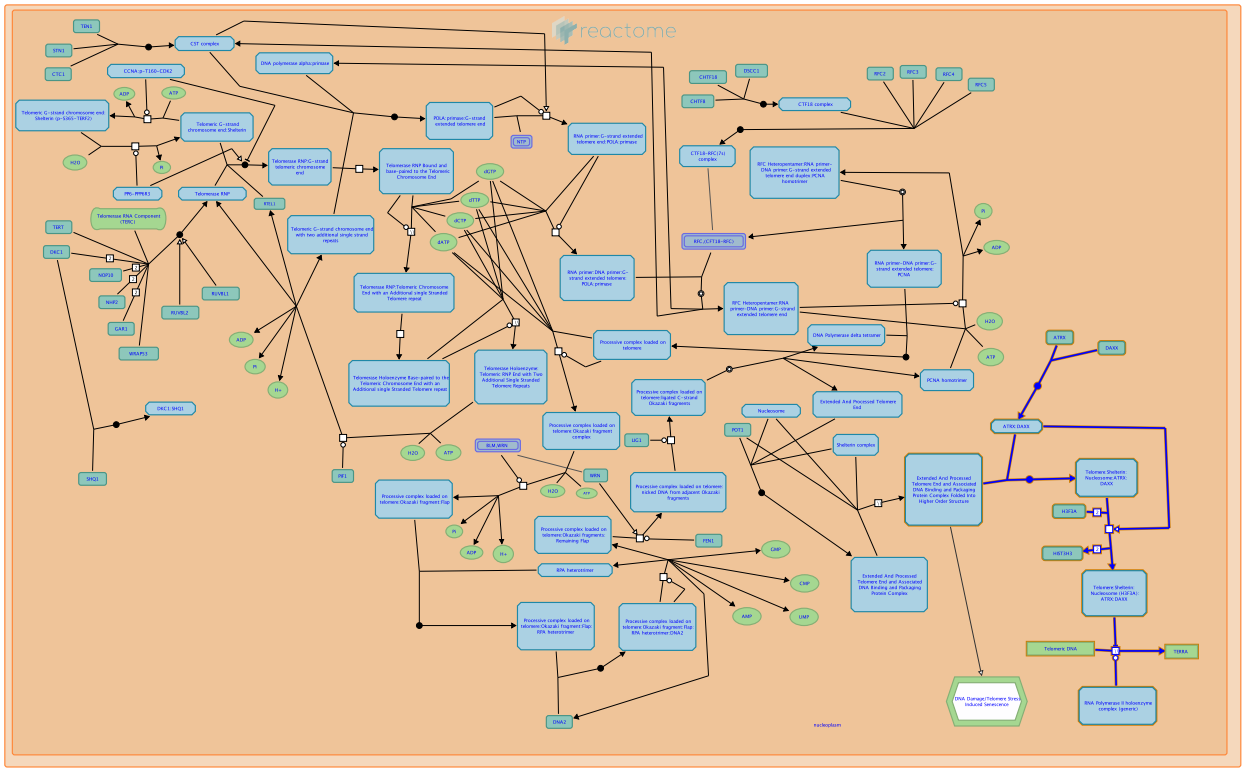
Inhibition of DNA recombination at telomere



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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.

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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. ↗

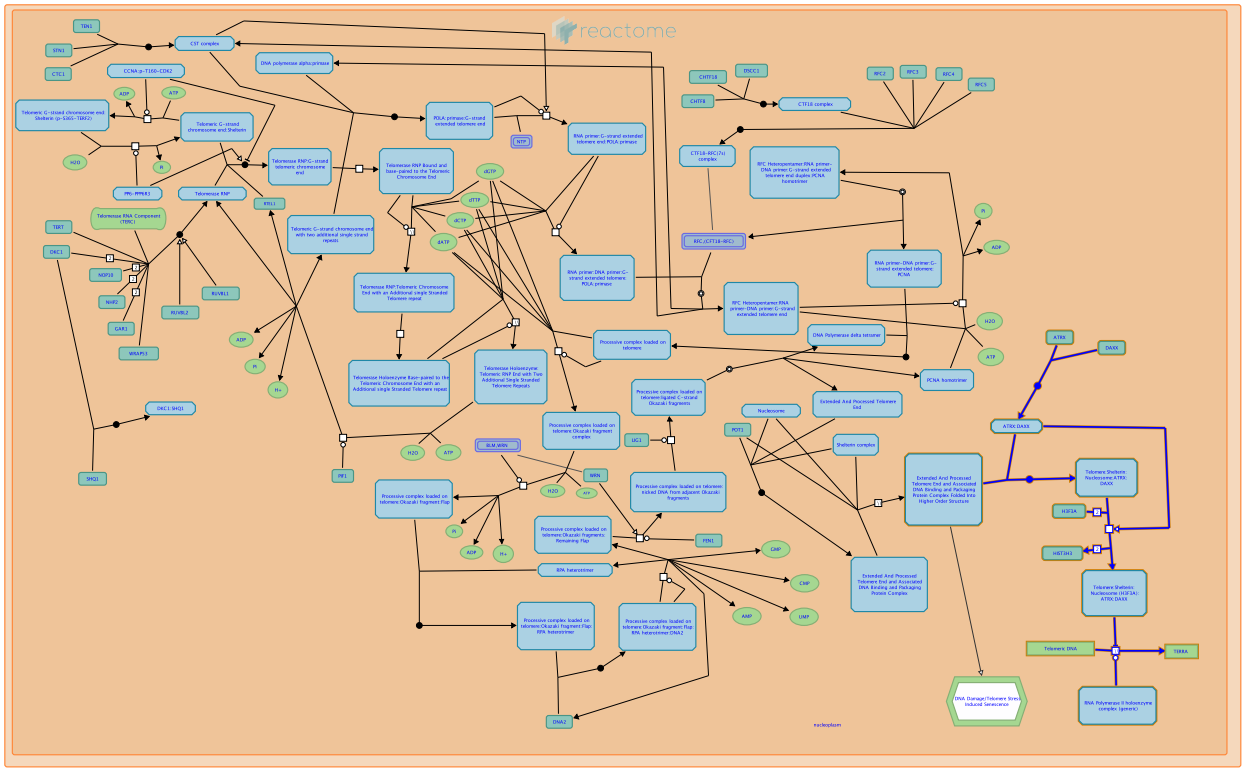
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Inhibition of DNA recombination at telomere ↗

Stable identifier: R-HSA-9670095

Compartments: nucleoplasm



Telomeres resemble double strand DNA breaks (DSBs) and, if not properly packaged and protected, are recognized by the DNA double strand break repair (DSBR) machinery. Initiation of DSB signaling at telomeres due to replicative shortening of telomeres is one of the triggers of cellular senescence, which can also be triggered by other cellular stressors, such as oxidative stress, and oncogenic signaling-induced mitotic arrest. The loss of telomere protection can result in telomere fusions via non-homologous end joining (NHEJ) of microhomology-mediated end joining (MMEJ). Loss of telomere protection accompanied by changes in the organization of telomeric chromatin (O'Sullivan et al. 2014) can trigger extension of telomeres via homologous recombination repair-mediated alternative lengthening of telomeres (ALT). ALT occurs in about 5-15% of cancers and is a telomerase-independent mechanism of replicative immortality. For review, please refer to Arnoult and Karlseder 2015 and Pickett and Reddel 2015.

Literature references

Arnoult, N., Karlseder, J. (2015). Complex interactions between the DNA-damage response and mammalian telomeres. *Nat. Struct. Mol. Biol., 22*, 859-66. ↗

Pickett, HA., Reddel, RR. (2015). Molecular mechanisms of activity and derepression of alternative lengthening of telomeres. *Nat. Struct. Mol. Biol., 22*, 875-80. ↗

O'Sullivan, RJ., Kubicek, S., Schreiber, SL., Karlseder, J. (2010). Reduced histone biosynthesis and chromatin changes arising from a damage signal at telomeres. *Nat. Struct. Mol. Biol., 17*, 1218-25. ↗

Editions

2019-12-19	Authored	Orlic-Milacic, M.
2020-04-29	Reviewed	Hayashi, MT.
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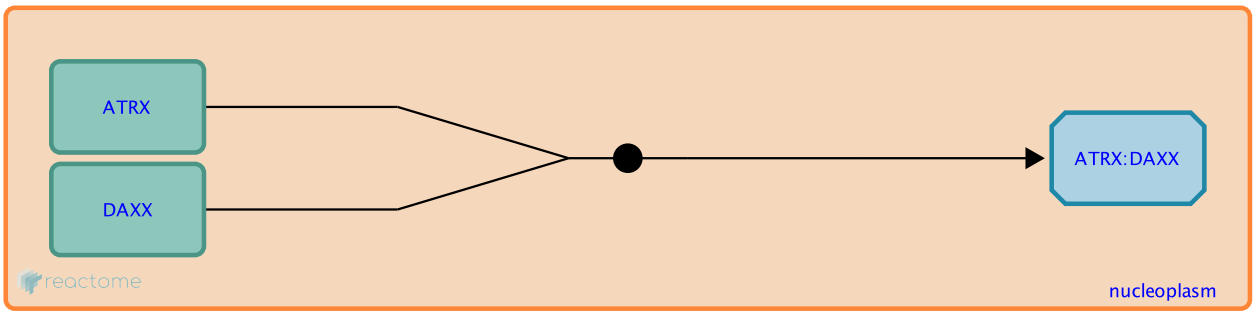
ATRX binds DAXX ↗

Location: Inhibition of DNA recombination at telomere

Stable identifier: R-HSA-9007926

Type: binding

Compartments: nucleoplasm



ATRX (Alpha-thalassemia mental retardation syndrome X-linked) binds to transcriptional co-activator DAXX (Death domain-associated protein 6) to form an ATP-dependent chromatin remodeling complex with triple-helix displacement activity (Xue et al. 2003).

Literature references

Xue, Y., Gibbons, R., Yan, Z., Yang, D., McDowell, TL., Sechi, S. et al. (2003). The ATRX syndrome protein forms a chromatin-remodeling complex with Daxx and localizes in promyelocytic leukemia nuclear bodies. *Proc. Natl. Acad. Sci. U.S.A., 100*, 10635-40. ↗

Editions

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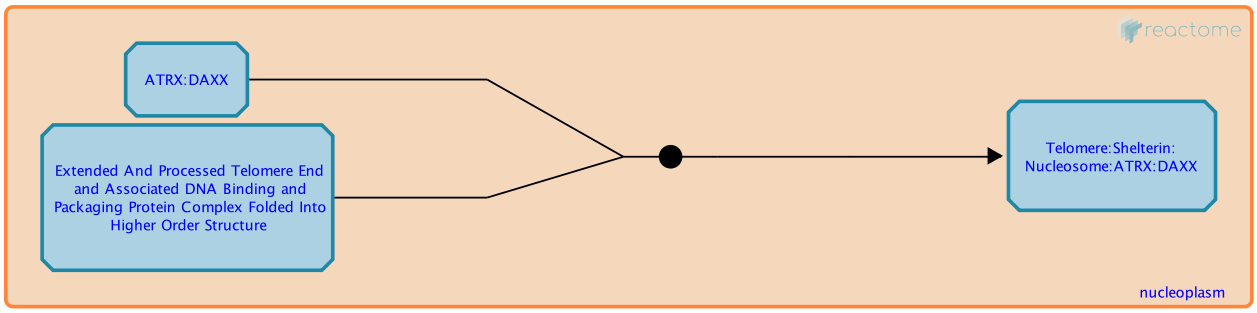
ATRX:DAXX binds to subtelomeric chromosomal regions ↗

Location: Inhibition of DNA recombination at telomere

Stable identifier: R-HSA-9670101

Type: binding

Compartments: nucleoplasm



The complex of ATRX (Alpha-thalassemia mental retardation syndrome X-linked) and DAXX (Death domain-associated protein 6) binds to subtelomeric chromosomal regions and plays a role in the recruitment of cohesin to subtelomeric regions and in the regulation of transcription of the noncoding telomeric repeat-containing RNA (TERRA) (Eid et al. 2015).

Followed by: Histone H3.3 deposition at telomere

Literature references

Eid, R., Demattei, MV., Episkopou, H., Augé-Gouillou, C., Decottignies, A., Grandin, N. et al. (2015). Genetic Inactivation of ATRX Leads to a Decrease in the Amount of Telomeric Cohesin and Level of Telomere Transcription in Human Glioma Cells. *Mol. Cell. Biol., 35*, 2818-30. ↗

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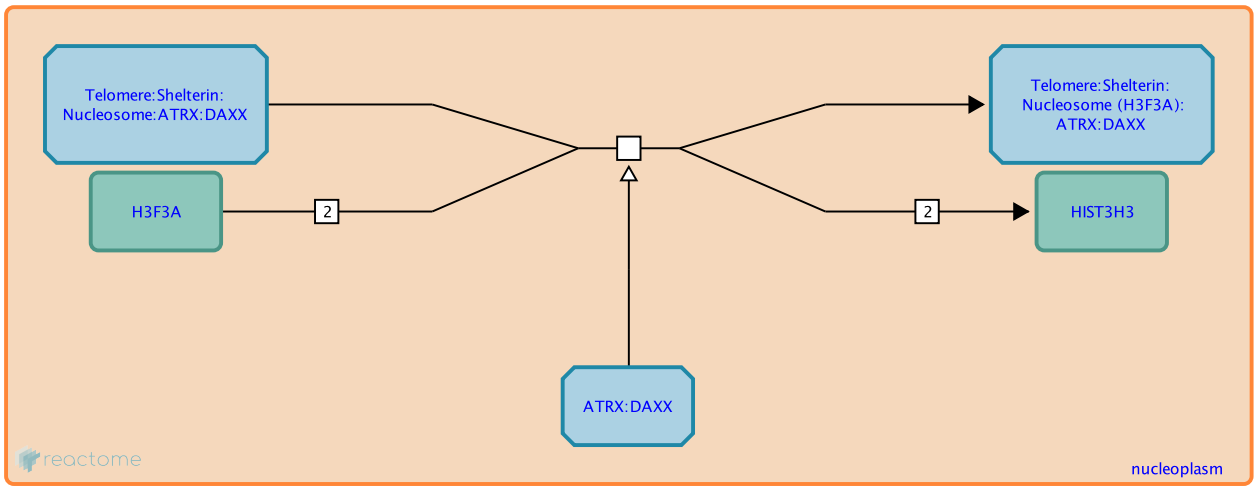
Histone H3.3 deposition at telomere ↗

Location: Inhibition of DNA recombination at telomere

Stable identifier: R-HSA-9670114

Type: transition

Compartments: nucleoplasm



ATRX (Alpha-thalassemia mental retardation syndrome X-linked) and its binding partner DAXX (Death domain-associated protein 6) are required for deposition of histone H3.3, encoded by either the H3F3A gene or the H3F3B gene, to telomeres, independently of the H3.3 chaperone HIRA, in both human and mouse embryonic stem cells. Highly evolutionarily conserved N-terminus of DAXX interacts directly with the H3.3 core (Goldberg et al. 2010, Lewis et al. 2010).

Preceded by: ATRX:DAXX binds to subtelomeric chromosomal regions

Literature references

Goldberg, AD., Banaszynski, LA., Noh, KM., Lewis, PW., Elsaesser, SJ., Stadler, S. et al. (2010). Distinct factors control histone variant H3.3 localization at specific genomic regions. *Cell, 140*, 678-91. ↗

Lewis, PW., Elsaesser, SJ., Noh, KM., Stadler, SC., Allis, CD. (2010). Daxx is an H3.3-specific histone chaperone and cooperates with ATRX in replication-independent chromatin assembly at telomeres. *Proc. Natl. Acad. Sci. U.S.A., 107*, 14075-80. ↗

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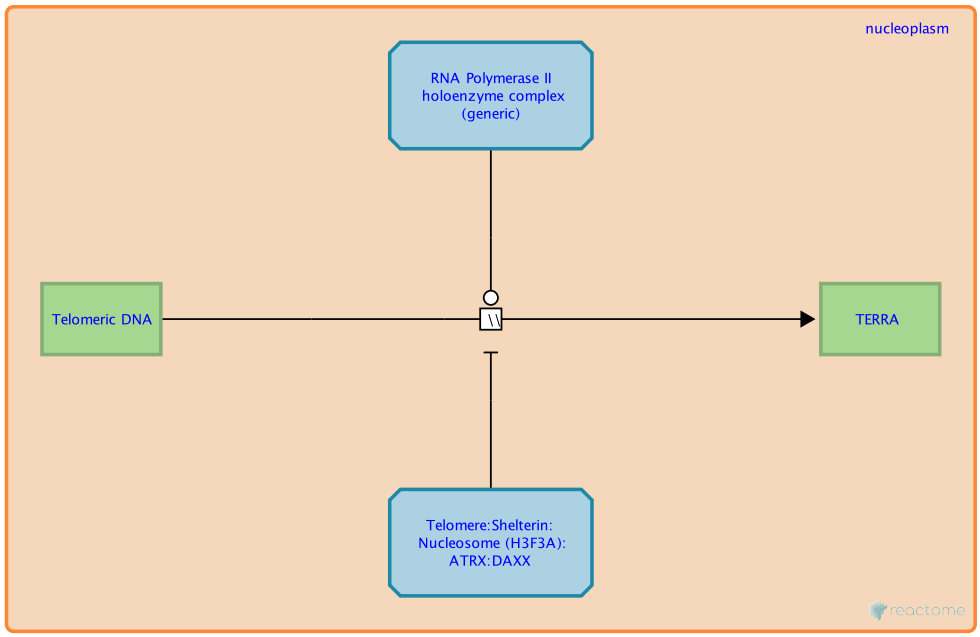
TERRA transcription ↗

Location: Inhibition of DNA recombination at telomere

Stable identifier: R-HSA-9670149

Type: omitted

Compartments: nucleoplasm



Transcription of the telomeric noncoding RNA TERRA (the telomere repeat-containing RNA) is inhibited by ATRX (Flynn et al. 2015). Tumors with ATRX and DAXX mutations associated with the alternative lengthening of telomeres (ALT) show increased TERRA levels (Barthel et al. 2017).

Literature references

Flynn, RL., Cox, KE., Jeitany, M., Wakimoto, H., Bryll, AR., Ganem, NJ. et al. (2015). Alternative lengthening of telomeres renders cancer cells hypersensitive to ATR inhibitors. *Science, 347*, 273-7. ↗

Editions

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