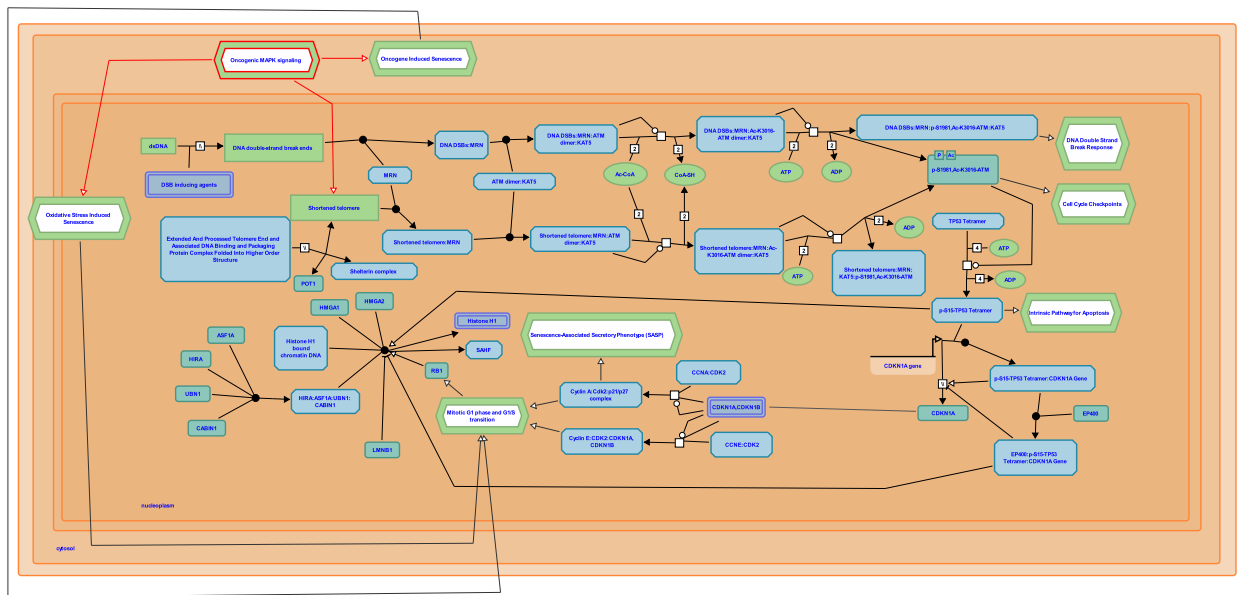


# DNA Damage/Telomere Stress Induced Senescence



Borowiec, JA., Coqueret, O., D'Eustachio, P., Du, F., Inga, A., Khanna, KK., Matthews, L., Orlic-Milacic, M., Pagano, M., Samarajiwa, S., Sanchez, Y., Sun, Y., Zaccara, S.

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

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/Textbook).

## 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

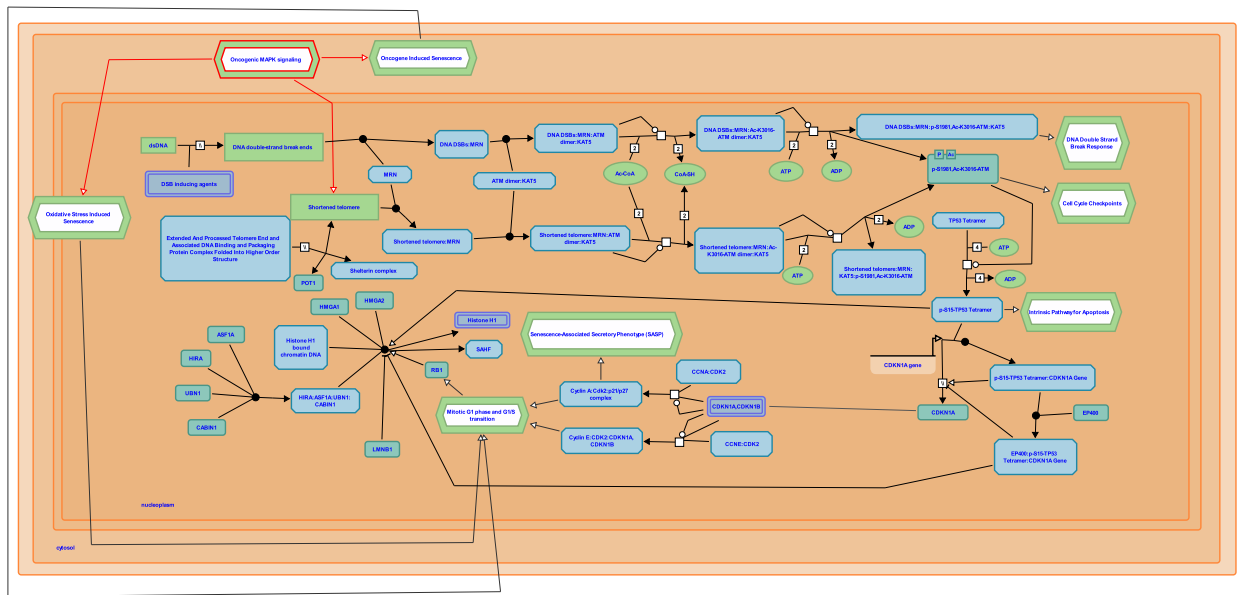
- Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics*, 18, 142. [↗](#)
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). 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 2 pathways and 16 reactions ([see Table of Contents](#))

# DNA Damage/Telomere Stress Induced Senescence ↗

Stable identifier: R-HSA-2559586



reactome

Reactive oxygen species (ROS), whose concentration increases in senescent cells due to oncogenic RAS-induced mitochondrial dysfunction (Moiseeva et al. 2009) or due to environmental stress, cause DNA damage in the form of double strand breaks (DSBs) (Yu and Anderson 1997). In addition, persistent cell division fueled by oncogenic signaling leads to replicative exhaustion, manifested in critically short telomeres (Harley et al. 1990, Hastie et al. 1990). Shortened telomeres are no longer able to bind the protective shelterin complex (Smogorzewska et al. 2000, de Lange 2005) and are recognized as damaged DNA.

The evolutionarily conserved MRN complex, consisting of MRE11A (MRE11), RAD50 and NBN (NBS1) subunits, binds DSBs (Lee and Paull 2005) and shortened telomeres that are no longer protected by shelterin (Wu et al. 2007). Once bound to the DNA, the MRN complex recruits and activates ATM kinase (Lee and Paull 2005, Wu et al. 2007), leading to phosphorylation of ATM targets, including TP53 (p53) (Banin et al. 1998, Canman et al. 1998, Khanna et al. 1998). TP53, phosphorylated on serine S15 by ATM, binds the CDKN1A (also known as p21, CIP1 or WAF1) promoter and induces CDKN1A transcription (El-Deiry et al. 1993, Karlseder et al. 1999). CDKN1A inhibits the activity of CDK2, leading to G1/S cell cycle arrest (Harper et al. 1993, El-Deiry et al. 1993).

SMURF2 is upregulated in response to telomere attrition in human fibroblasts and induces senescent phenotype through RB1 and TP53, independently of its role in TGF-beta-1 signaling (Zhang and Cohen 2004). The exact mechanism of SMURF2 involvement in senescence has not been elucidated.

## Literature references

Paull, TT., Lee, JH. (2005). ATM activation by DNA double-strand breaks through the Mre11-Rad50-Nbs1 complex. *Science*, 308, 551-4. ↗

Anderson, D., Yu, TW. (1997). Reactive oxygen species-induced DNA damage and its modification: a chemical investigation. *Mutat. Res.*, 379, 201-10. ↗

Cohen, SN., Zhang, H. (2004). Smurf2 up-regulation activates telomere-dependent senescence. *Genes Dev.*, 18, 3028-40. ↗

Tokino, T., el-Deiry, WS., Kinzler, KW., Vogelstein, B., Lin, D., Mercer, WE. et al. (1993). WAF1, a potential mediator of p53 tumor suppression. *Cell*, 75, 817-25. ↗

Gatei, M., Hobson, K., Taya, Y., Kozlov, S., Scott, S., Keating, KE. et al. (1998). ATM associates with and phosphorylates p53: mapping the region of interaction. *Nat Genet*, 20, 398-400. ↗

## Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

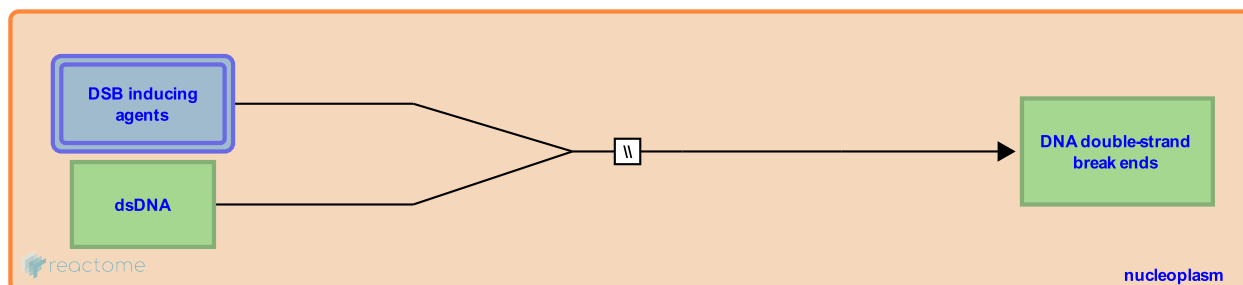
## DSB inducing agents induce double strand DNA breaks ↗

**Location:** [DNA Damage/Telomere Stress Induced Senescence](#)

**Stable identifier:** R-HSA-3785704

**Type:** omitted

**Compartments:** nucleoplasm



Reactive oxygen species (ROS) induce DNA double-strand breaks (DSBs) (Yu and Anderson 1997) in cells undergoing oxidative stress. In addition to ROS, DSBs can also be directly generated by ionizing radiation. Agents that interfere with the progression of replication forks, such as topoisomerase poisons used in chemotherapy, induce DSBs indirectly (Curtin 2012).

**Followed by:** [MRN complex binds DNA double strand breaks](#)

### Literature references

Anderson, D., Yu, TW. (1997). Reactive oxygen species-induced DNA damage and its modification: a chemical investigation. *Mutat. Res.*, 379, 201-10. ↗

Curtin, NJ. (2012). DNA repair dysregulation from cancer driver to therapeutic target. *Nat. Rev. Cancer*, 12, 801-17. ↗

### Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.
2015-05-12	Edited	Orlic-Milacic, M.
2015-06-12	Reviewed	Borowiec, JA.
2015-06-17	Revised	Orlic-Milacic, M.

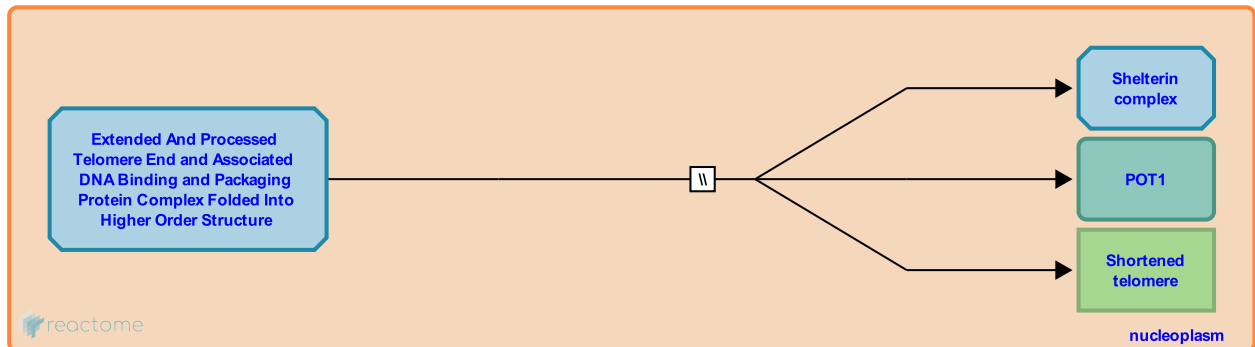
## Telomere shortening during replicative exhaustion ↗

**Location:** DNA Damage/Telomere Stress Induced Senescence

**Stable identifier:** R-HSA-3785711

**Type:** omitted

**Compartments:** nucleoplasm



In somatic cells where telomerase is not active, telomeric DNA shortens with each cell division (Harley et al. 1990, Hastie et al. 1990). This may be especially pronounced in cells undergoing replicative exhaustion due to oncogenic signaling-driven cell division. The shelterin complex, which protects telomeres from being recognized as double strand DNA breaks (reviewed by de Lange 2005), binds telomeric DNA through interaction of its subunits TREF1 (TRF1) and TREF2 (TRF2) with long TTAGGG repeat tracts (Smogorzewska et al. 2000). Telomere shortening due to replicative exhaustion results in a decreased number of TTAGGG repeats, which negatively impacts shelterin binding to telomeric DNA.

**Followed by:** MRN complex binds shortened telomeres

### Literature references

- de Lange, T. (2005). Shelterin: the protein complex that shapes and safeguards human telomeres. *Genes Dev*, 19, 2100-10. ↗
- van Steensel, B., Schnapp, G., Schaefer, MR., Oelmann, S., Smogorzewska, A., de Lange, T. et al. (2000). Control of human telomere length by TRF1 and TRF2. *Mol. Cell. Biol.*, 20, 1659-68. ↗
- Greider, CW., Futcher, AB., Harley, CB. (1990). Telomeres shorten during ageing of human fibroblasts. *Nature*, 345, 458-60. ↗
- Dempster, M., Thompson, AM., Dunlop, MG., Allshire, RC., Green, DK., Hastie, ND. (1990). Telomere reduction in human colorectal carcinoma and with ageing. *Nature*, 346, 866-8. ↗

### Editions

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2013-09-03	Reviewed	Samarajiwa, S.

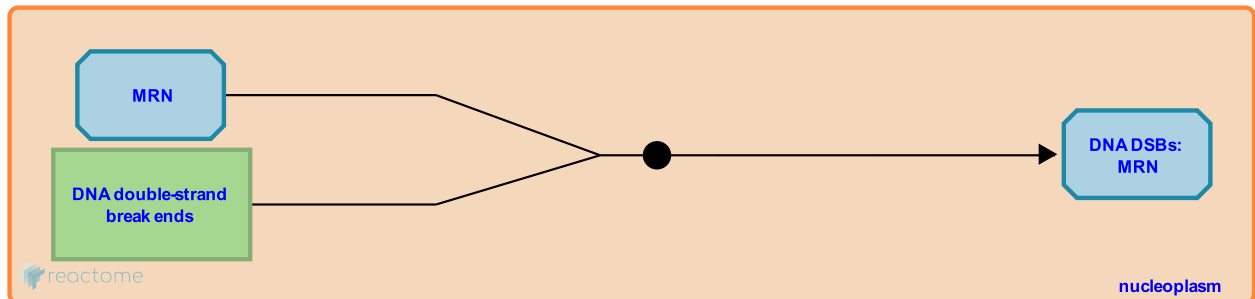
## MRN complex binds DNA double strand breaks ↗

**Location:** [DNA Damage/Telomere Stress Induced Senescence](#)

**Stable identifier:** R-HSA-3785768

**Type:** binding

**Compartments:** nucleoplasm



The MRN complex (MRE11A:RAD50:NBN) binds to DNA ends found at double-strand breaks (DNA DSBs) (Lee and Paull 2005). In budding yeast, the Mre11:Rad50:Xrs2 complex, homologous to human MRN, rapidly localizes to DNA breaks (Shroff et al. 2004, Lisby et al. 2004).

**Preceded by:** [DSB inducing agents induce double strand DNA breaks](#)

**Followed by:** [MRN complex bound to DNA ends recruits ATM](#)

### Literature references

Arbel-Eden, A., Haber, JE., Ira, G., Bonner, WM., Shroff, R., Petrini, JH. et al. (2004). Distribution and dynamics of chromatin modification induced by a defined DNA double-strand break. *Curr. Biol.*, 14, 1703-11. ↗

Paull, TT., Lee, JH. (2005). ATM activation by DNA double-strand breaks through the Mre11-Rad50-Nbs1 complex. *Science*, 308, 551-4. ↗

Lisby, M., Burgess, RC., Barlow, JH., Rothstein, R. (2004). Choreography of the DNA damage response: spatiotemporal relationships among checkpoint and repair proteins. *Cell*, 118, 699-713. ↗

### Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
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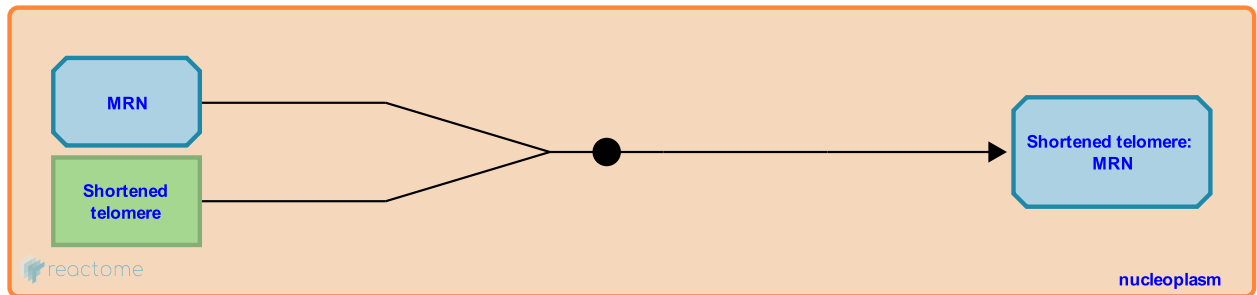
## MRN complex binds shortened telomeres ↗

**Location:** DNA Damage/Telomere Stress Induced Senescence

**Stable identifier:** R-HSA-5682020

**Type:** binding

**Compartments:** nucleoplasm



The MRN complex (MRE11:RAD50:NBS1 also known as MRE11A:RAD50:NBN) binds telomeric DNA, and MRN association with telomeric DNA is mutually exclusive with shelterin binding (Wu et al. 2007).

**Preceded by:** Telomere shortening during replicative exhaustion

**Followed by:** MRN complex bound to shortened telomeres recruits ATM

### Literature references

Xiao, S., Wu, Y., Zhu, XD. (2007). MRE11-RAD50-NBS1 and ATM function as co-mediators of TRF1 in telomere length control. *Nat. Struct. Mol. Biol.*, 14, 832-40. ↗

### Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.



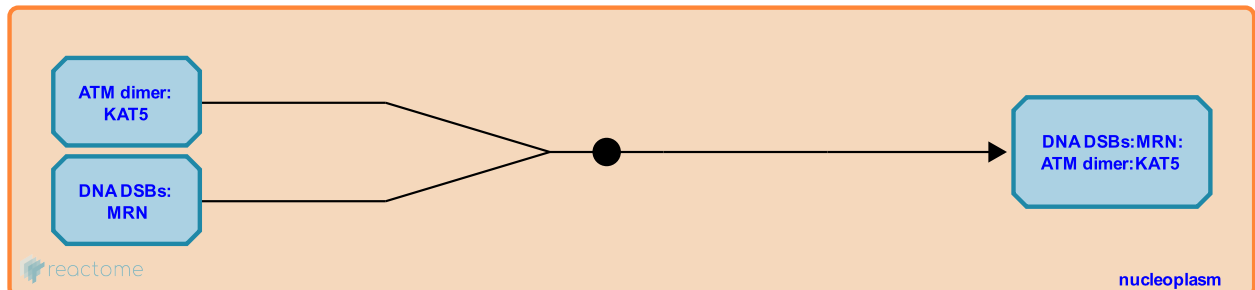
## MRN complex bound to DNA ends recruits ATM [↗](#)

**Location:** [DNA Damage/Telomere Stress Induced Senescence](#)

**Stable identifier:** R-HSA-5693612

**Type:** binding

**Compartments:** nucleoplasm



Activation of ATM kinase in response to DNA damage in the form of DNA double-strand breaks (DSBs) requires association of ATM dimers with the MRN complex bound to DNA ends. MRN subunit RAD50 is essential for ATM dimer binding (Lee and Paull 2005, Wu et al. 2007). ATM dimer exists in a preformed complex with KAT5 (Tip60) histone acetyltransferase (Sun et al. 2005).

**Preceded by:** [MRN complex binds DNA double strand breaks](#)

**Followed by:** [KAT5 acetylates ATM at DNA DSBs](#)

### Literature references

Chen, S., Fernandes, N., Sun, Y., Jiang, X., Price, BD. (2005). A role for the Tip60 histone acetyltransferase in the acetylation and activation of ATM. *Proc. Natl. Acad. Sci. U.S.A.*, 102, 13182-7. [↗](#)

Paull, TT., Lee, JH. (2005). ATM activation by DNA double-strand breaks through the Mre11-Rad50-Nbs1 complex. *Science*, 308, 551-4. [↗](#)

Xiao, S., Wu, Y., Zhu, XD. (2007). MRE11-RAD50-NBS1 and ATM function as co-mediators of TRF1 in telomere length control. *Nat. Struct. Mol. Biol.*, 14, 832-40. [↗](#)

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2015-06-12	Reviewed	Borowiec, JA.

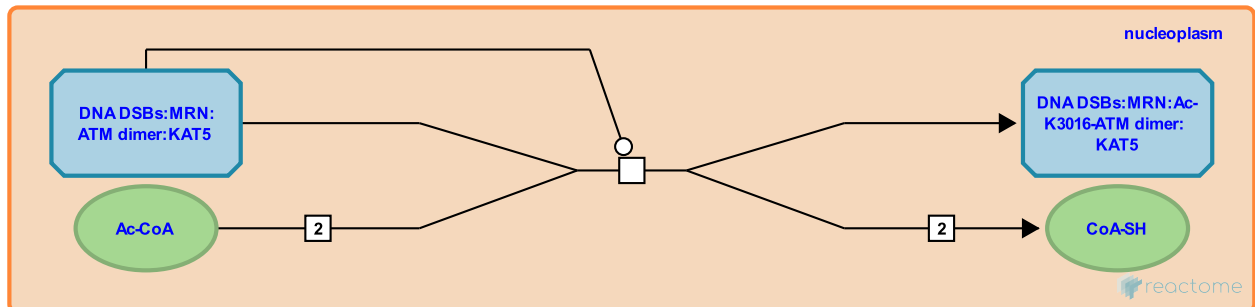
## KAT5 acetylates ATM at DNA DSBs ↗

**Location:** DNA Damage/Telomere Stress Induced Senescence

**Stable identifier:** R-HSA-5682044

**Type:** transition

**Compartments:** nucleoplasm



The histone acetyltransferase Tip60 (KAT5), in addition to forming a histone acetyltransferase complex with NuA4, forms another complex with ATM dimers. The ATM dimer:KAT5 complex is formed in the absence of DNA damage, but the acetyltransferase activity of KAT5 is activated by double-strand DNA breaks (DNA DSBs) (Sun et al. 2005). In response to DNA DSBs, the MRN complex targets KAT5 to chromatin, where KAT5 associates with histone H3 trimethylated on lysine 10 (commonly known as H3K9me3 mark). Besides the MRN complex, the ability of KAT5 to access H3K9me3 depends on the DNA damage-induced displacement of HP1beta (CBX1) from H3K9me3 (Ayoub et al. 2008). Binding to H3K9me3 activates the acetyltransferase activity of KAT5 (Sun et al. 2009). KAT5 acetylates ATM on lysine residue K3016 in the highly conserved C-terminal FATC domain of ATM. ATM acetylation is needed for the activation of ATM kinase activity in response to DNA damage (Sun et al. 2007).

**Preceded by:** MRN complex bound to DNA ends recruits ATM

**Followed by:** MRN activates ATM

### Literature references

- Chen, S., Fernandes, N., Sun, Y., Jiang, X., Price, BD. (2005). A role for the Tip60 histone acetyltransferase in the acetylation and activation of ATM. *Proc. Natl. Acad. Sci. U.S.A.*, 102, 13182-7. ↗
- Bernal, JA., Ayoub, N., Venkitaraman, AR., Jeyasekharan, AD. (2008). HP1-beta mobilization promotes chromatin changes that initiate the DNA damage response. *Nature*, 453, 682-6. ↗
- Xu, Y., Ayrappetov, MK., Moreau, LA., Sun, Y., Jiang, X., Price, BD. et al. (2009). Histone H3 methylation links DNA damage detection to activation of the tumour suppressor Tip60. *Nat. Cell Biol.*, 11, 1376-82. ↗
- Xu, Y., Sun, Y., Roy, K., Price, BD. (2007). DNA damage-induced acetylation of lysine 3016 of ATM activates ATM kinase activity. *Mol. Cell. Biol.*, 27, 8502-9. ↗

### Editions

2015-05-12	Authored, Edited	Orlic-Milacic, M.
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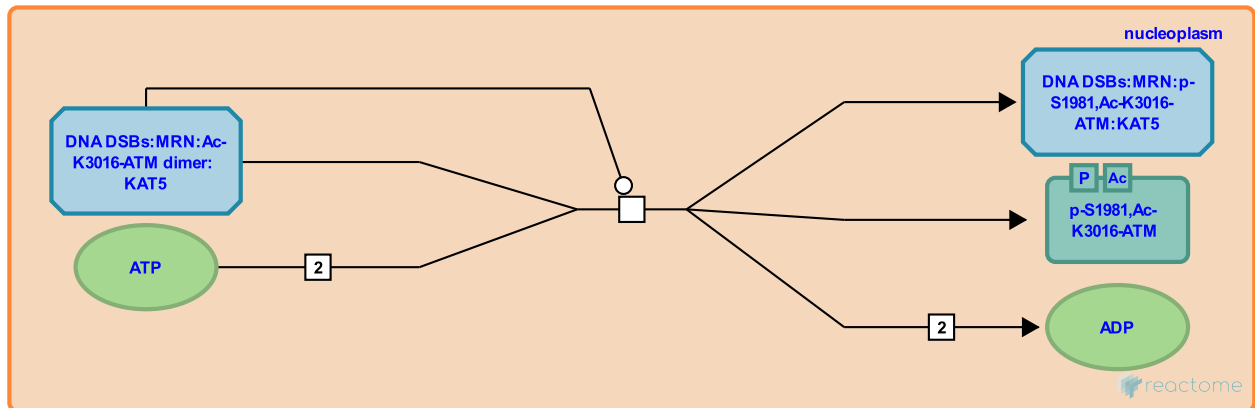
## MRN activates ATM ↗

**Location:** DNA Damage/Telomere Stress Induced Senescence

**Stable identifier:** R-HSA-5693540

**Type:** transition

**Compartments:** nucleoplasm



MRN promotes dissociation of ATM dimers to ATM monomers which is accompanied by ATM trans-autophosphorylation on serine residue S1981 (Bakkenist et al. 2003, Du et al. 2014). ATM autophosphorylation at serine residues S367 and S1893 is also implicated in ATM activation (Kozlov et al. 2006). Dissociation of ATM dimers requires the ATP-dependent DNA-helicase activity of the MRN subunit RAD50 (Lee and Paull 2005). KAT5 (Tip60) mediated acetylation of ATM dimers at lysine K3016 is a prerequisite for ATM kinase activity (Sun et al. 2007). Upon the dissociation of ATM dimers induced by DNA double-strand breaks (DSBs), a fraction of activated ATM is retained at DSB sites, co-localizing with the MRN complex (Andegeko et al. 2001, Uziel et al. 2003) at ionizing radiation-induced foci (IRIF). MRN facilitates the binding of a portion of ATM substrates to ATM (Lee and Paull 2004).

After DSBs are repaired, ATM is dephosphorylated by an unidentified PP2A phosphatase complex, leading to dimer reformation (Goodarzi et al. 2004).

**Preceded by:** KAT5 acetylates ATM at DNA DSBs

**Followed by:** ATM phosphorylates TP53 at S15

## Literature references

- Meng, H., Xu, Y., Zhang, M., Du, F., Chang, S., Sun, Y. et al. (2014). Dimer monomer transition and dimer re-formation play important role for ATM cellular function during DNA repair. *Biochem. Biophys. Res. Commun.*, 452, 1034-9. ↗
- Lee, JH., Paull, TT. (2004). Direct activation of the ATM protein kinase by the Mre11/Rad50/Nbs1 complex. *Science*, 304, 93-6. ↗
- Kastan, MB., Bakkenist, CJ. (2003). DNA damage activates ATM through intermolecular autophosphorylation and dimer dissociation. *Nature*, 421, 499-506. ↗
- Xu, Y., Sun, Y., Roy, K., Price, BD. (2007). DNA damage-induced acetylation of lysine 3016 of ATM activates ATM kinase activity. *Mol. Cell. Biol.*, 27, 8502-9. ↗
- Ye, R., Douglas, P., Jonnalagadda, JC., Lees-Miller, SP., Goodarzi, AA., Young, D. et al. (2004). Autophosphorylation of ataxia-telangiectasia mutated is regulated by protein phosphatase 2A. *EMBO J.*, 23, 4451-61. ↗

## Editions

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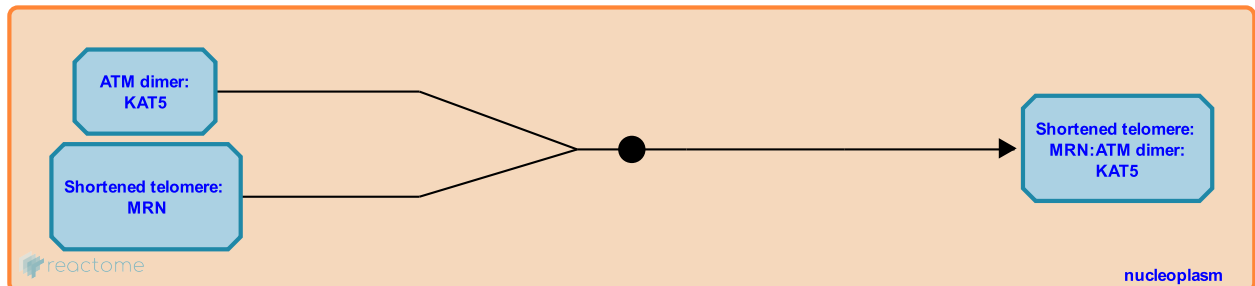
## MRN complex bound to shortened telomeres recruits ATM ↗

**Location:** [DNA Damage/Telomere Stress Induced Senescence](#)

**Stable identifier:** R-HSA-5682018

**Type:** binding

**Compartments:** nucleoplasm



Activation of ATM kinase in response to shortened telomeres requires association of ATM dimers with the MRN complex bound to DNA ends. MRN subunit RAD50 is essential for ATM dimer binding (Lee and Paull 2005, Wu et al. 2007). Dissociation of the shelterin complex from telomeres activates ATM (Karlseder et al. 1999), consistent with a mutually exclusive binding of shelterin and MRN to telomeric DNA (Wu et al. 2007).

**Preceded by:** [MRN complex binds shortened telomeres](#)

**Followed by:** [KAT5 acetylates ATM at shortened telomeres](#)

### Literature references

Paull, TT., Lee, JH. (2005). ATM activation by DNA double-strand breaks through the Mre11-Rad50-Nbs1 complex. *Science*, 308, 551-4. ↗

Karlseder, J., Broccoli, D., Hardy, S., Dai, Y., de Lange, T. (1999). p53- and ATM-dependent apoptosis induced by telomeres lacking TRF2. *Science*, 283, 1321-5. ↗

Xiao, S., Wu, Y., Zhu, XD. (2007). MRE11-RAD50-NBS1 and ATM function as co-mediators of TRF1 in telomere length control. *Nat. Struct. Mol. Biol.*, 14, 832-40. ↗

### Editions

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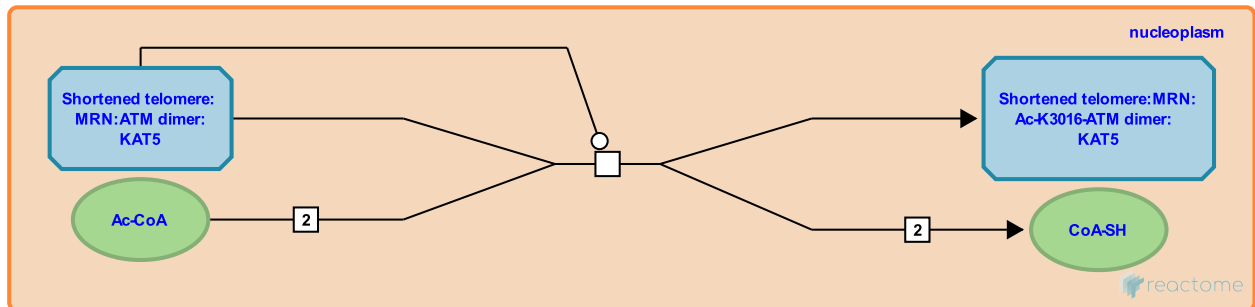
## KAT5 acetylates ATM at shortened telomeres ↗

**Location:** DNA Damage/Telomere Stress Induced Senescence

**Stable identifier:** R-HSA-6792712

**Type:** transition

**Compartments:** nucleoplasm



The histone acetyltransferase Tip60 (KAT5), in addition to forming a histone acetyltransferase complex with NuA4, forms another complex with ATM dimers. The ATM dimer:KAT5 complex is formed in the absence of DNA damage, but the acetyltransferase activity of KAT5 is activated by double strand DNA breaks (DNA DSBs) (Sun et al. 2005). The activation of KAT5 at shortened telomeres has not been experimentally studied, but KAT5 is assumed to be recruited to shortened telomeres, together with ATM, based on the analogy with ATM activation at DNA DSBs. It is likely that at shortened telomeres, similar to DNA DSBs, the MRN complex targets KAT5 to chromatin, where KAT5 associates with histone H3 trimethylated on lysine 10 (commonly known as H3K9me3 mark). Besides the MRN complex, the ability of KAT5 to access H3K9me3 depends on the DNA damage-induced displacement of HP1beta (CBX1) from H3K9me3 (Ayoub et al. 2008). Similar to DNA DSBs, HP1beta is also displaced from unprotected telomeres (Koering et al. 2002). Binding to H3K9me3 activates the acetyltransferase activity of KAT5 (Sun et al. 2009). KAT5 acetylates ATM on lysine residue K3016 in the highly conserved C-terminal FATC domain of ATM. ATM acetylation is likely needed for the activation of ATM kinase activity at shortened telomeres, as it needed for ATM activation at DNA DSBs (Sun et al. 2007).

**Preceded by:** MRN complex bound to shortened telomeres recruits ATM

**Followed by:** MRN bound to shortened telomeres activates ATM

### Literature references

- Chen, S., Fernandes, N., Sun, Y., Jiang, X., Price, BD. (2005). A role for the Tip60 histone acetyltransferase in the acetylation and activation of ATM. *Proc. Natl. Acad. Sci. U.S.A.*, 102, 13182-7. ↗
- Bernal, JA., Ayoub, N., Venkitaraman, AR., Jeyasekharan, AD. (2008). HP1-beta mobilization promotes chromatin changes that initiate the DNA damage response. *Nature*, 453, 682-6. ↗
- Xu, Y., Ayrappetov, MK., Moreau, LA., Sun, Y., Jiang, X., Price, BD. et al. (2009). Histone H3 methylation links DNA damage detection to activation of the tumour suppressor Tip60. *Nat. Cell Biol.*, 11, 1376-82. ↗
- Xu, Y., Sun, Y., Roy, K., Price, BD. (2007). DNA damage-induced acetylation of lysine 3016 of ATM activates ATM kinase activity. *Mol. Cell. Biol.*, 27, 8502-9. ↗
- Puisieux, A., Sabatier, L., Brun, C., Koering, CE., Brunori, M., Gilson, E. et al. (2002). Human telomeric position effect is determined by chromosomal context and telomeric chromatin integrity. *EMBO Rep.*, 3, 1055-61. ↗

### Editions

2015-05-12	Authored, Edited	Orlic-Milacic, M.
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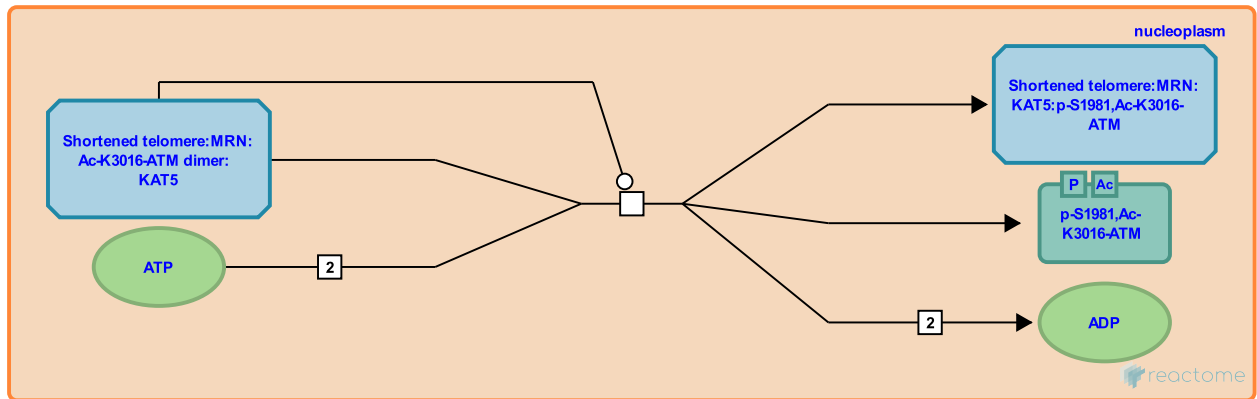
## MRN bound to shortened telomeres activates ATM ↗

**Location:** DNA Damage/Telomere Stress Induced Senescence

**Stable identifier:** R-HSA-5682026

**Type:** transition

**Compartments:** nucleoplasm



MRN bound to shortened telomeres promotes dissociation of ATM dimers to ATM monomers which is accompanied by ATM autophosphorylation on serine residue S1981. Dissociation of ATM dimers requires the ATP-dependent DNA-helicase activity of the MRN subunit RAD50 (Lee and Paull 2005, Wu et al. 2007).

**Preceded by:** [KAT5 acetylates ATM at shortened telomeres](#)

**Followed by:** [ATM phosphorylates TP53 at S15](#)

### Literature references

Paull, TT., Lee, JH. (2005). ATM activation by DNA double-strand breaks through the Mre11-Rad50-Nbs1 complex. *Science*, 308, 551-4. ↗

Xiao, S., Wu, Y., Zhu, XD. (2007). MRE11-RAD50-NBS1 and ATM function as co-mediators of TRF1 in telomere length control. *Nat. Struct. Mol. Biol.*, 14, 832-40. ↗

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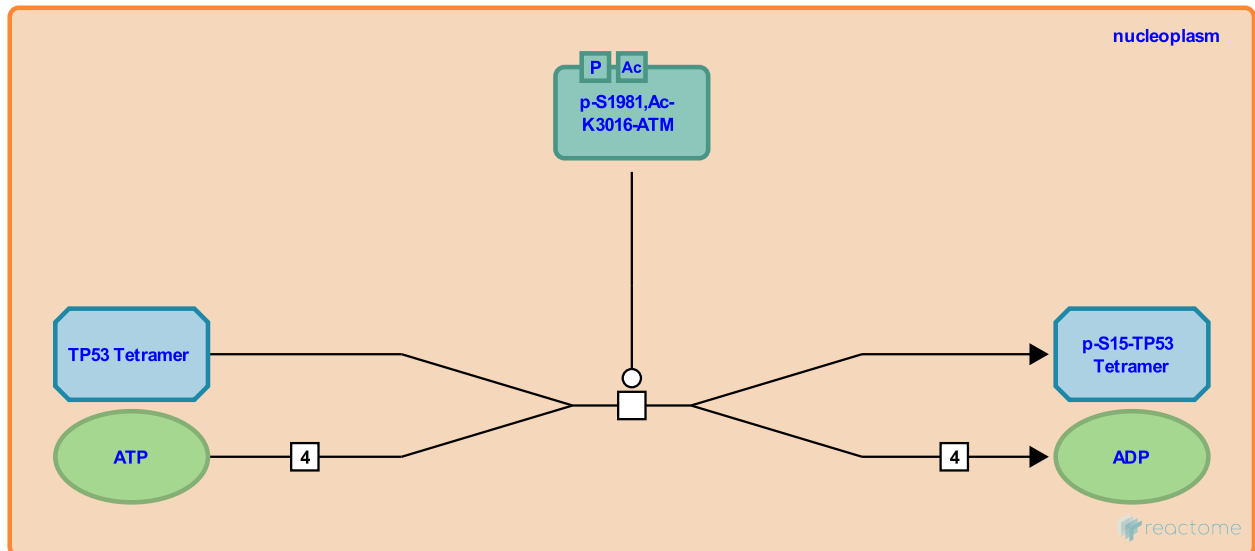
## ATM phosphorylates TP53 at S15 ↗

**Location:** [DNA Damage/Telomere Stress Induced Senescence](#)

**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).

**Preceded by:** [MRN bound to shortened telomeres activates ATM](#), [MRN activates ATM](#)

**Followed by:** [TP53 binds the CDKN1A promoter](#)

### Literature references

Gatei, M., Hobson, K., Taya, Y., Kozlov, S., Scott, S., Keating, KE. et al. (1998). ATM associates with and phosphorylates p53: mapping the region of interaction. *Nat Genet*, 20, 398-400. ↗

Appella, E., Siliciano, JD., Kastan, MB., Tamai, K., Taya, Y., Sakaguchi, K. et al. (1998). Activation of the ATM kinase by ionizing radiation and phosphorylation of p53. *Science*, 281, 1677-9. ↗

Shiloh, Y., Taya, Y., Reiss, Y., Ziv, Y., Smorodinsky, NI., Prives, C. et al. (1998). Enhanced phosphorylation of p53 by ATM in response to DNA damage. *Science*, 281, 1674-7. ↗

### Editions

2003-06-05	Authored	Khanna, KK.
2008-05-08	Reviewed	Sanchez, Y.
2015-05-12	Edited	Orlic-Milacic, M.
2015-06-12	Reviewed	Borowiec, JA.
2016-02-04	Reviewed	Inga, A., Zaccara, S.



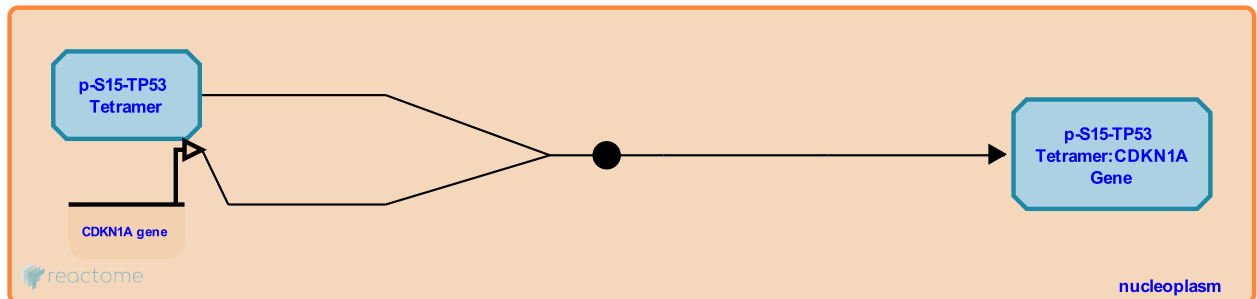
## TP53 binds the CDKN1A promoter ↗

**Location:** DNA Damage/Telomere Stress Induced Senescence

**Stable identifier:** R-HSA-3786258

**Type:** binding

**Compartments:** nucleoplasm



TP53 (p53), stabilized by ATM-mediated phosphorylation on S15 (Karlseder et al. 1999) binds CDKN1A (p21) promoter (El-Deiry et al. 1993).

**Preceded by:** ATM phosphorylates TP53 at S15

**Followed by:** EP400 binds CDKN1A promoter, Transcriptional activation of CDKN1A by TP53 is inhibited by EP400

## Literature references

Karlseder, J., Broccoli, D., Hardy, S., Dai, Y., de Lange, T. (1999). p53- and ATM-dependent apoptosis induced by telomeres lacking TRF2. *Science*, 283, 1321-5. ↗

Tokino, T., el-Deiry, WS., Kinzler, KW., Vogelstein, B., Lin, D., Mercer, WE. et al. (1993). WAF1, a potential mediator of p53 tumor suppression. *Cell*, 75, 817-25. ↗

## Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

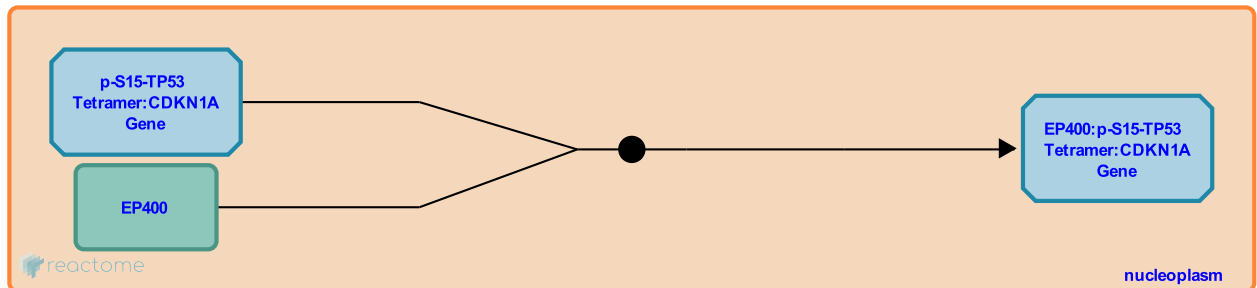
## EP400 binds CDKN1A promoter ↗

**Location:** DNA Damage/Telomere Stress Induced Senescence

**Stable identifier:** R-HSA-4647593

**Type:** binding

**Compartments:** nucleoplasm



EP400 (p400) binds to a CDKN1A promoter region that overlaps with the distal TP53-binding site and can co-localize with TP53 on CDKN1A promoter (Chan et al. 2005).

**Preceded by:** TP53 binds the CDKN1A promoter

**Followed by:** Transcriptional activation of CDKN1A by TP53 is inhibited by EP400

### Literature references

Livingston, DM., Lowe, SW., Narita, M., Chan, HM. (2005). The p400 E1A-associated protein is a novel component of the p53 --> p21 senescence pathway. *Genes Dev.*, 19, 196-201. ↗

### Editions

2013-09-03	Reviewed	Samarajiwa, S.
2013-09-30	Authored	Orlic-Milacic, M.
2013-11-08	Edited	Orlic-Milacic, M.

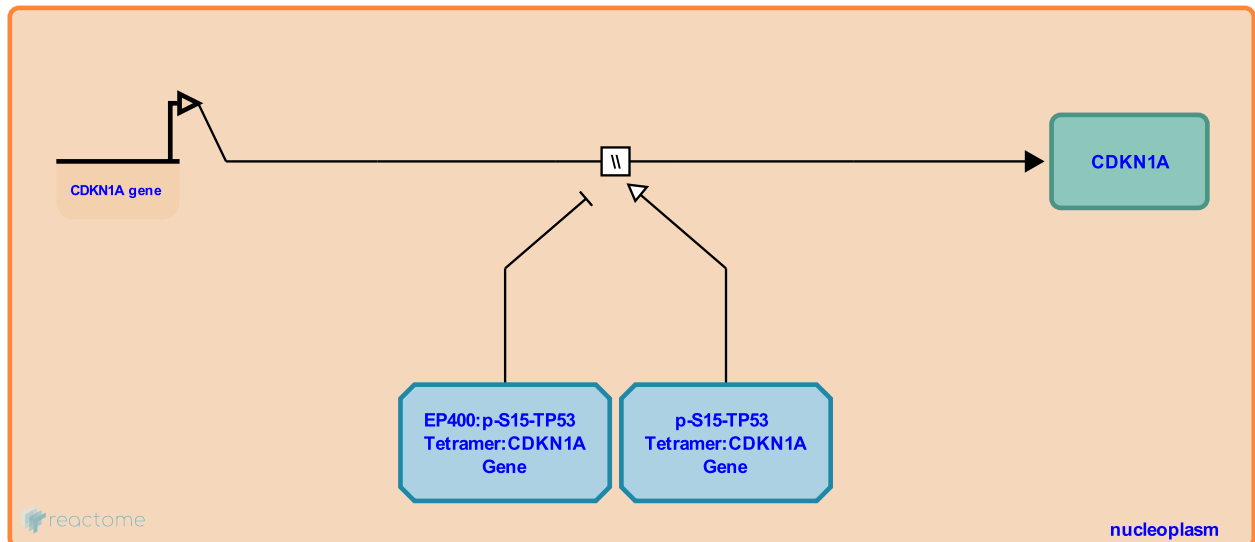
## Transcriptional activation of CDKN1A by TP53 is inhibited by EP400 ↗

**Location:** DNA Damage/Telomere Stress Induced Senescence

**Stable identifier:** R-HSA-4647613

**Type:** omitted

**Compartments:** nucleoplasm



CDKN1A (p21) is transcriptionally activated by TP53 (p53) after DNA damage (el-Deiry et al. 1993). EP400 (p400) binds to a CDKN1A promoter region that overlaps with the distal TP53-binding site and can co-localize with TP53 on CDKN1A promoter. The presence of EP400 results in the downregulation of CDKN1A transcription without affecting the phosphorylation of TP53 on serine S15 (Chan et al. 2005).

**Preceded by:** EP400 binds CDKN1A promoter, TP53 binds the CDKN1A promoter

**Followed by:** Inactivation of Cyclin A:Cdk2 complexes by p27/p21, Inactivation of Cyclin E:Cdk2 complexes by p27/p21

### Literature references

Livingston, DM., Lowe, SW., Narita, M., Chan, HM. (2005). The p400 E1A-associated protein is a novel component of the p53 --> p21 senescence pathway. *Genes Dev.*, 19, 196-201. ↗

Tokino, T., el-Deiry, WS., Kinzler, KW., Vogelstein, B., Lin, D., Mercer, WE. et al. (1993). WAF1, a potential mediator of p53 tumor suppression. *Cell*, 75, 817-25. ↗

### Editions

2006-09-29	Authored	Matthews, L.
2006-10-10	Edited	Matthews, L.
2013-09-03	Reviewed	Samarajiwa, S.
2013-09-30	Revised	Orlic-Milacic, M.

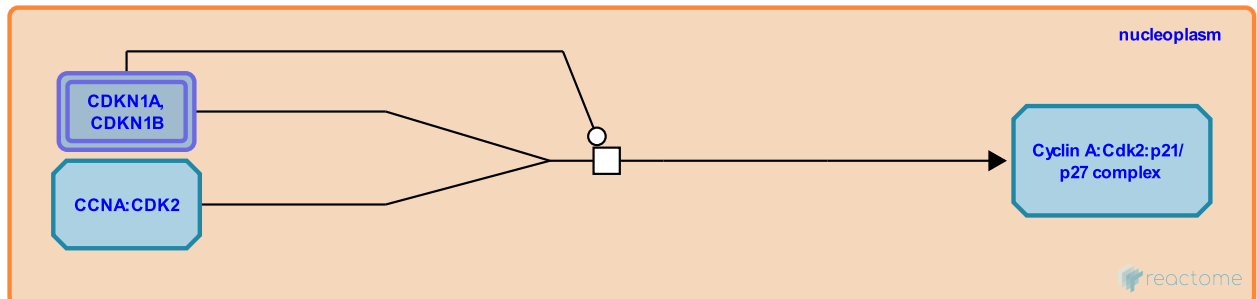
## Inactivation of Cyclin A:Cdk2 complexes by p27/p21 ↗

**Location:** DNA Damage/Telomere Stress Induced Senescence

**Stable identifier:** R-HSA-187934

**Type:** transition

**Compartments:** nucleoplasm



During G1, the activity of cyclin-dependent kinases (CDKs) is controlled by the CDK inhibitors (CKIs) CDKN1A (p21) and CDKN1B (p27), thereby preventing premature entry into S phase (Guardavaccaro and Pagano, 2006).

**Preceded by:** [Transcriptional activation of CDKN1A by TP53 is inhibited by EP400](#)

### Literature references

Eytan, E., Draetta, GF., Hershko, A., Montagnoli, A., Pagano, M., Carrano, AC. et al. (1999). Ubiquitination of p27 is regulated by Cdk-dependent phosphorylation and trimeric complex formation. *Genes Dev*, 13, 1181-9. ↗

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

### Editions

2006-09-19	Authored	Pagano, M.
2006-09-28	Edited	Matthews, L.
2006-10-06	Reviewed	Coqueret, O.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

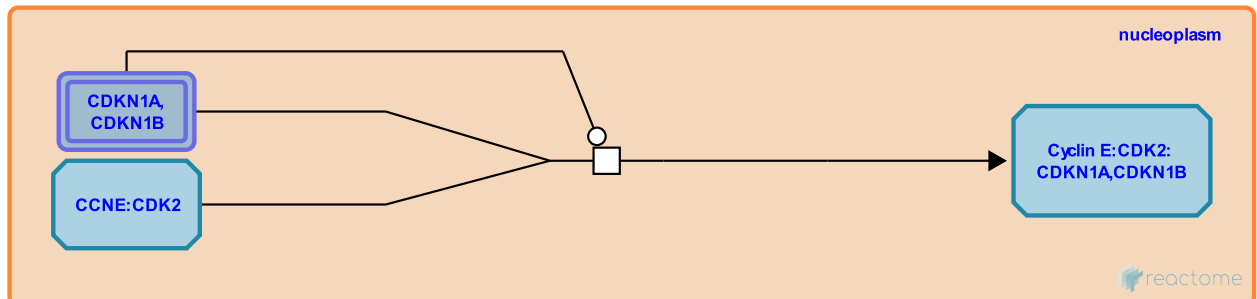
## Inactivation of Cyclin E:Cdk2 complexes by p27/p21 ↗

**Location:** DNA Damage/Telomere Stress Induced Senescence

**Stable identifier:** R-HSA-69562

**Type:** transition

**Compartments:** nucleoplasm



During G1, the activity of cyclin-dependent kinases (CDKs) is controlled by the CDK inhibitors (CKIs) CDKN1A (p21) and CDKN1B (p27), thereby preventing premature entry into S phase (see Guardavaccaro and Pagano, 2006). The efficient recognition and ubiquitination of p27 by the SCF (Skp2) complex requires the formation of a trimeric complex containing p27 and cyclin E/A:Cdk2.

**Preceded by:** [Transcriptional activation of CDKN1A by TP53 is inhibited by EP400](#)

### Literature references

Eytan, E., Draetta, GF., Hershko, A., Montagnoli, A., Pagano, M., Carrano, AC. et al. (1999). Ubiquitination of p27 is regulated by Cdk-dependent phosphorylation and trimeric complex formation. *Genes Dev*, 13, 1181-9. ↗

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

Liu, X., Nacusi, L., Wang, W., Sheaff, RJ. (2005). Ubiquitination of p21Cip1/WAF1 by SCFSkp2: substrate requirement and ubiquitination site selection. *Biochemistry*, 44, 14553-64. ↗

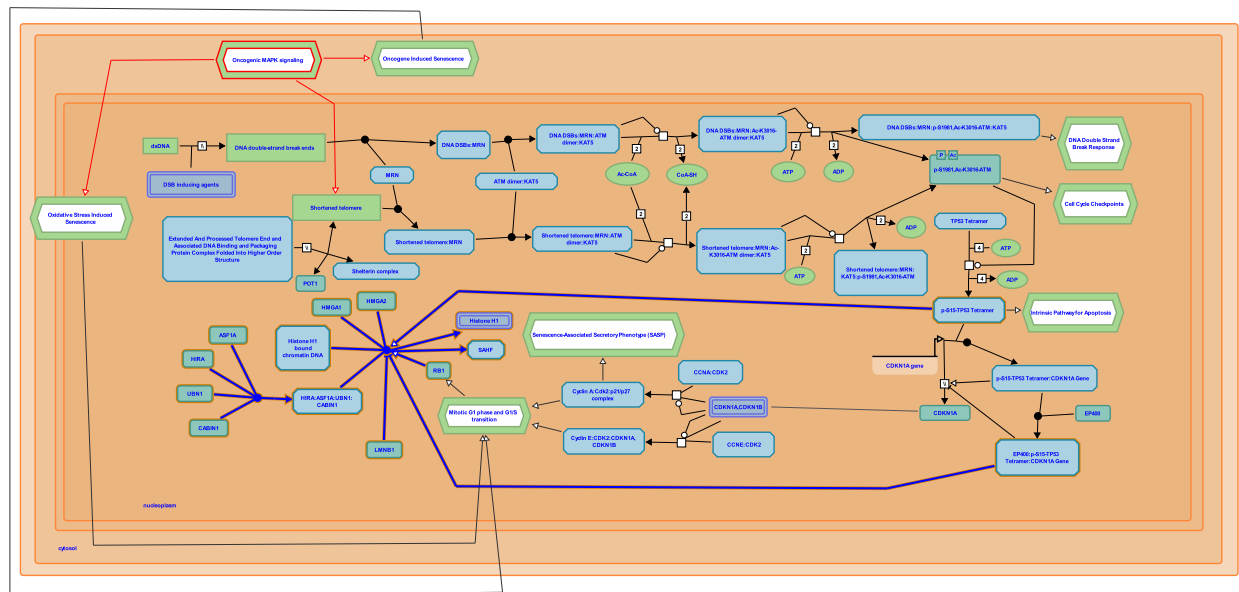
### Editions

2006-10-02	Edited, Revised	Matthews, L.
2015-10-14	Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

# Formation of Senescence-Associated Heterochromatin Foci (SAHF) ↗

**Location:** DNA Damage/Telomere Stress Induced Senescence

**Stable identifier:** R-HSA-2559584



reactome

The process of DNA damage/telomere stress induced senescence culminates in the formation of senescence associated heterochromatin foci (SAHF). These foci represent facultative heterochromatin that is formed in senescent cells. They contribute to the repression of proliferation promoting genes and play an important role in the permanent cell cycle exit that characterizes senescence (Narita et al. 2003 and 2006). SAHF appear as compacted, punctate DAPI stained foci of DNA. Each chromosome is condensed into a single SAH focus, with telomeric and centromeric chromatin located predominantly at its periphery (Funayama et al. 2006, Zhang et al. 2007).

An evolutionarily conserved protein complex of HIRA, ASF1A, UBN1 and CABIN1 plays a crucial role in the SAHF formation. As cells approach senescence, HIRA, ASF1A, UBN1 and CABIN1 accumulate at the PML bodies (Zhang et al. 2005, Banumathy et al. 2009, Rai et al. 2011). PML bodies are punctate nuclear structures that contain PML protein and numerous other proteins and are proposed to be the sites of assembly of macromolecular regulatory complexes and protein modification (Fogal et al. 2000, Guo et al. 2000, Pearson et al. 2000). Recruitment of HIRA to PML bodies coincides with altered chromatin structure and deposition of macroH2A histone H2A variant onto chromatin. As cells become senescent, HIRA, ASF1A, UBN1 and CABIN1 relocate from PML bodies to SAHF. HIRA accumulation at PML bodies is RB1 and TP53 independent, but may require phosphorylation of HIRA serine S697 by GSK3B (Ye, Zerlanko, Kennedy et al. 2007). SAHF formation itself, however, requires functional RB1 and TP53 pathways (Ye, Zerlanko, Zhang et al. 2007).

SAHF contain H3K9Me mark, characteristic of transcriptionally silent chromatin, and HP1, macroH2A histone H2A variant and HMGAs proteins are also components of SAHF (Narita et al. 2006), besides the HIRA:ASF1A:UBN1:CABIN1 complex. A yet unidentified H3K9Me histone methyltransferase may be recruited to SAHF by UBN1 (Banumathy et al. 2009). One of the functions of the HIRA:ASF1A:UBN1:CABIN1 complex is to deposit histone H3.3. variant to chromatin, which influences gene expression (Zhang et al. 2007, Rai et al. 2011).

Further studies are needed to fully elucidate the mechanism of SAHF formation and mechanism by which SAHF promote cell senescence.

## Literature references

- Sandy, P., Fogal, V., Pandolfi, PP., Sternsdorf, T., Del Sal, G., Will, H. et al. (2000). Regulation of p53 activity in nucleolar bodies by a specific PML isoform. *EMBO J.*, 19, 6185-95. ↗
- Erzberger, JP., Ye, X., Poustovoitov, MV., Adams, PD., Dunbrack, RL., Santos, HA. et al. (2005). Formation of MacroH2A-containing senescence-associated heterochromatin foci and senescence driven by ASF1a and HIRA. *Dev. Cell*, 8, 19-30. ↗

Lowe, SW., Nuñez, S., Krizhanovsky, V., Narita, M., Narita, M., Myers, MP. et al. (2006). A novel role for high-mobility group a proteins in cellular senescence and heterochromatin formation. *Cell*, 126, 503-14. ↗

Ye, X., Zhang, R., Banumathy, G., Zerlanko, B., Adams, PD., Kennedy, A. (2007). Downregulation of Wnt signaling is a trigger for formation of facultative heterochromatin and onset of cell senescence in primary human cells. *Mol. Cell*, 27, 183-96. ↗

Ye, X., Somaiah, N., Zhang, R., Zerlanko, B., Salomoni, P., Adams, PD. et al. (2007). Definition of pRB- and p53-dependent and -independent steps in HIRA/ASF1a-mediated formation of senescence-associated heterochromatin foci. *Mol. Cell. Biol.*, 27, 2452-65. ↗

## Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

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