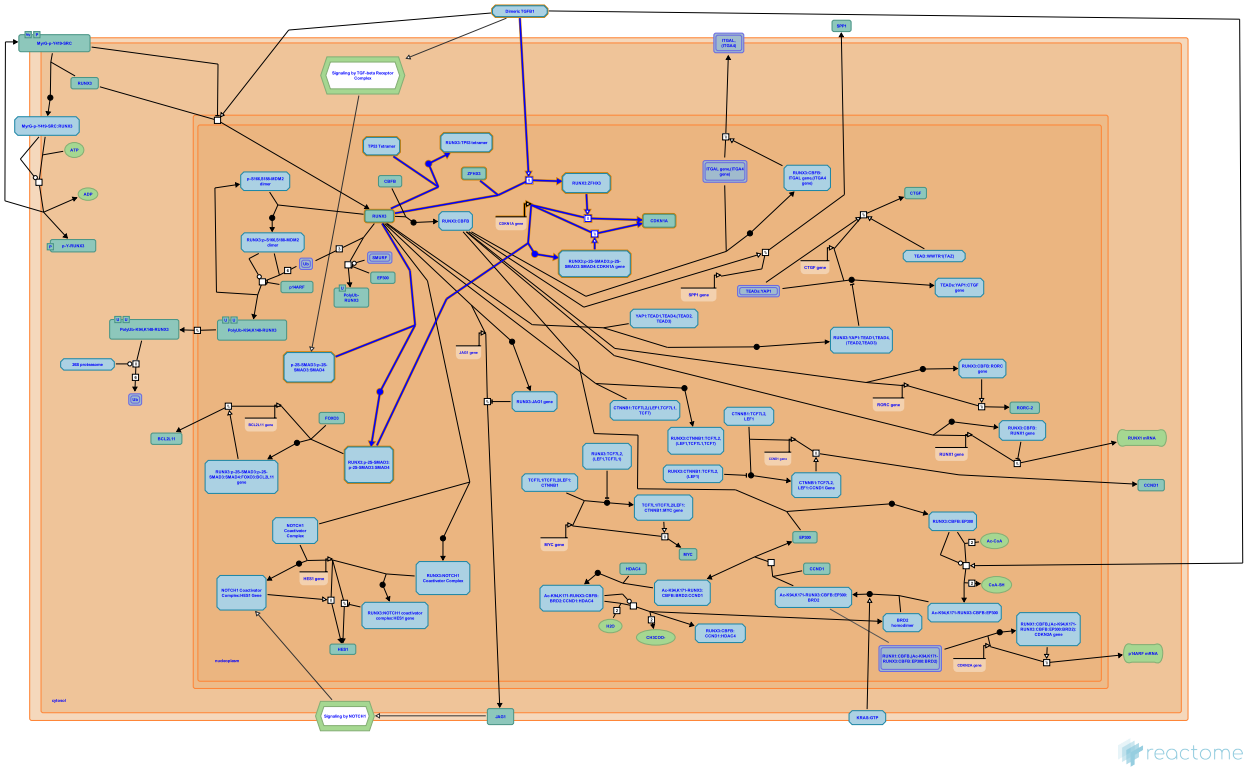
RUNX3 regulates CDKN1A transcription



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26/01/2021

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.

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. ↗

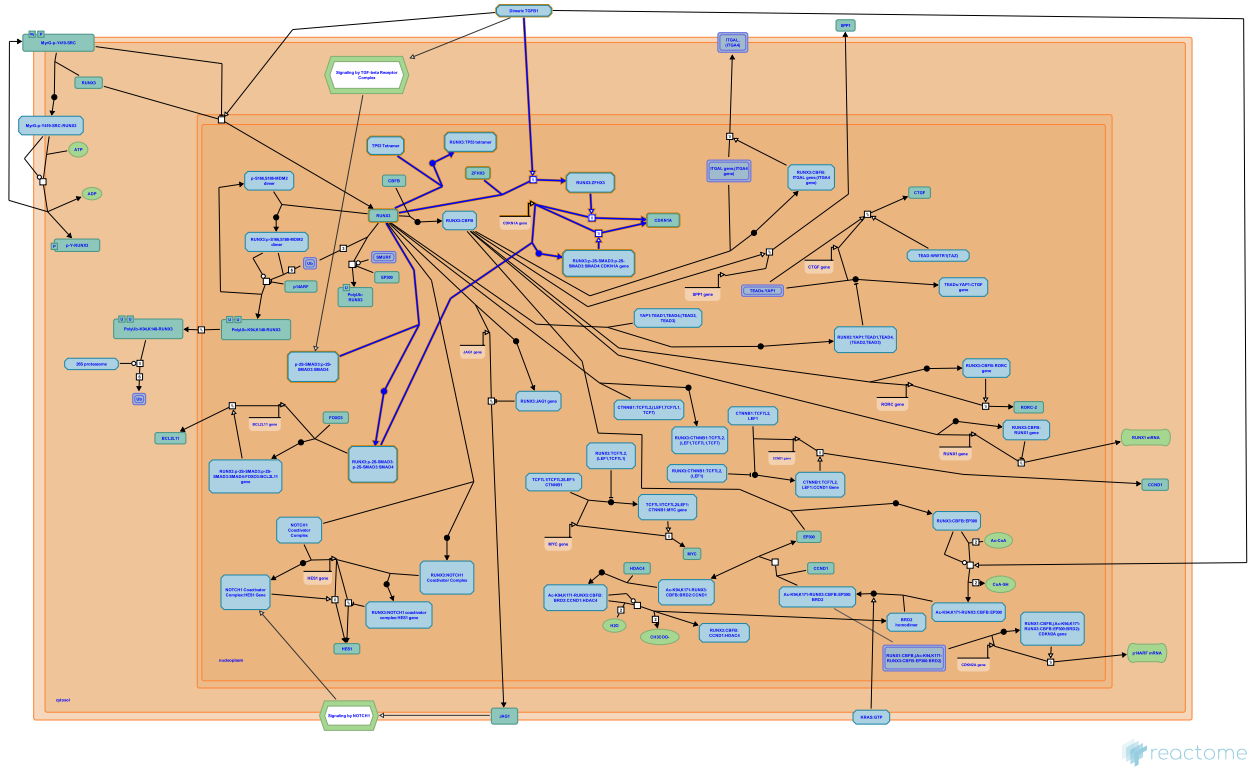
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

RUNX3 regulates CDKN1A transcription ↗

Stable identifier: R-HSA-8941855



RUNX3 contributes to the upregulation of the CDKN1A (p21) gene transcription in response to TGF-beta (TGFB1) signaling. RUNX3 binds to SMAD3 and SMAD4, and cooperates with the activated SMAD3:SMAD4 complex in transactivation of CDKN1A. Runx3 knockout mice exhibit decreased sensitivity to TGF-beta and develop gastric epithelial hyperplasia (Chi et al. 2005). In response to TGF-beta signaling, the CBFB:RUNX3 complex binds to the tumor suppressor ZFHX3 (ATBF1) and, through an unknown mechanism, this complex positively regulates the CDKN1A transcription (Mabuchi et al. 2010).

In addition, RUNX3 may act as a TP53 co-factor, stimulating TP53-mediated transcription of target genes, including CDKN1A (p21) (Yamada et al. 2010).

Literature references

Chi, XZ., Yang, JO., Lee, KY., Ito, K., Sakakura, C., Li, QL. et al. (2005). RUNX3 suppresses gastric epithelial cell growth by inducing p21(WAF1/Cip1) expression in cooperation with transforming growth factor {beta}-activated SMAD. *Mol. Cell. Biol., 25*, 8097-107. ↗

Yamada, C., Ozaki, T., Ando, K., Suenaga, Y., Inoue, K., Ito, Y. et al. (2010). RUNX3 modulates DNA damage-mediated phosphorylation of tumor suppressor p53 at Ser-15 and acts as a co-activator for p53. *J. Biol. Chem., 285*, 16693-703. ↗

Mabuchi, M., Kataoka, H., Miura, Y., Kim, TS., Kawaguchi, M., Ebi, M. et al. (2010). Tumor suppressor, AT motif binding factor 1 (ATBF1), translocates to the nucleus with runt domain transcription factor 3 (RUNX3) in response to TGF-beta signal transduction. *Biochem. Biophys. Res. Commun., 398*, 321-5. ↗

Editions

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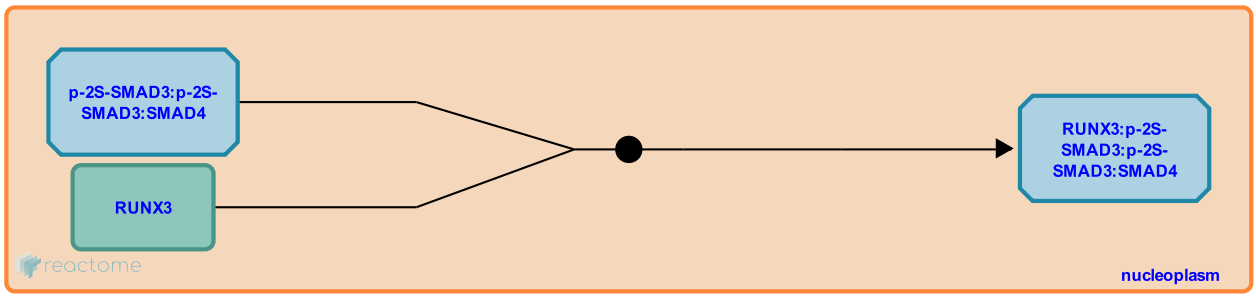
RUNX3 binds SMAD3 and SMAD4 ↗

Location: RUNX3 regulates CDKN1A transcription

Stable identifier: R-HSA-8878143

Type: binding

Compartments: nucleoplasm



RUNX3 binds the complex of SMAD3 and SMAD4, formed in response to TGF-beta (TGFB1) signaling (Hanai et al. 1999, Chi et al. 2005).

Followed by: The complex of RUNX3, SMAD3 and SMAD4 binds the CDKN1A gene promoter

Literature references

Chi, XZ., Yang, JO., Lee, KY., Ito, K., Sakakura, C., Li, QL. et al. (2005). RUNX3 suppresses gastric epithelial cell growth by inducing p21(WAF1/Cip1) expression in cooperation with transforming growth factor {beta}-activated SMAD. *Mol. Cell. Biol., 25*, 8097-107. ↗

Hanai, J., Chen, LF., Kanno, T., Ohtani-Fujita, N., Kim, WY., Guo, WH. et al. (1999). Interaction and functional cooperation of PEBP2/CBF with Smads. Synergistic induction of the immunoglobulin germline Calpha promoter. *J. Biol. Chem., 274*, 31577-82. ↗

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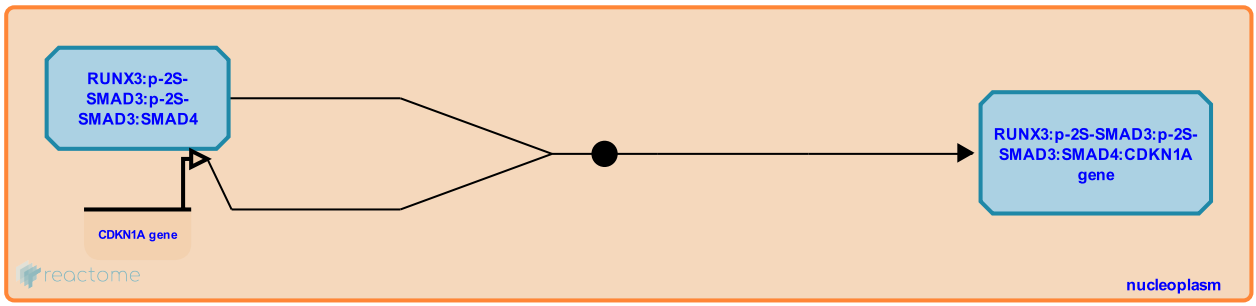
The complex of RUNX3, SMAD3 and SMAD4 binds the CDKN1A gene promoter ↗

Location: RUNX3 regulates CDKN1A transcription

Stable identifier: R-HSA-8878178

Type: binding

Compartments: nucleoplasm



The CDKN1A (p21) gene promoter contains five putative RUNX3 binding sites. RUNX3 binds the CDKN1A promoter. The complex of SMAD4 and activated SMAD3, a known CDKN1A transcriptional activator, can bind to RUNX3 to cooperatively activate the CDKN1A gene transcription (Chi et al. 2005).

Preceded by: RUNX3 binds SMAD3 and SMAD4

Followed by: CDKN1A gene expression is synergistically activated by RUNX3, SMAD3 and SMAD4

Literature references

Chi, XZ., Yang, JO., Lee, KY., Ito, K., Sakakura, C., Li, QL. et al. (2005). RUNX3 suppresses gastric epithelial cell growth by inducing p21(WAF1/Cip1) expression in cooperation with transforming growth factor {beta}-activated SMAD. *Mol. Cell. Biol., 25*, 8097-107. ↗

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CDKN1A gene expression is synergistically activated by RUNX3, SMAD3 and SMAD4

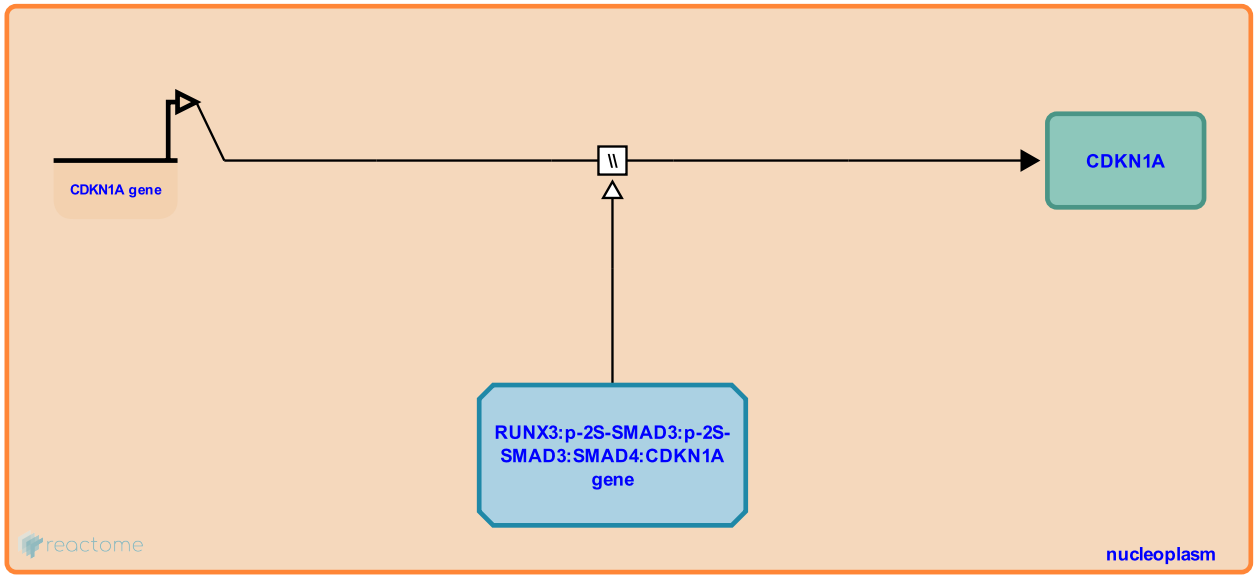
↗

Location: RUNX3 regulates CDKN1A transcription

Stable identifier: R-HSA-8878186

Type: omitted

Compartments: nucleoplasm



RUNX3 binds the complex of SMAD4 and SMAD3, generated in response to TGF-beta (TGFB1) signaling. While the individual action of the SMAD3:SMAD4 complex or RUNX3 can induce 2-3-fold activation of CDKN1A transcription, the synergistic action of SMAD3, SMAD4 and RUNX3 induces 10-fold activation of CDKN1A transcription. Runx3 knockout mice exhibit decreased sensitivity to TGF-beta and develop gastric epithelial hyperplasia (Chi et al. 2005).

Preceded by: The complex of RUNX3, SMAD3 and SMAD4 binds the CDKN1A gene promoter

Literature references

Chi, XZ., Yang, JO., Lee, KY., Ito, K., Sakakura, C., Li, QL. et al. (2005). RUNX3 suppresses gastric epithelial cell growth by inducing p21(WAF1/Cip1) expression in cooperation with transforming growth factor {beta}-activated SMAD. *Mol. Cell. Biol., 25*, 8097-107. ↗

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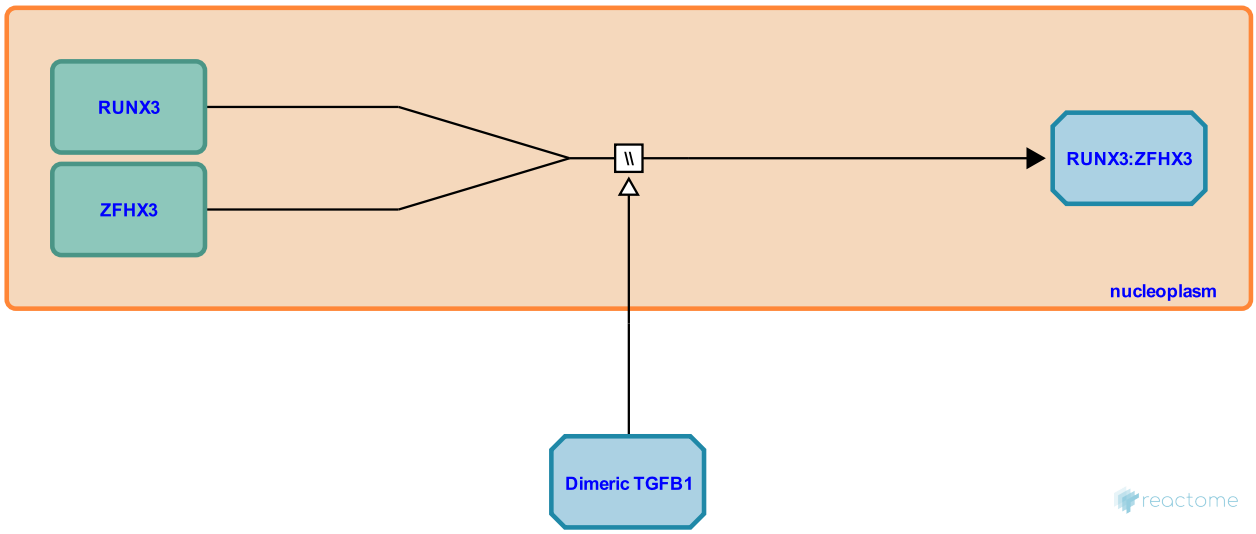
RUNX3 binds ZFHX3 ↗

Location: RUNX3 regulates CDKN1A transcription

Stable identifier: R-HSA-8878117

Type: omitted

Compartments: nucleoplasm



In response to TGF-beta (TGFB1) signaling, RUNX3 binds to the homeobox transcription factor and tumor suppressor ZFHX3 (ATBF1). The exact mechanism and regulation of RUNX3 and ATBF1 binding is not known (Mabuchi et al. 2010).

Followed by: CDKN1A (p21) gene expression is positively regulated by RUNX3 and ZFHX3

Literature references

Mabuchi, M., Kataoka, H., Miura, Y., Kim, TS., Kawaguchi, M., Ebi, M. et al. (2010). Tumor suppressor, AT motif binding factor 1 (ATBF1), translocates to the nucleus with runt domain transcription factor 3 (RUNX3) in response to TGF-beta signal transduction. *Biochem. Biophys. Res. Commun., 398*, 321-5. ↗

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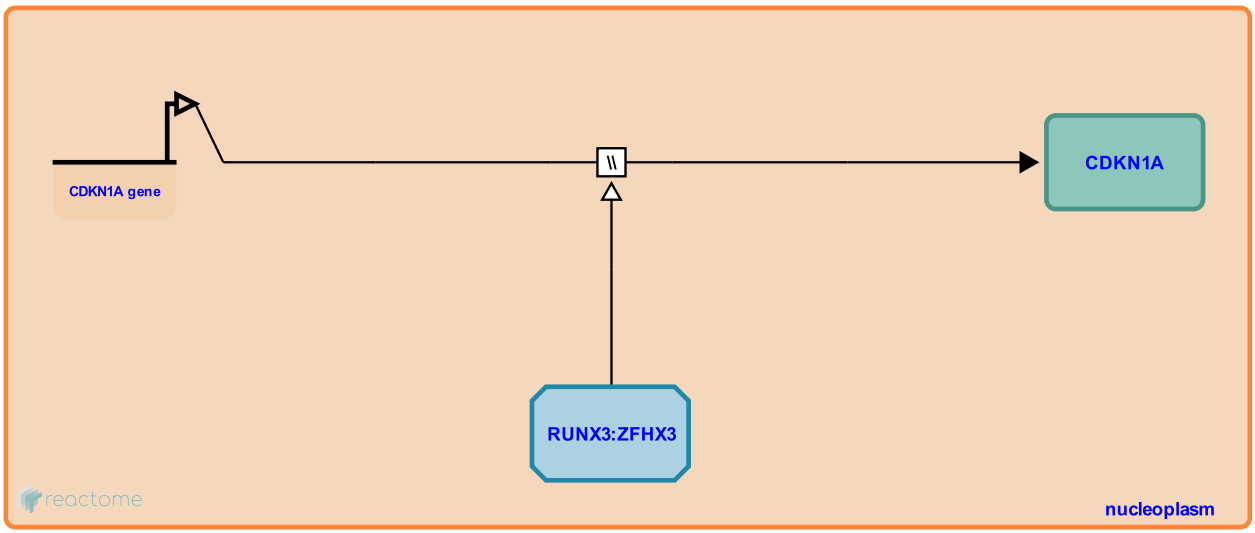
CDKN1A (p21) gene expression is positively regulated by RUNX3 and ZFHX3

Location: RUNX3 regulates CDKN1A transcription

Stable identifier: R-HSA-8878130

Type: omitted

Compartments: nucleoplasm



Transcription of the CDKN1A (p21) gene is synergistically stimulated by RUNX3 and ZFHX3 (ATBF1), presumably through formation of the complex between RUNX3 and ZFHX3. RUNX3 and ZFHX3 can also stimulate CDKN1A transcription independently of one another, albeit to a lower level than when they act in tandem (Mabuchi et al. 2010).

Preceded by: RUNX3 binds ZFHX3

Literature references

Mabuchi, M., Kataoka, H., Miura, Y., Kim, TS., Kawaguchi, M., Ebi, M. et al. (2010). Tumor suppressor, AT motif binding factor 1 (ATBF1), translocates to the nucleus with runt domain transcription factor 3 (RUNX3) in response to TGF-beta signal transduction. *Biochem. Biophys. Res. Commun., 398*, 321-5.

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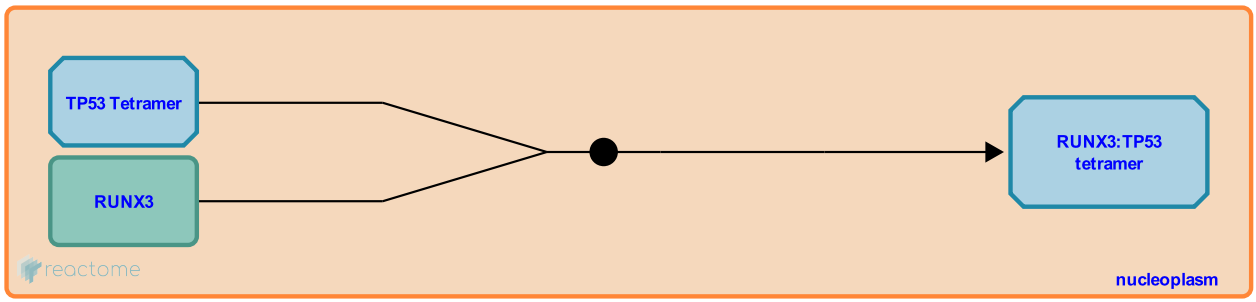
RUNX3 binds TP53 ↗

Location: RUNX3 regulates CDKN1A transcription

Stable identifier: R-HSA-8952128

Type: binding

Compartments: nucleoplasm



RUNX3 can bind to TP53 (p53). The interaction involves the C-termini of both RUNX3 and TP53. RUNX3 may act as a TP53 co-factor, stimulating TP53-mediated transcription of target genes, including CDKN1A (p21). RUNX3 may also interact with phosphorylated ATM kinase in response to DNA damage and facilitate ATM-mediated phosphorylation and stabilization of TP53 (Yamada et al. 2010).

Literature references

Yamada, C., Ozaki, T., Ando, K., Suenaga, Y., Inoue, K., Ito, Y. et al. (2010). RUNX3 modulates DNA damage-mediated phosphorylation of tumor suppressor p53 at Ser-15 and acts as a co-activator for p53. *J. Biol. Chem., 285*, 16693-703. ↗

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