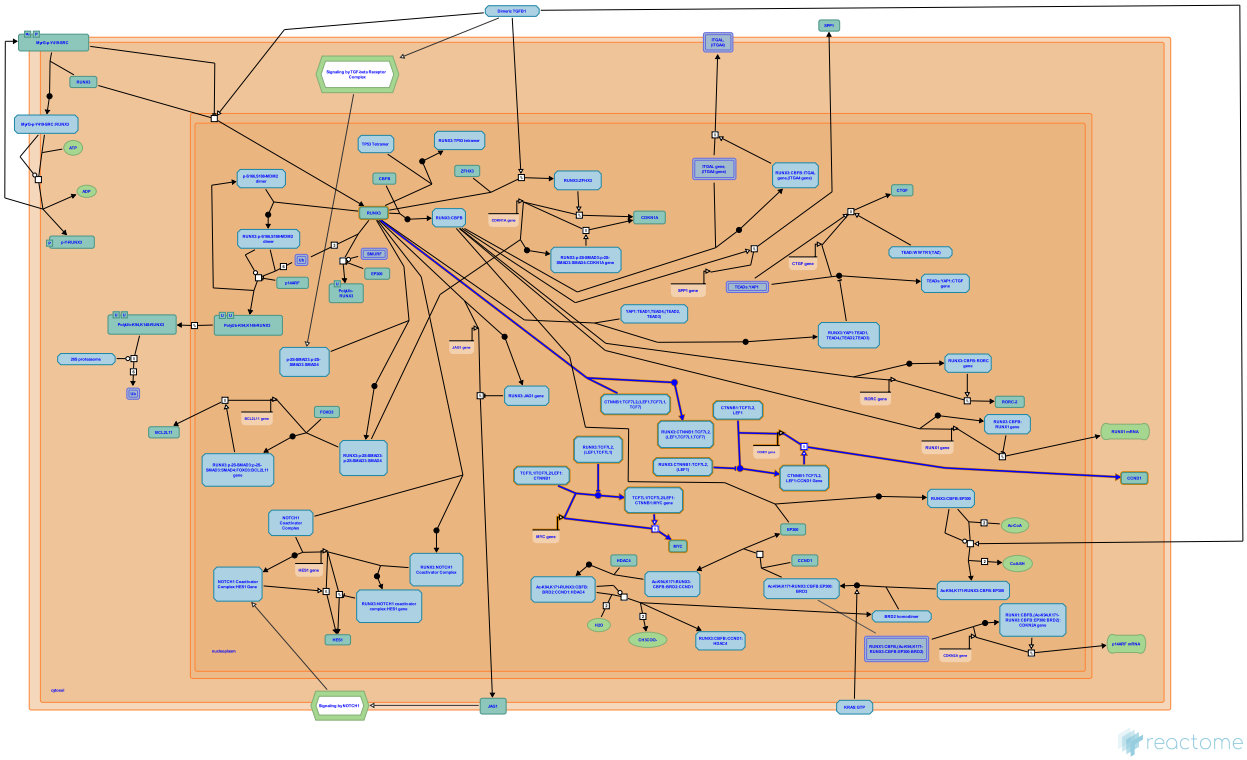
RUNX3 regulates WNT signaling



Chuang, LS., Gillespie, ME., Ito, Y., Kikuchi, A., Orlic-Milacic, M., Rajakulendran, N., Rothfels, K., van Amerongen, R.

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

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.

28/04/2024

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. ↗

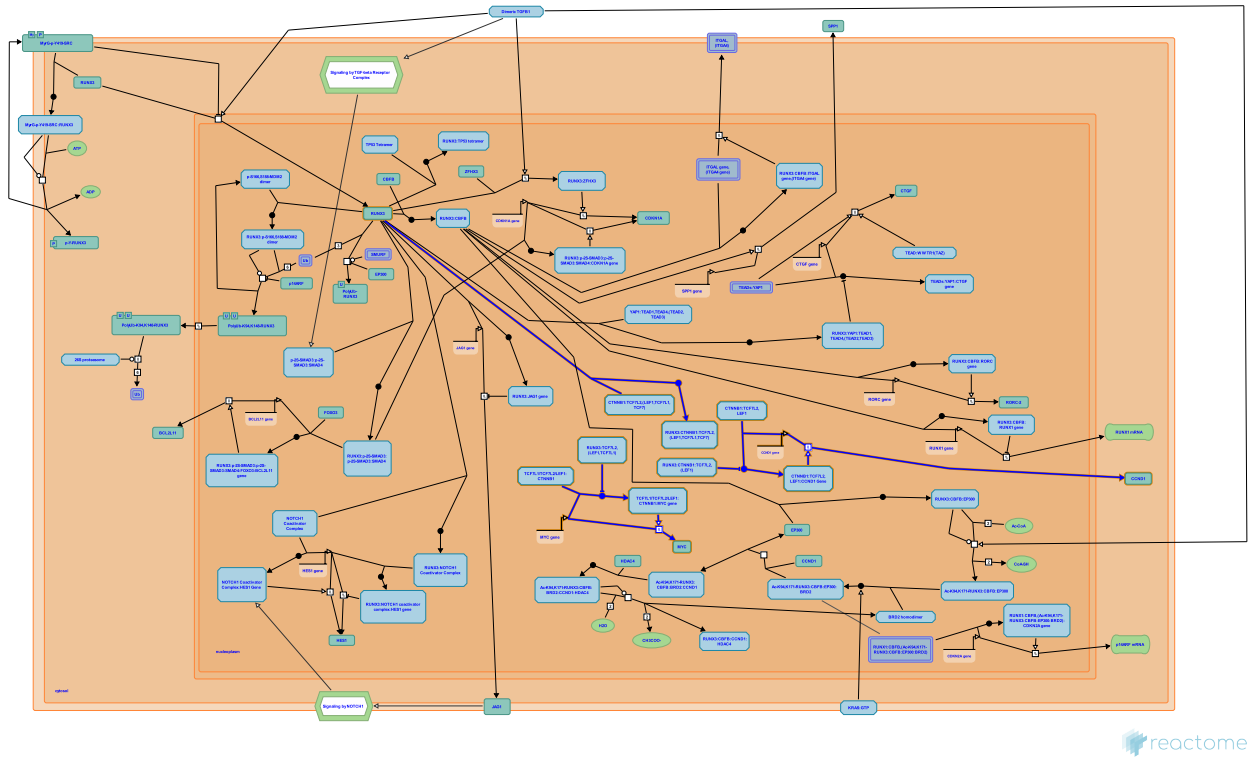
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

RUNX3 regulates WNT signaling ↗

Stable identifier: R-HSA-8951430



RUNX3 binds to complexes of beta-catenin (CTNNB1) and TCF/LEF family members. Binding of RUNX3 to CTNNB1:TCF/LEF complexes prevents their loading onto cyclin D1 (CCND1) and MYC gene promoters and interferes with WNT signaling-mediated activation of CCND1 and MYC1 transcription. RUNX3 therefore inhibits WNT-induced cellular proliferation (Ito et al. 2008).

Literature references

Ito, Y., Osato, M., Voon, DC., Lee, CW., Salto-Tellez, M., Fukamachi, H. et al. (2008). RUNX3 attenuates beta-catenin/T cell factors in intestinal tumorigenesis. *Cancer Cell, 14*, 226-37. ↗

Editions

2016-12-13	Authored	Orlic-Milacic, M.
2017-01-31	Reviewed	Ito, Y., Chuang, LS.
2017-01-31	Edited	Orlic-Milacic, M.

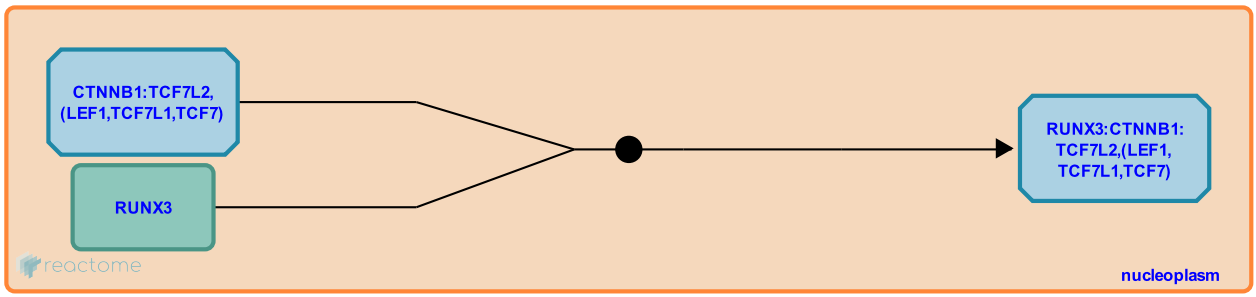
RUNX3 binds CTNNB1:TCF7L2,(LEF1,TCF7L1,TCF7) ↗

Location: RUNX3 regulates WNT signaling

Stable identifier: R-HSA-8951428

Type: binding

Compartments: nucleoplasm



RUNX3 forms a ternary complex with beta-catenin (CTNNB1) and its binding partner TCF7L2 (TCF4). In addition to TCF7L2, RUNX3 is also able to interact with LEF1, TCF7L1 (TCF3) and TCF7 (also known as TCF1). The interaction involves the Runt domain of RUNX3 and the HMG box of TCF7L2 (Ito et al. 2008).

Followed by: CTNNB1:TCF7L2,LEF1 binds the CCND1 gene promoter, TCF7L1/TCF7L2/LEF1:CTNNB1 bind the MYC gene

Literature references

Ito, Y., Osato, M., Voon, DC., Lee, CW., Salto-Tellez, M., Fukamachi, H. et al. (2008). RUNX3 attenuates beta-catenin/T cell factors in intestinal tumorigenesis. *Cancer Cell, 14*, 226-37. ↗

Editions

2016-12-13	Authored	Orlic-Milacic, M.
2017-01-31	Reviewed	Ito, Y., Chuang, LS.
2017-01-31	Edited	Orlic-Milacic, M.

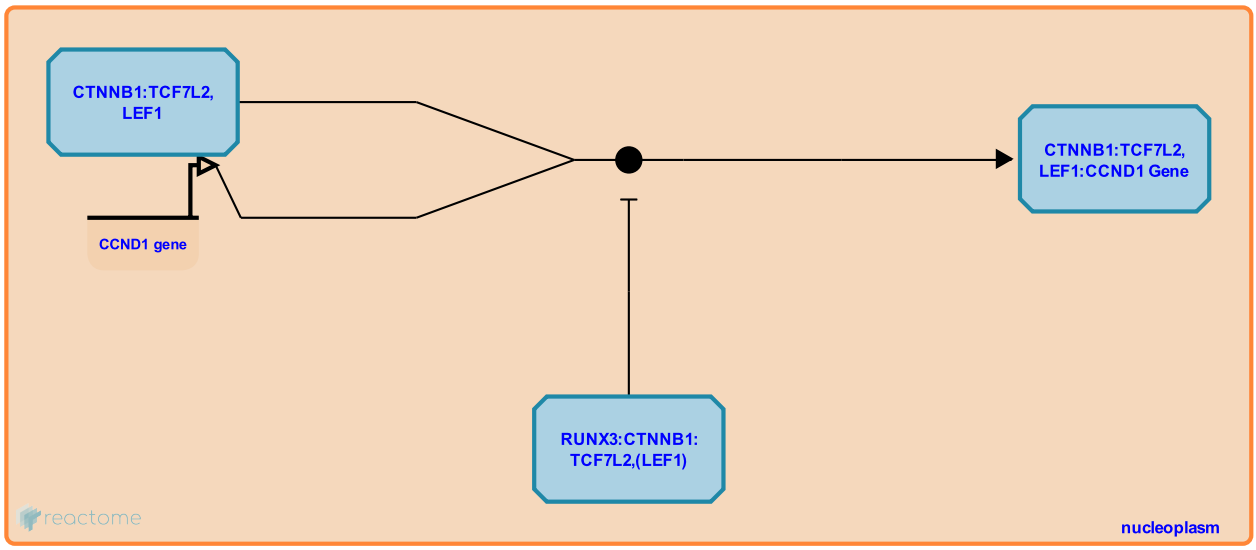
CTNNB1:TCF7L2,LEF1 binds the CCND1 gene promoter ↗

Location: RUNX3 regulates WNT signaling

Stable identifier: R-HSA-8951442

Type: binding

Compartments: nucleoplasm



Beta-catenin (CTNNB1), in complex with TCF7L2 (TCF4) or LEF1, binds to TCF/LEF binding sites in the promoter of the cyclin D1 (CCND1) gene (Tetsu and McCormick 1999, Shtutman et al. 1999). Binding of RUNX3 to the CTNNB1:TCF7L2 and possibly to the CTNNB1:LEF1 complex, prevents binding of CTNNB1 complexes to the CCND1 promoter, thus negatively regulating CCND1 transcription (Ito et al. 2008).

Preceded by: RUNX3 binds CTNNB1:TCF7L2,(LEF1,TCF7L1,TCF7)

Followed by: Expression of CCND1 is stimulated by CTNNB1:TCF4,LEF1

Literature references

Shtutman, M., Albanese, C., D'Amico, M., Zhurinsky, J., Simcha, I., Pestell, R. et al. (1999). The cyclin D1 gene is a target of the beta-catenin/LEF-1 pathway. *Proc. Natl. Acad. Sci. U.S.A., 96*, 5522-7. ↗

Ito, Y., Osato, M., Voon, DC., Lee, CW., Salto-Tellez, M., Fukamachi, H. et al. (2008). RUNX3 attenuates beta-catenin/T cell factors in intestinal tumorigenesis. *Cancer Cell, 14*, 226-37. ↗

McCormick, F., Tetsu, O. (1999). Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells. *Nature, 398*, 422-6. ↗

Editions

2016-12-13	Authored	Orlic-Milacic, M.
2017-01-31	Reviewed	Ito, Y., Chuang, LS.
2017-01-31	Edited	Orlic-Milacic, M.

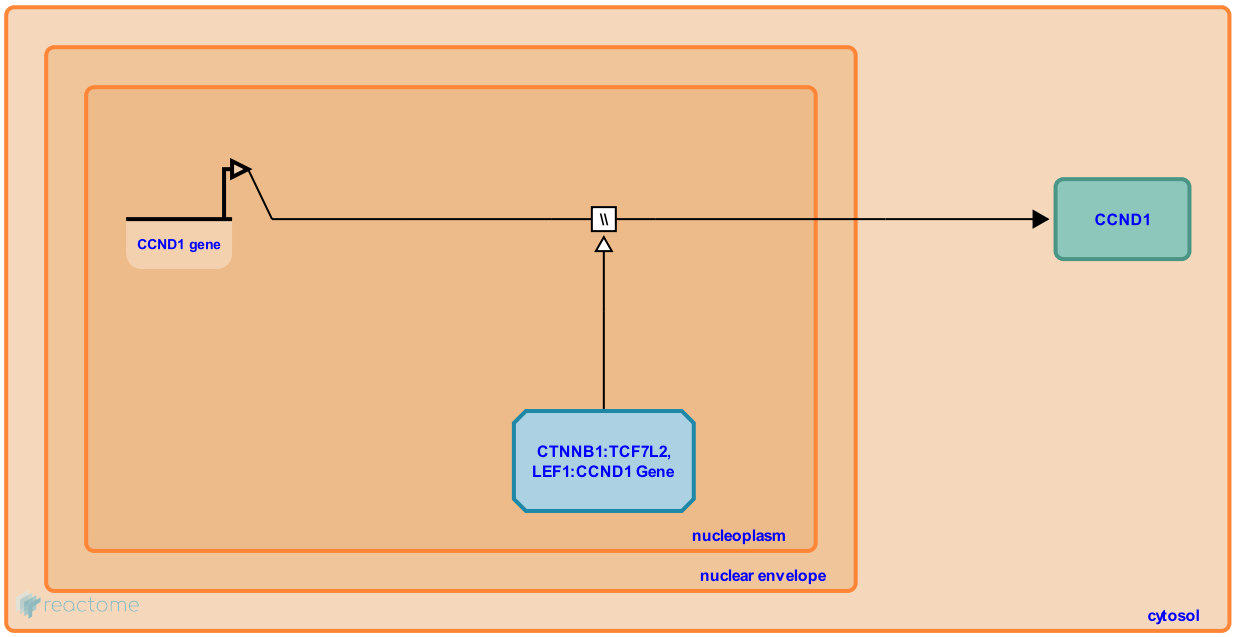
Expression of CCND1 is stimulated by CTNNB1:TCF4,LEF1 ↗

Location: RUNX3 regulates WNT signaling

Stable identifier: R-HSA-8951443

Type: omitted

Compartments: nucleoplasm



Binding of the complex of beta-catenin (CTNNB1) and TCF7L2 (TCF4) or LEF1 transcription factors to TCF/LEF binding sites in the promoter of the cyclin D1 (CCND1) gene stimulates CCND1 transcription (Tetsu and McCormick 1999, Shtutman et al. 1999).

Preceded by: CTNNB1:TCF7L2,LEF1 binds the CCND1 gene promoter

Literature references

Shtutman, M., Albanese, C., D'Amico, M., Zhurinsky, J., Simcha, I., Pestell, R. et al. (1999). The cyclin D1 gene is a target of the beta-catenin/LEF-1 pathway. *Proc. Natl. Acad. Sci. U.S.A., 96*, 5522-7. ↗

McCormick, F., Tetsu, O. (1999). Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells. *Nature, 398*, 422-6. ↗

Editions

2016-12-13	Authored	Orlic-Milacic, M.
2017-01-31	Reviewed	Ito, Y., Chuang, LS.
2017-01-31	Edited	Orlic-Milacic, M.

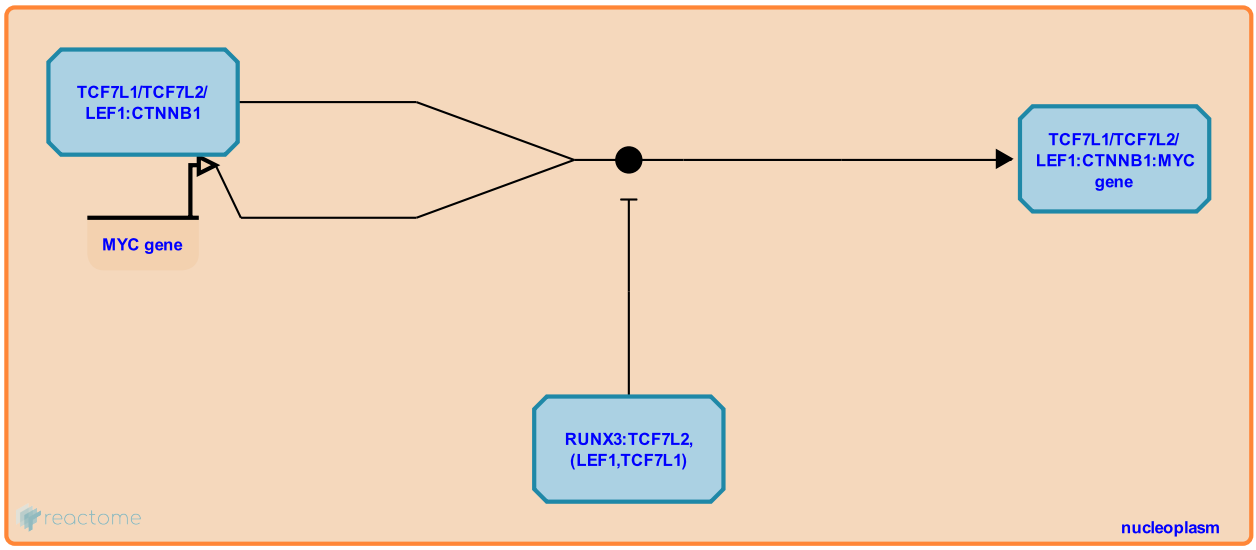
TCF7L1/TCF7L2/LEF1:CTNNB1 bind the MYC gene ↗

Location: RUNX3 regulates WNT signaling

Stable identifier: R-HSA-4411367

Type: binding

Compartments: nucleoplasm



TCF7L1 (also known as TCF3), TCF7L3 (also known as LEF1) and TCF7L2 (also known as TCF4) have been demonstrated to bind to the MYC gene in vivo and in vitro and to mediate beta-catenin dependent transcription (Park et al, 2009; He et al, 1998; Sierra et al, 2006). Aberrant beta-catenin dependent activation of the MYC gene contributes to oncogenic signaling and cellular proliferation in colorectal and other cancers (see for instance Sansom et al, 2007; Moumen et al, 2013; reviewed in Wilkins and Sansom, 2008; Cairo et al, 2012).
Binding of RUNX3 to the CTNNB1:TCF7L2 and possibly to the CTNNB1:LEF1 and TCF7L1 complexes, prevents binding of CTNNB1 complexes to the MYC promoter, thus negatively regulating MYC transcription (Ito et al. 2008).

Preceded by: RUNX3 binds CTNNB1:TCF7L2,(LEF1,TCF7L1,TCF7)

Followed by: TCF7L1/TCF7L2/LEF1:CTNNB1 promote transcription of the MYC gene

Literature references

Armengol, C., Buendia, MA., Cairo, S. (2012). Activation of Wnt and Myc signaling in hepatoblastoma. *Front Biosci (Elite Ed), 4*, 480-6. ↗

Yoshida, T., Jones, KA., Sierra, J., Joazeiro, CA. (2006). The APC tumor suppressor counteracts beta-catenin activation and H3K4 methylation at Wnt target genes. *Genes Dev., 20*, 586-600. ↗

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Reed, KR., Muncan, V., Clevers, HC., Clarke, AR., Meniel, VS., Vass, JK. et al. (2007). Myc deletion rescues Apc deficiency in the small intestine. *Nature, 446*, 676-9. ↗

Rago, C., Zawel, L., Morin, PJ., da Costa, LT., Kinzler, KW., Hermeking, H. et al. (1998). Identification of c-MYC as a target of the APC pathway. *Science, 281*, 1509-12. ↗

Editions

2013-08-24	Authored	Rothfels, K.
2013-10-03	Edited	Gillespie, ME.
2014-01-22	Reviewed	Rajakulendran, N.
2014-02-15	Reviewed	van Amerongen, R.
2014-04-22	Reviewed	Kikuchi, A.
2017-01-31	Reviewed	Ito, Y., Chuang, LS.
2017-01-31	Edited	Orlic-Milacic, M.

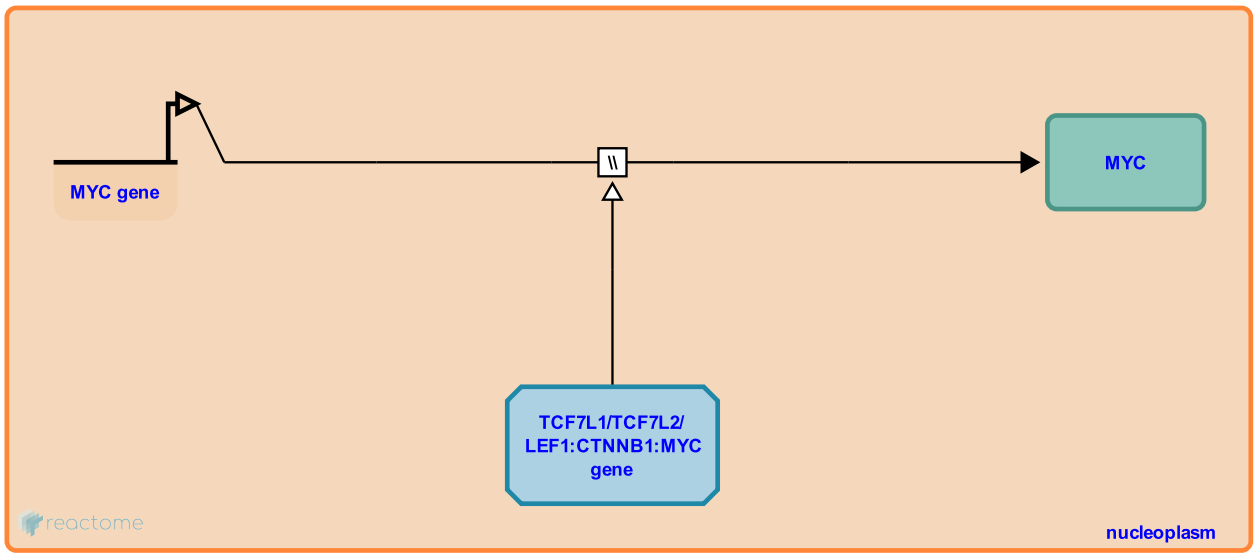
TCF7L1/TCF7L2/LEF1:CTNNB1 promote transcription of the MYC gene ↗

Location: RUNX3 regulates WNT signaling

Stable identifier: R-HSA-4411357

Type: omitted

Compartments: nucleoplasm



TCF7L1 (also known as TCF3), TCF7L3 (also known as LEF1) and TCF7L2 (also known as TCF4) have been demonstrated to bind to the MYC gene in vivo and in vitro and to mediate beta-catenin dependent transcription (Park et al, 2009; He et al, 1998; Sierra et al, 2006). Aberrant beta-catenin dependent activation of the MYC gene contributes to oncogenic signaling and cellular proliferation in colorectal and other cancers (see for instance Sansom et al, 2007; Moumen et al, 2013; reviewed in Wilkins and Sansom, 2008; Cairo et al, 2012).
Binding of RUNX3 to the CTNNB1:TCF7L2 and possibly to the CTNNB1:LEF1 and TCF7L1 complexes, prevents binding of CTNNB1 complexes to the MYC promoter, thus negatively regulating MYC transcription (Ito et al. 2008).

Preceded by: TCF7L1/TCF7L2/LEF1:CTNNB1 bind the MYC gene

Literature references

Yoshida, T., Jones, KA., Sierra, J., Joazeiro, CA. (2006). The APC tumor suppressor counteracts beta-catenin activation and H3K4 methylation at Wnt target genes. *Genes Dev., 20*, 586-600. ↗

Venteicher, AS., Park, JI., Jun, S., Artandi, SE., Nusse, R., Ji, H. et al. (2009). Telomerase modulates Wnt signalling by association with target gene chromatin. *Nature, 460*, 66-72. ↗

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