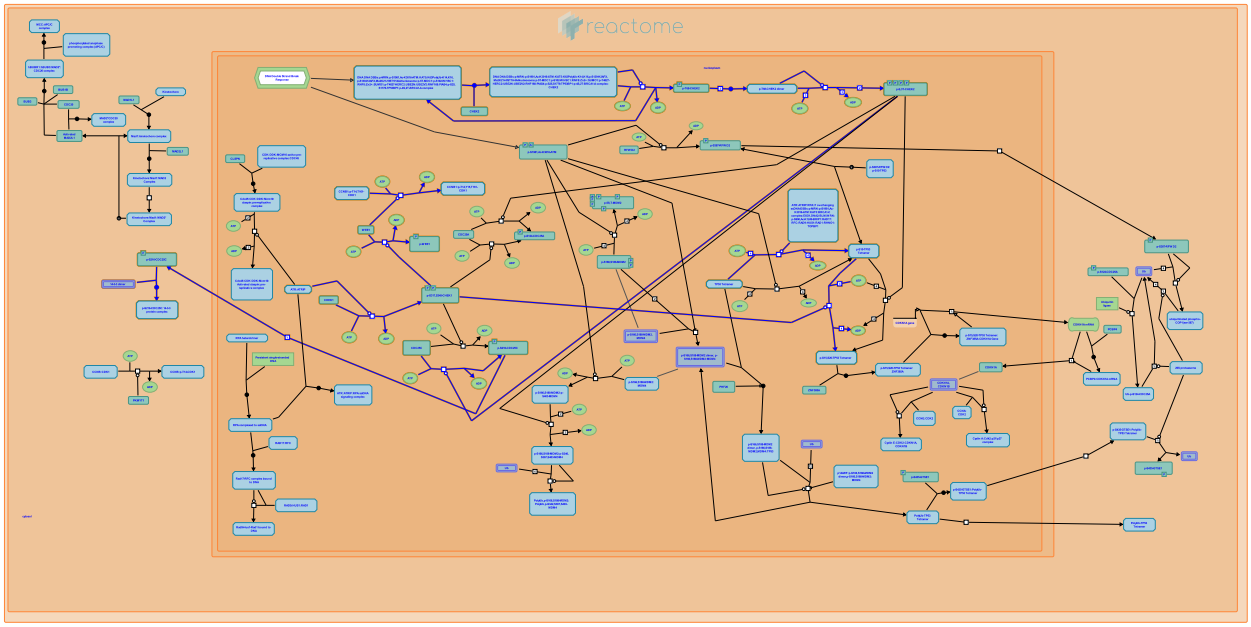
The G2/M checkpoints can fail due to the presence of unreplicated DNA or damaged DNA. In such instances, the cyclin-dependent kinase, Cdc2(Cdk1), is maintained in its inactive, phosphorylated state, and mitotic entry is prevented. Events that ensure that origins of DNA replication fire once and only once per cell cycle are also an example of a G2/M checkpoint.

In the event of high levels of DNA damage, the cells may also be directed to undergo apopotosis (not covered).

G2/M DNA damage checkpoint ↗

Location: G2/M Checkpoints

Stable identifier: R-HSA-69473

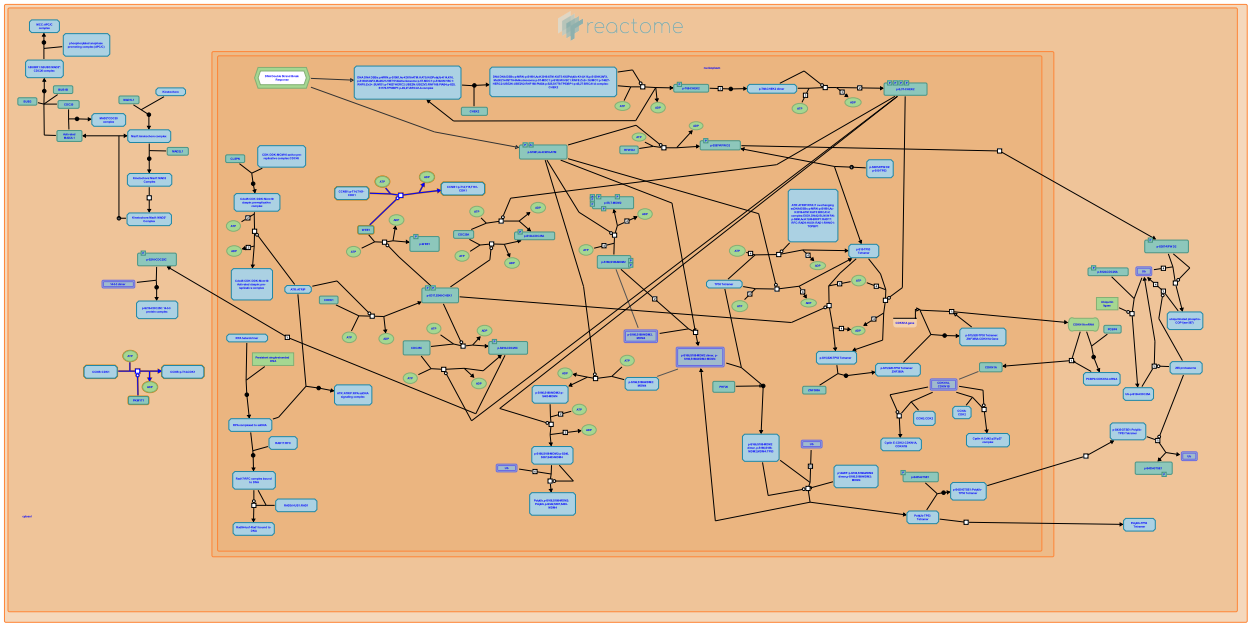


Throughout the cell cycle, the genome is constantly monitored for damage, resulting either from errors of replication, by-products of metabolism or through extrinsic sources such as ultra-violet or ionizing radiation. The different DNA damage checkpoints act to inhibit or maintain the inhibition of the relevant CDK that will control the next cell cycle transition. The G2 DNA damage checkpoint prevents mitotic entry solely through T14Y15 phosphorylation of Cdc2 (Cdk1). Failure of the G2 DNA damage checkpoint leads to catastrophic attempts to segregate unrepaired chromosomes.

G2/M DNA replication checkpoint ↗

Location: G2/M Checkpoints

Stable identifier: R-HSA-69478



The G2/M DNA replication checkpoint ensures that mitosis is not initiated until DNA replication is complete. If replication is blocked, the DNA replication checkpoint signals to maintain Cyclin B - Cdc2 complexes in their T14Y15 phosphorylated and inactive state. This prevents the phosphorylation of proteins involved in G2/M transition, and prevents mitotic entry.

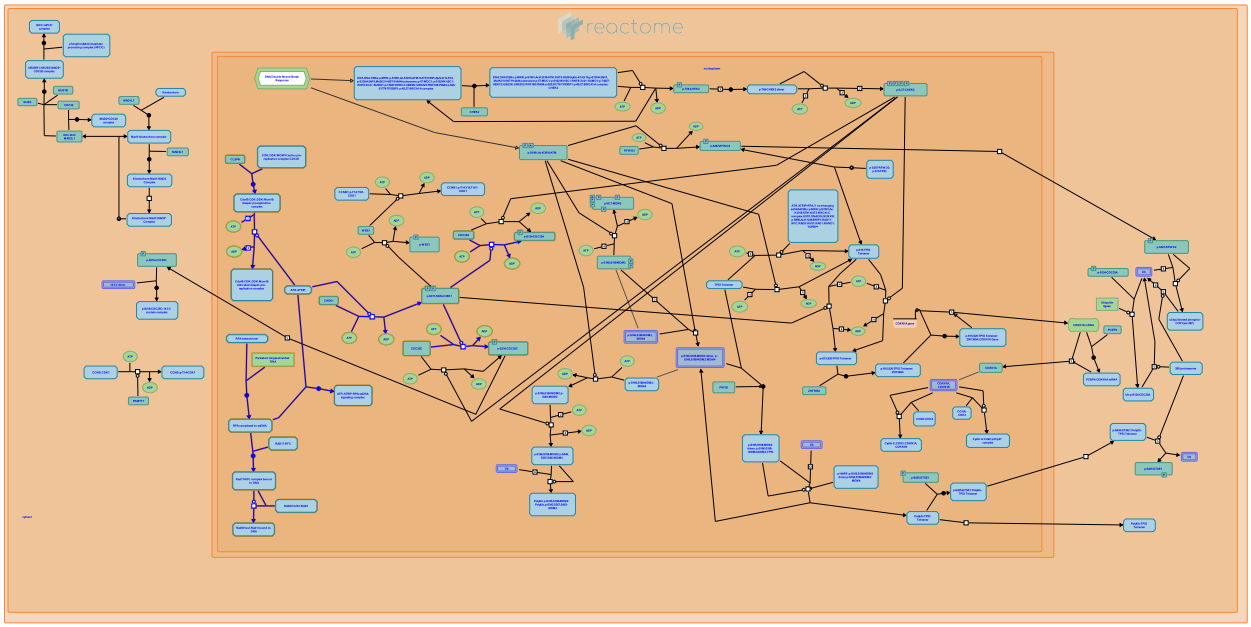
Failure of these checkpoints results in changes of ploidy: in the case of mitosis without completion of DNA replication, aneuploidy of <2C will result, and the opposite is true if DNA replication is completed more than once in a single cell cycle with an overall increase in ploidy. The mechanism by which unreplicated DNA is first detected by the cell is unknown.

Activation of ATR in response to replication stress ↗

Location: G2/M Checkpoints

Stable identifier: R-HSA-176187

Compartments: nucleoplasm



Genotoxic stress caused by DNA damage or stalled replication forks can lead to genomic instability. To guard against such instability, genotoxically-stressed cells activate checkpoint factors that halt or slow cell cycle progression. Among the pathways affected are DNA replication by reduction of replication origin firing, and mitosis by inhibiting activation of cyclin-dependent kinases (Cdks). A key factor involved in the response to stalled replication forks is the ATM- and rad3-related (ATR) kinase, a member of the phosphoinositide-3-kinase-related kinase (PIKK) family. Rather than responding to particular lesions in DNA, ATR and its binding partner ATRIP (ATR-interacting protein) sense replication fork stalling indirectly by associating with persistent ssDNA bound by RPA. These structures would be formed, for example, by dissociation of the replicative helicase from the leading or lagging strand DNA polymerase when the polymerase encounters a DNA lesion that blocks DNA synthesis. Along with phosphorylating the downstream transducer kinase Chk1 and the tumor suppressor p53, activated ATR modifies numerous factors that regulate cell cycle progression or the repair of DNA damage. The persistent ssDNA also stimulates recruitment of the RFC-like Rad17-Rfc2-5 alternative clamp-loading complex, which subsequently loads the Rad9-Hus1-Rad1 complex onto the DNA. The latter '9-1-1' complex serves to facilitate Chk1 binding to the stalled replication fork, where Chk1 is phosphorylated by ATR and thereby activated. Upon activation, Chk1 can phosphorylate additional substrates including the Cdc25 family of phosphatases (Cdc25A, Cdc25B, and Cdc25C). These enzymes catalyze the removal of inhibitory phosphate residues from cyclin-dependent kinases (Cdks), allowing their activation. In particular, Cdc25A primarily functions at the G1/S transition to dephosphorylate Cdk2 at Thr 14 and Tyr 15, thus positively regulating the Cdk2-cyclin E complex for S-phase entry. Cdc25A also has mitotic functions. Phosphorylation of Cdc25A at Ser125 by Chk1 leads to Cdc25A ubiquitination and degradation, thus inhibiting DNA replication origin firing. In contrast, Cdc25B and Cdc25C regulate the onset of mitosis through dephosphorylation and activation of Cdk1-cyclin B complexes. In response to replication stress, Chk1 phosphorylates Cdc25B and Cdc25C leading to Cdc25B/C complex formation with 14-3-3 proteins. As these complexes are sequestered in the cytoplasm, they are unable to activate the nuclear Cdk1-cyclin B complex for mitotic entry.

These events are outlined in the figure. Persistent single-stranded DNA associated with RPA binds claspin (A) and ATR:ATRIP (B), leading to claspin phosphorylation (C). In parallel, the same single-stranded DNA:RPA complex binds RAD17:RFC (D), enabling the loading of RAD9:HUS1:RAD1 (9-1-1) complex onto the DNA (E). The resulting complex of proteins can then repeatedly bind (F) and phosphorylate (G) CHK1, activating multiple copies of CHK1.

Literature references

Zou, L., Elledge, SJ. (2003). Sensing DNA damage through ATRIP recognition of RPA-ssDNA complexes. *Science, 300*, 1542-8. ↗

Editions

2006-02-25	Authored	Borowiec, JA.
2006-02-25	Edited	D'Eustachio, P.

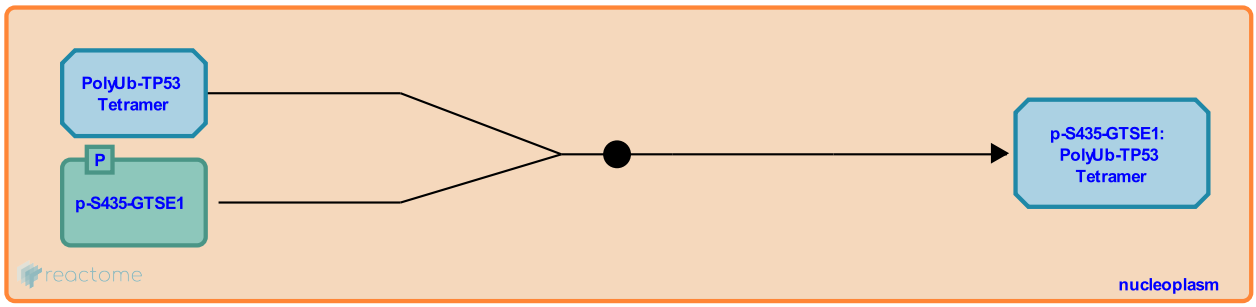
GTSE1 binds TP53 ↗

Location: G2/M Checkpoints

Stable identifier: R-HSA-8852337

Type: binding

Compartments: nucleoplasm



Since MDM2-mediated ubiquitination of TP53 promotes translocation of TP53 to the cytosol, and since GTSE1-facilitated translocation of TP53 to the cytosol depends on the functional MDM2 (with no reported interaction between GTSE1 and MDM2) (Monte et al. 2004), it is plausible that GTSE1 binds to TP53 polyubiquitinated by MDM2. The interaction between TP53 and GTSE1 involves the C-terminal regulatory domain of TP53 and the C-terminus of GTSE1 (Monte et al. 2003).

Followed by: GTSE1 promotes translocation of TP53 to the cytosol

Literature references

Del Sal, G., Schneider, C., Buscemi, G., Sandy, P., Monte, M., Benetti, R. (2003). The cell cycle-regulated protein human GTSE-1 controls DNA damage-induced apoptosis by affecting p53 function. *J. Biol. Chem., 278*, 30356-64. ↗

Del Sal, G., Collavin, L., Schneider, C., Monte, M., Marchionni, L., Benetti, R. (2004). hGTSE-1 expression stimulates cytoplasmic localization of p53. *J. Biol. Chem., 279*, 11744-52. ↗

Editions

2016-01-15	Authored, Edited	Orlic-Milacic, M.
2016-01-22	Reviewed	Bird, AW.

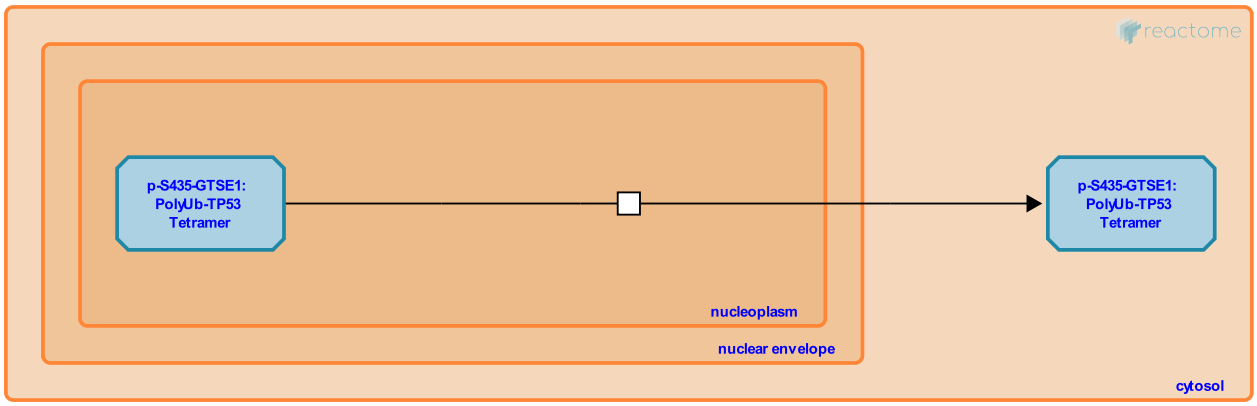
GTSE1 promotes translocation of TP53 to the cytosol ↗

Location: G2/M Checkpoints

Stable identifier: R-HSA-8852351

Type: transition

Compartments: nucleoplasm, cytosol



Binding of GTSE1 to TP53 (p53) in the nucleus promotes translocation of TP53 to the cytosol. This process is dependent on the nuclear export signal (NES) of GTSE1 (Monte et al. 2004).

Preceded by: GTSE1 binds TP53

Followed by: GTSE1 facilitates proteasome-mediated degradation of TP53

Literature references

Del Sal, G., Collavin, L., Schneider, C., Monte, M., Marchionni, L., Benetti, R. (2004). hGTSE-1 expression stimulates cytoplasmic localization of p53. *J. Biol. Chem., 279*, 11744-52. ↗

Editions

2016-01-15	Authored, Edited	Orlic-Milacic, M.
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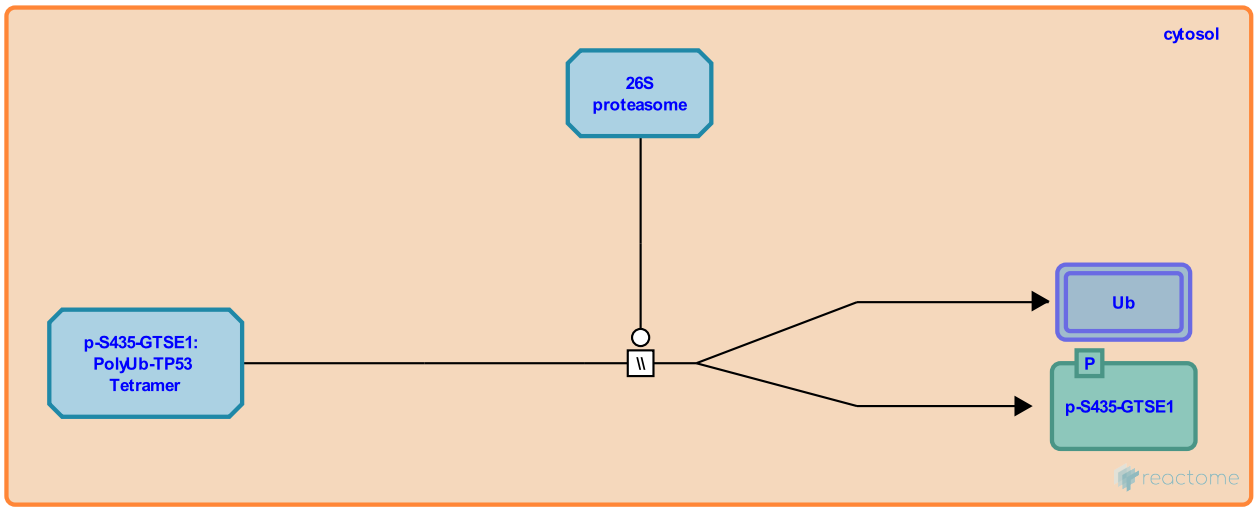
GTSE1 facilitates proteasome-mediated degradation of TP53

Location: G2/M Checkpoints

Stable identifier: R-HSA-8852354

Type: omitted

Compartments: cytosol



GTSE1 promotes down-regulation of TP53 in a proteasome-dependent way. Nuclear export of TP53 facilitated by GTSE1 and MDM2likely makes ubiquitinated TP53 available to the proteasome machinery. GTSE1-mediated decrease of TP53 levels is needed for the G2 checkpoint recovery (cell cycle re-entry after DNA damage induced G2 arrest) and rescues cells from DNA damage induced apoptosis during S/G2 phase (Monte et al. 2003, Monte et al. 2004).

Preceded by: GTSE1 promotes translocation of TP53 to the cytosol

Literature references

Del Sal, G., Schneider, C., Buscemi, G., Sandy, P., Monte, M., Benetti, R. (2003). The cell cycle-regulated protein human GTSE-1 controls DNA damage-induced apoptosis by affecting p53 function. *J. Biol. Chem., 278*, 30356-64.

Del Sal, G., Collavin, L., Schneider, C., Monte, M., Marchionni, L., Benetti, R. (2004). hGTSE-1 expression stimulates cytoplasmic localization of p53. *J. Biol. Chem., 279*, 11744-52.

Editions

2016-01-15	Authored, Edited	Orlic-Milacic, M.
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