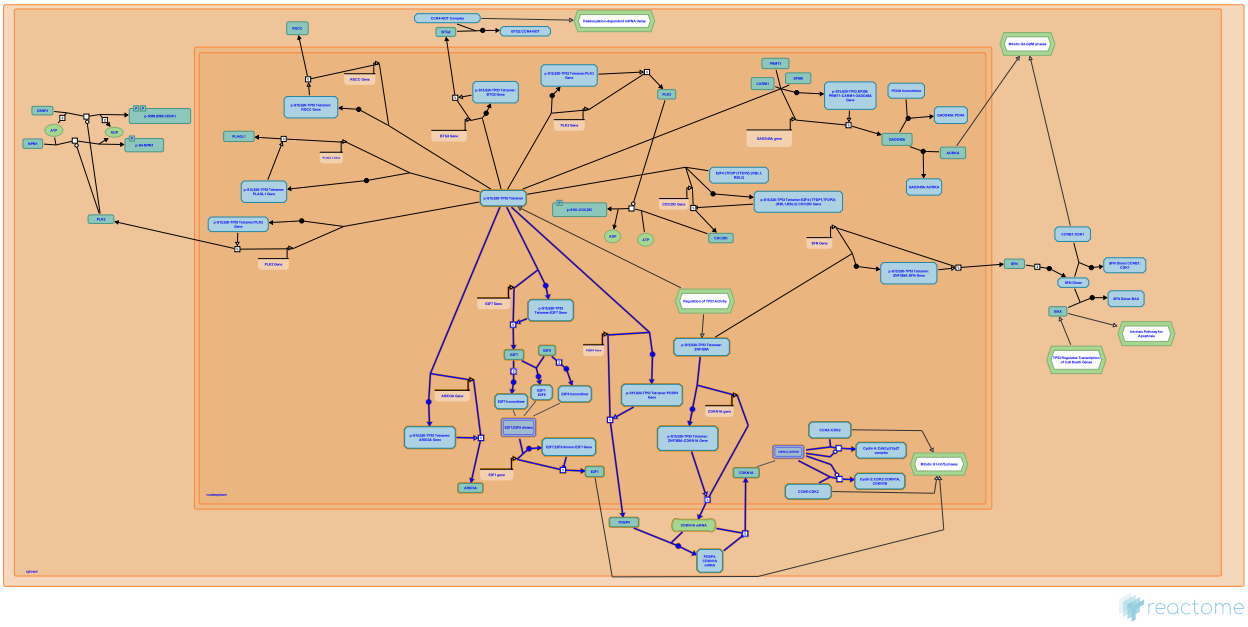
TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest



Bertaggia, E., Coqueret, O., Di Stefano, L., Donlon, T., Inga, A., Matthews, L., Orlic-Milacic, M., Pagano, M., Samarajiwa, S., Westendorp, B., Zaccara, S., de Bruin, A.

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13/11/2019

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. ↗

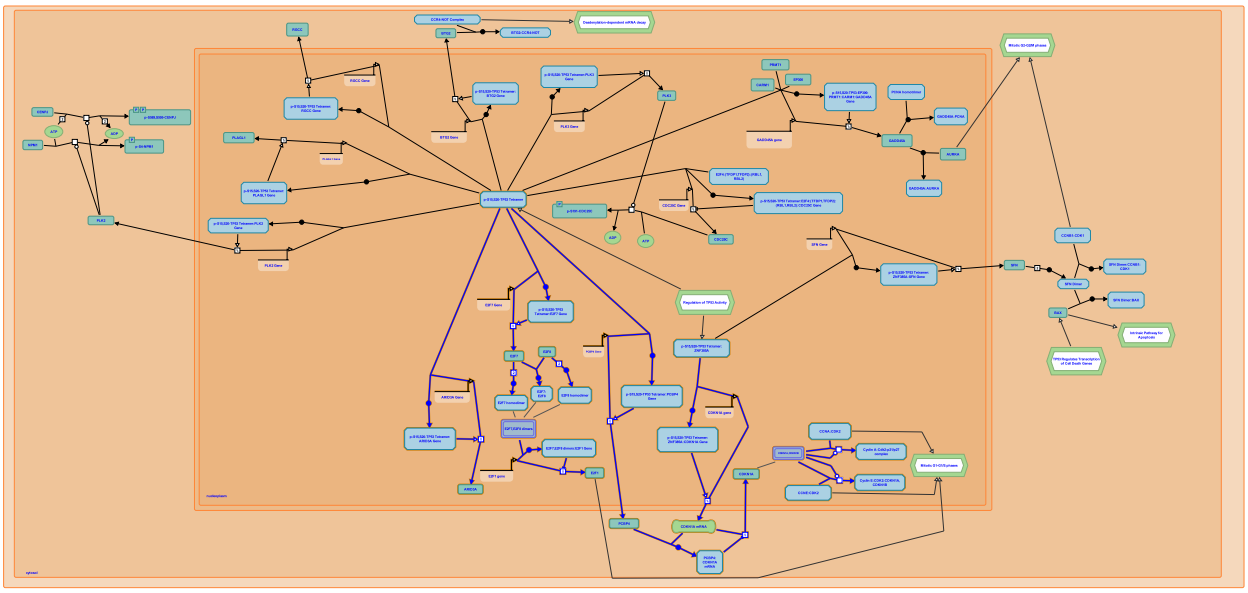
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest ↗

Stable identifier: R-HSA-6804116



The most prominent TP53 target involved in G1 arrest is the inhibitor of cyclin-dependent kinases CDKN1A (p21). CDKN1A is one of the earliest genes induced by TP53 (El-Deiry et al. 1993). CDKN1A binds and inactivates CDK2 in complex with cyclin A (CCNA) or E (CCNE), thus preventing G1/S transition (Harper et al. 1993). Considering its impact on the cell cycle outcome, CDKN1A expression levels are tightly regulated. For instance, under prolonged stress, TP53 can induce the transcription of an RNA binding protein PCBP4, which can bind and destabilize CDKN1A mRNA, thus alleviating G1 arrest and directing the affected cell towards G2 arrest and, possibly, apoptosis (Zhu and Chen 2000, Scoumanne et al. 2011). Expression of E2F7 is directly induced by TP53. E2F7 contributes to G1 cell cycle arrest by repressing transcription of E2F1, a transcription factor that promotes expression of many genes needed for G1/S transition (Aksoy et al. 2012, Carvajal et al. 2012). ARID3A is a direct transcriptional target of TP53 (Ma et al. 2003) that may promote G1 arrest by cooperating with TP53 in induction of CDKN1A transcription (Lestari et al. 2012). However, ARID3A may also promote G1/S transition by stimulating transcriptional activity of E2F1 (Suzuki et al. 1998, Peeper et al. 2002).

TP53 has co-factors that are key determinants of transcriptional selectivity within the p53 network. For instance, the zinc finger transcription factor ZNF385A (HZF) is a direct transcriptional target of TP53 that can form a complex with TP53 and facilitate TP53-mediated induction of CDKN1A, strongly favouring cell cycle arrest over apoptosis (Das et al. 2007).

Literature references

Peeper, DS., Shvarts, A., Brummelkamp, T., Douma, S., Koh, EY., Daley, GQ. et al. (2002). A functional screen identifies hDRIL1 as an oncogene that rescues RAS-induced senescence. *Nat. Cell Biol., 4*, 148-53. ↗

Suzuki, M., Okuyama, S., Okamoto, S., Shirasuna, K., Nakajima, T., Hachiya, T. et al. (1998). A novel E2F binding protein with Myc-type HLH motif stimulates E2F-dependent transcription by forming a heterodimer. *Oncogene, 17*, 853-65. ↗

Lestari, W., Ichwan, SJ., Otsu, M., Yamada, S., Iseki, S., Shimizu, S. et al. (2012). Cooperation between ARID3A and p53 in the transcriptional activation of p21WAF1 in response to DNA damage. *Biochem. Biophys. Res. Commun., 417*, 710-6. ↗

Zhu, J., Chen, X. (2000). MCG10, a novel p53 target gene that encodes a KH domain RNA-binding protein, is capable of inducing apoptosis and cell cycle arrest in G(2)-M. *Mol. Cell. Biol., 20*, 5602-18. ↗

Scoumanne, A., Cho, SJ., Zhang, J., Chen, X. (2011). The cyclin-dependent kinase inhibitor p21 is regulated by RNA-binding protein PCBP4 via mRNA stability. *Nucleic Acids Res., 39*, 213-24. ↗

Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.
2017-01-03	Revised	Orlic-Milacic, M.

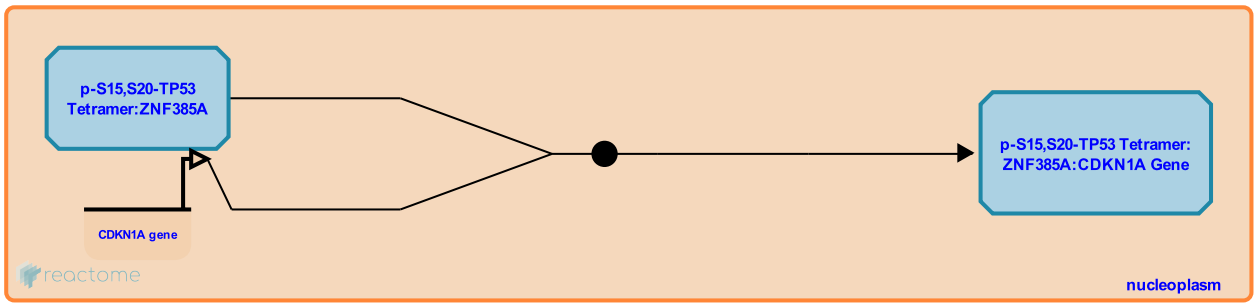
TP53 in complex with ZNF385A binds the CDKN1A promoter ↗

Location: TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest

Stable identifier: R-HSA-6803801

Type: binding

Compartments: nucleoplasm



TP53 (p53) binds at least two p53 response elements in the promoter of the CDKN1A (p21, WAF1) gene (El-Deiry et al. 1993, Espinosa et al. 2003). Formation of the complex of TP53 and ZNF385A (HZF) facilitates binding of TP53 to the CDKN1A promoter (Das et al. 2007).

Followed by: TP53 stimulates CDKN1A (p21) transcription

Literature references

el-Deiry, WS., Tokino, T., Velculescu, VE., Levy, DB., Parsons, R., Trent, JM. et al. (1993). WAF1, a potential mediator of p53 tumor suppression. *Cell, 75*, 817-25. ↗

Das, S., Raj, L., Zhao, B., Kimura, Y., Bernstein, A., Aaronson, SA. et al. (2007). Hzf Determines cell survival upon genotoxic stress by modulating p53 transactivation. *Cell, 130*, 624-37. ↗

Espinosa, JM., Verdun, RE., Emerson, BM. (2003). p53 functions through stress- and promoter-specific recruitment of transcription initiation components before and after DNA damage. *Mol. Cell, 12*, 1015-27. ↗

Editions

2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.
2015-10-07	Revised	Orlic-Milacic, M.
2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

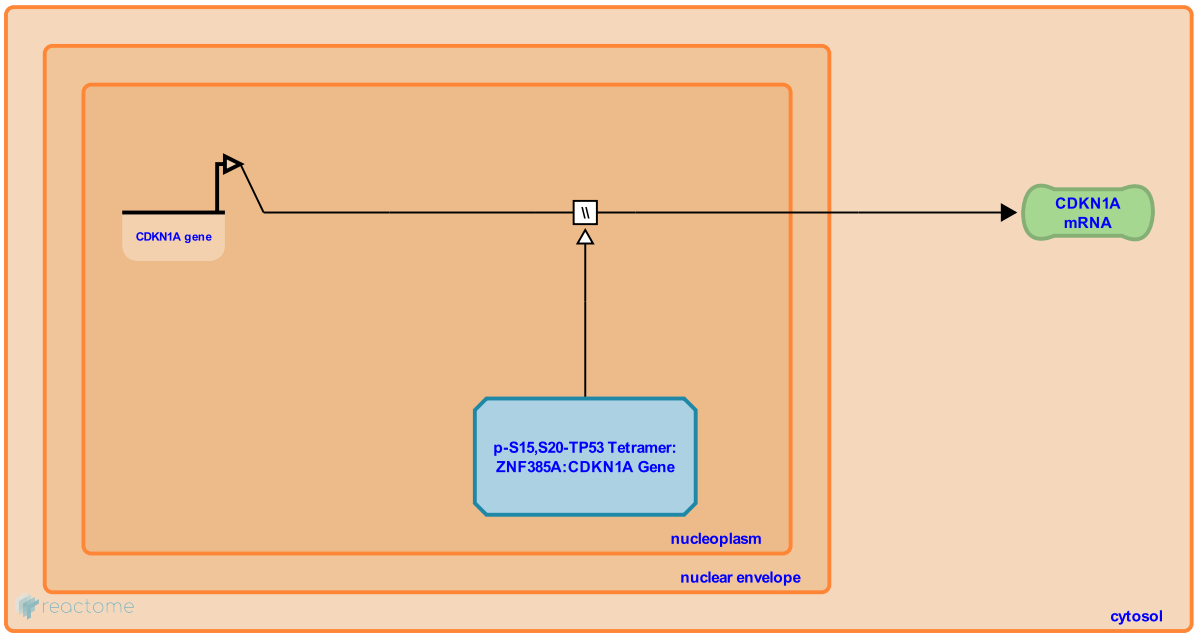
TP53 stimulates CDKN1A (p21) transcription ↗

Location: TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest

Stable identifier: R-HSA-6803388

Type: omitted

Compartments: nucleoplasm, cytosol



Binding of TP53 (p53) to its response elements in the promoter of the CDKN1A (p21) gene stimulates CDKN1A transcription (El-Deiry et al. 1993). Binding of ZNF385A (HZF) to the DNA binding domain of TP53 facilitates CDKN1A induction and the consequent cell cycle arrest (Das et al. 2007).

Preceded by: TP53 in complex with ZNF385A binds the CDKN1A promoter

Followed by: PCBP4 binds the CDKN1A mRNA

Literature references

el-Deiry, WS., Tokino, T., Velculescu, VE., Levy, DB., Parsons, R., Trent, JM. et al. (1993). WAF1, a potential mediator of p53 tumor suppression. *Cell, 75*, 817-25. ↗

Das, S., Raj, L., Zhao, B., Kimura, Y., Bernstein, A., Aaronson, SA. et al. (2007). Hzf Determines cell survival upon genotoxic stress by modulating p53 transactivation. *Cell, 130*, 624-37. ↗

Editions

2006-09-29	Authored	Matthews, L.
2006-10-06	Reviewed	Coqueret, O.
2015-10-06	Revised	Orlic-Milacic, M.
2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

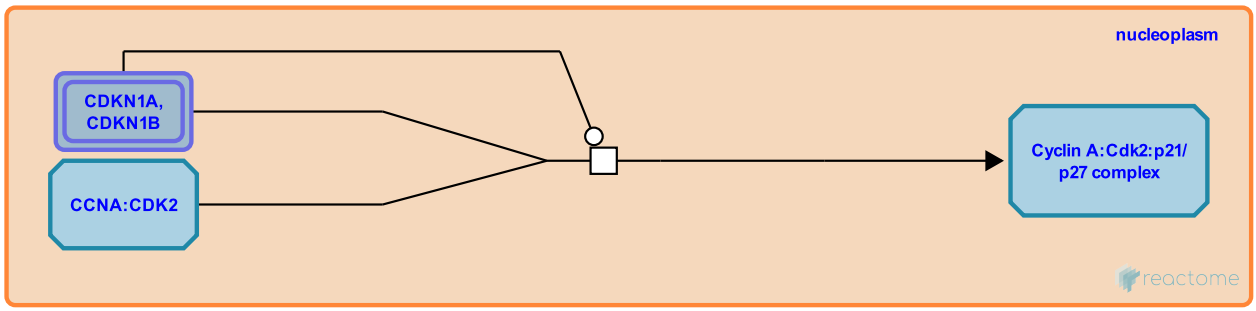
Inactivation of Cyclin A:Cdk2 complexes by p27/p21 ↗

Location: TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest

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: PCBP4 modulates CDKN1A translation

Literature references

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

Harper, JW., Adami, GR., Wei, N., Keyomarsi, K., Elledge, SJ. (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.

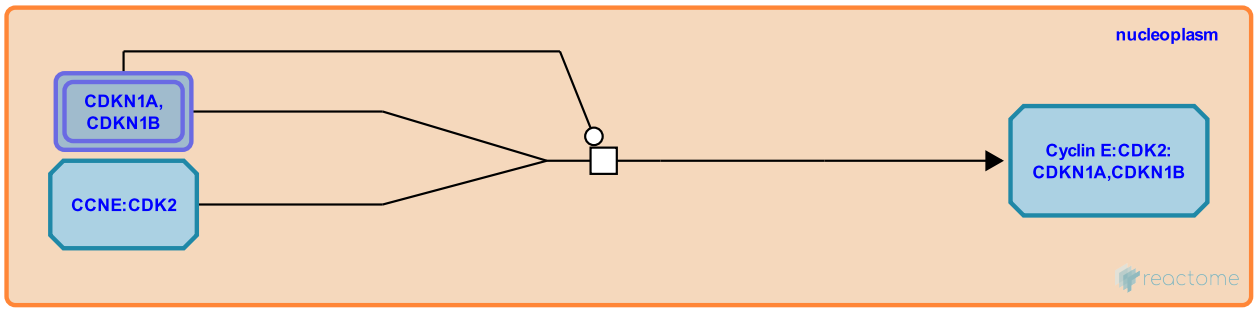
Inactivation of Cyclin E:Cdk2 complexes by p27/p21 ↗

Location: TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest

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: PCBP4 modulates CDKN1A translation

Literature references

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

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

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

Editions

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

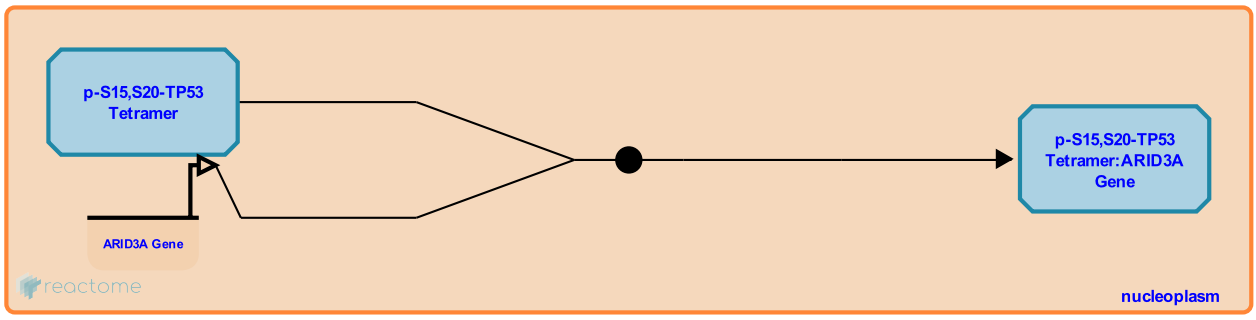
TP53 binds the ARID3A gene ↗

Location: TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest

Stable identifier: R-HSA-6791387

Type: binding

Compartments: nucleoplasm



TP53 (p53) binds the p53 response element located in the second intron of the ARID3A gene (Ma et al. 2003).

Followed by: TP53 stimulates ARID3A gene expression

Literature references

Ma, K., Araki, K., Ichwan, SJ., Suganuma, T., Tamamori-Adachi, M., Ikeda, MA. (2003). E2FBP1/DRIL1, an AT-rich interaction domain-family transcription factor, is regulated by p53. *Mol. Cancer Res., 1*, 438-44. ↗

Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

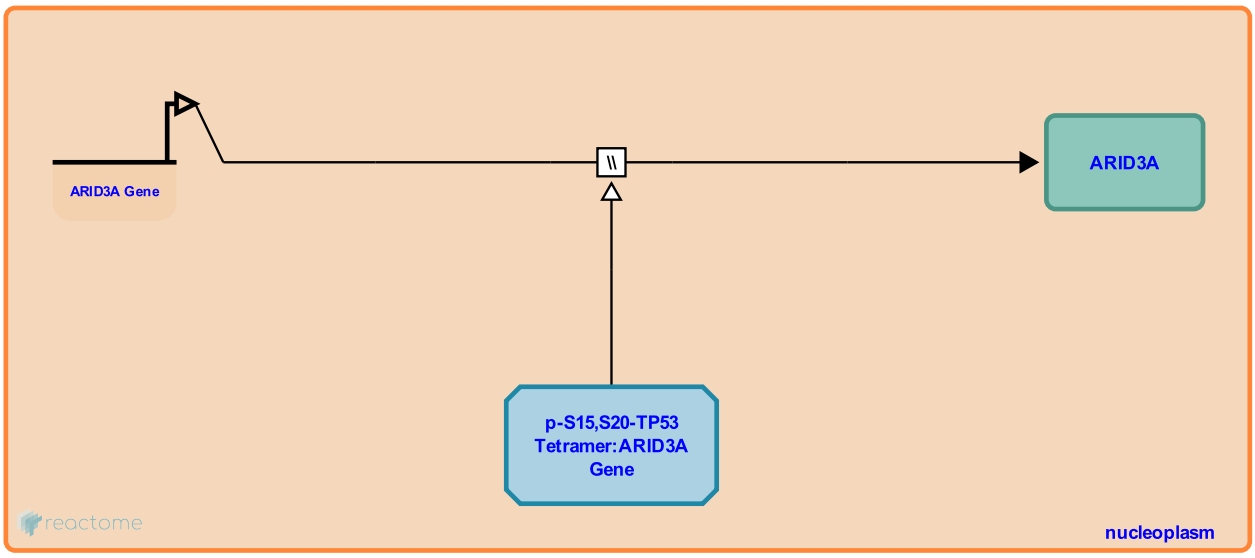
TP53 stimulates ARID3A gene expression ↗

Location: TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest

Stable identifier: R-HSA-6791363

Type: omitted

Compartments: nucleoplasm



TP53 (p53) stimulates transcription of the ARID3A gene upon binding to the p53 response element in the second intron of the ARID3A gene (Ma et al. 2003). ARID3A is implicated as both a positive and a negative cell cycle regulator. It interacts with E2F1 and stimulates E2F1 transcriptional activity (Suzuki et al. 1998, Peeper et al. 2002). It may also cooperate with TP53 in the activation of CDKN1A (p21) transcription (L-estari et al. 2012).

Preceded by: TP53 binds the ARID3A gene

Literature references

Ma, K., Araki, K., Ichwan, SJ., Suganuma, T., Tamamori-Adachi, M., Ikeda, MA. (2003). E2FBP1/DRIL1, an AT-rich interaction domain-family transcription factor, is regulated by p53. *Mol. Cancer Res., 1*, 438-44. ↗

Lestari, W., Ichwan, SJ., Otsu, M., Yamada, S., Iseki, S., Shimizu, S. et al. (2012). Cooperation between ARID3A and p53 in the transcriptional activation of p21WAF1 in response to DNA damage. *Biochem. Biophys. Res. Commun., 417*, 710-6. ↗

Suzuki, M., Okuyama, S., Okamoto, S., Shirasuna, K., Nakajima, T., Hachiya, T. et al. (1998). A novel E2F binding protein with Myc-type HLH motif stimulates E2F-dependent transcription by forming a heterodimer. *Oncogene, 17*, 853-65. ↗

Peeper, DS., Shvarts, A., Brummelkamp, T., Douma, S., Koh, EY., Daley, GQ. et al. (2002). A functional screen identifies hDRIL1 as an oncogene that rescues RAS-induced senescence. *Nat. Cell Biol., 4*, 148-53. ↗

Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

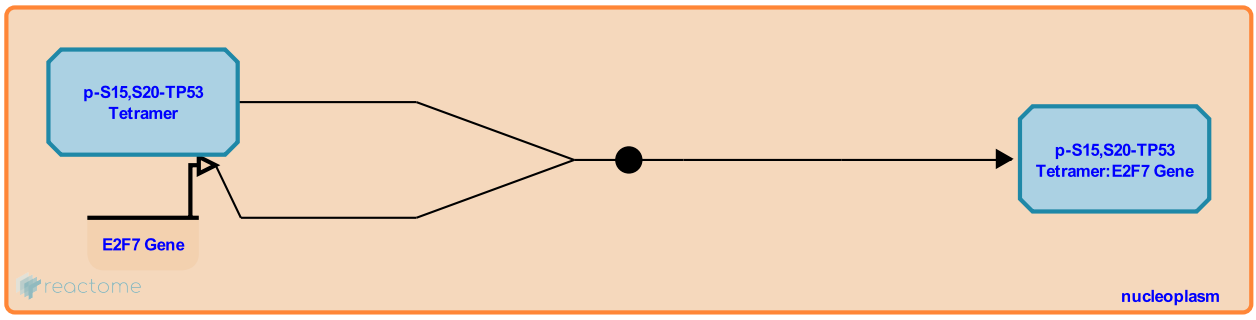
TP53 binds the E2F7 gene ↗

Location: TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest

Stable identifier: R-HSA-6798304

Type: binding

Compartments: nucleoplasm



TP53 (p53) binds the p53 response element in the promoter of the E2F7 gene (Carvajal et al. 2012, Aksoy et al. 2012).

Followed by: TP53 stimulates E2F7 expression

Literature references

Carvajal, LA., Hamard, PJ., Tonnessen, C., Manfredi, JJ. (2012). E2F7, a novel target, is up-regulated by p53 and mediates DNA damage-dependent transcriptional repression. *Genes Dev., 26*, 1533-45. ↗

Aksoy, O., Chicas, A., Zeng, T., Zhao, Z., McCurrach, M., Wang, X. et al. (2012). The atypical E2F family member E2F7 couples the p53 and RB pathways during cellular senescence. *Genes Dev., 26*, 1546-57. ↗

Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

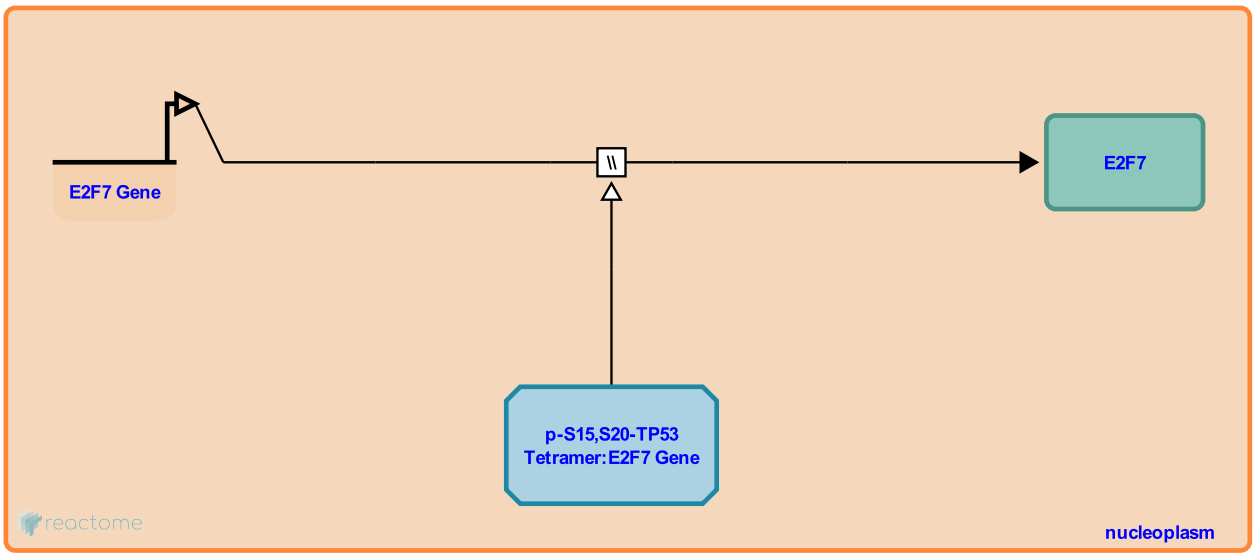
TP53 stimulates E2F7 expression ↗

Location: TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest

Stable identifier: R-HSA-6798299

Type: omitted

Compartments: nucleoplasm



Binding of TP53 (p53) to the p53 response element in the promoter of the E2F7 gene stimulates E2F7 transcription (Carvajal et al. 2012, Aksoy et al. 2012).

Preceded by: TP53 binds the E2F7 gene

Followed by: E2F7 forms homodimers, E2F7 binds E2F8

Literature references

Carvajal, LA., Hamard, PJ., Tonnessen, C., Manfredi, JJ. (2012). E2F7, a novel target, is up-regulated by p53 and mediates DNA damage-dependent transcriptional repression. *Genes Dev., 26*, 1533-45. ↗

Aksoy, O., Chicas, A., Zeng, T., Zhao, Z., McCurrach, M., Wang, X. et al. (2012). The atypical E2F family member E2F7 couples the p53 and RB pathways during cellular senescence. *Genes Dev., 26*, 1546-57. ↗

Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
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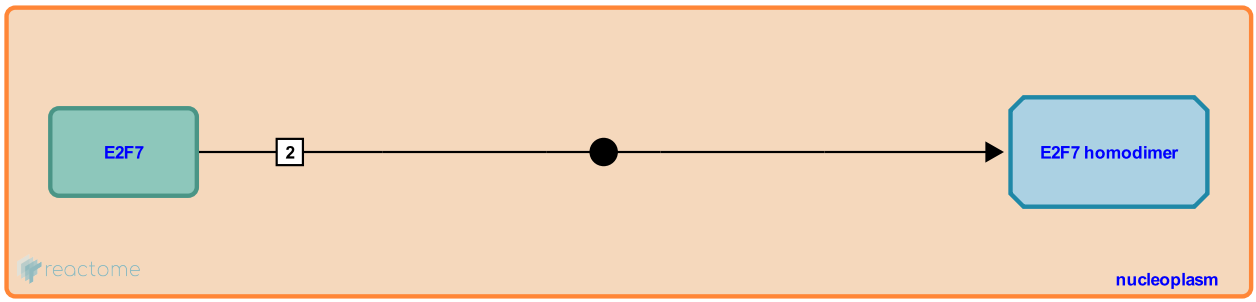
E2F7 forms homodimers ↗

Location: TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest

Stable identifier: R-HSA-8952996

Type: binding

Compartments: nucleoplasm



E2F7 forms homodimers (Di Stefano et al. 2003, Logan et al. 2004). While E2F7 also forms heterodimers with E2F8, co-immunoprecipitation experiments suggest that E2F7 has higher affinity for itself than for E2F8 (Li et al. 2008)

Preceded by: TP53 stimulates E2F7 expression

Followed by: E2F7 and E2F8 homo- and heterodimers bind the E2F1 gene promoter

Literature references

Logan, N., Delavaine, L., Graham, A., Reilly, C., Wilson, J., Brummelkamp, TR. et al. (2004). E2F-7: a distinctive E2F family member with an unusual organization of DNA-binding domains. *Oncogene, 23*, 5138-50. ↗

Di Stefano, L., Jensen, MR., Helin, K. (2003). E2F7, a novel E2F featuring DP-independent repression of a subset of E2F-regulated genes. *EMBO J., 22*, 6289-98. ↗

Li, J., Ran, C., Li, E., Gordon, F., Comstock, G., Siddiqui, H. et al. (2008). Synergistic function of E2F7 and E2F8 is essential for cell survival and embryonic development. *Dev. Cell, 14*, 62-75. ↗

Editions

2016-12-21	Authored	Orlic-Milacic, M.
2017-01-03	Reviewed	Di Stefano, L.
2017-01-03	Edited	Orlic-Milacic, M.
2017-01-24	Reviewed	de Bruin, A., Westendorp, B.
2017-01-27	Edited	Orlic-Milacic, M.

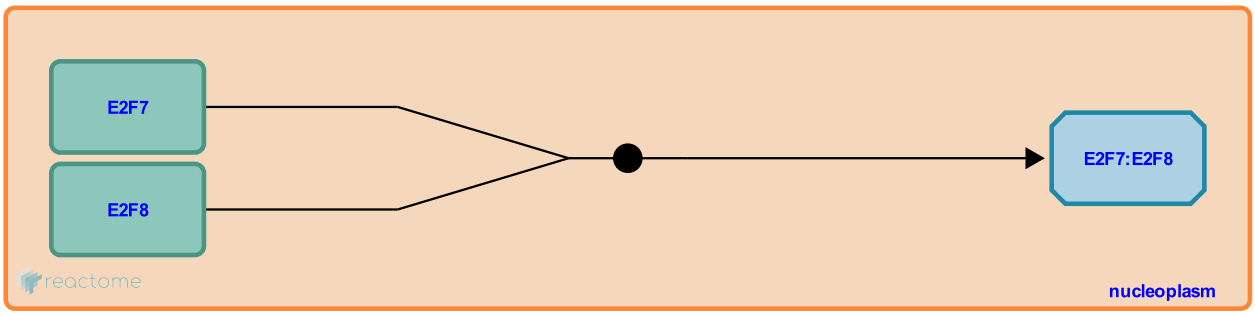
E2F7 binds E2F8 ↗

Location: TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest

Stable identifier: R-HSA-8953013

Type: binding

Compartments: nucleoplasm



E2F7 forms heterodimers with E2F8 (Li et al. 2008, Zalmas et al. 2008).

Preceded by: TP53 stimulates E2F7 expression

Followed by: E2F7 and E2F8 homo- and heterodimers bind the E2F1 gene promoter

Literature references

Li, J., Ran, C., Li, E., Gordon, F., Comstock, G., Siddiqui, H. et al. (2008). Synergistic function of E2F7 and E2F8 is essential for cell survival and embryonic development. *Dev. Cell, 14*, 62-75. ↗

Zalmas, LP., Zhao, X., Graham, AL., Fisher, R., Reilly, C., Coutts, AS. et al. (2008). DNA-damage response control of E2F7 and E2F8. *EMBO Rep., 9*, 252-9. ↗

Editions

2016-12-21	Authored	Orlic-Milacic, M.
2017-01-03	Reviewed	Di Stefano, L.
2017-01-03	Edited	Orlic-Milacic, M.
2017-01-24	Reviewed	de Bruin, A., Westendorp, B.
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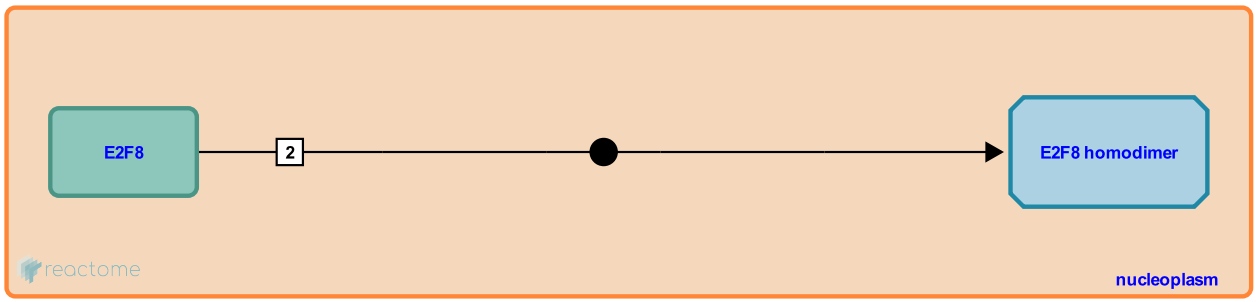
E2F8 forms homodimers ↗

Location: TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest

Stable identifier: R-HSA-8953037

Type: binding

Compartments: nucleoplasm



E2F8 forms homodimers (Maiti et al. 2005, Li et al. 2008). E2F8 also forms heterodimers with E2F7 and co-immunoprecipitation experiments suggest that E2F8 has higher affinity for E2F7 than for itself (Zalmas et al. 2008, Li et al. 2008).

Followed by: E2F7 and E2F8 homo- and heterodimers bind the E2F1 gene promoter

Literature references

Maiti, B., Li, J., de Bruin, A., Gordon, F., Timmers, C., Opavsky, R. et al. (2005). Cloning and characterization of mouse E2F8, a novel mammalian E2F family member capable of blocking cellular proliferation. *J. Biol. Chem., 280*, 18211-20. ↗

Li, J., Ran, C., Li, E., Gordon, F., Comstock, G., Siddiqui, H. et al. (2008). Synergistic function of E2F7 and E2F8 is essential for cell survival and embryonic development. *Dev. Cell, 14*, 62-75. ↗

Zalmas, LP., Zhao, X., Graham, AL., Fisher, R., Reilly, C., Coutts, AS. et al. (2008). DNA-damage response control of E2F7 and E2F8. *EMBO Rep., 9*, 252-9. ↗

Editions

2016-12-21	Authored	Orlic-Milacic, M.
2017-01-03	Reviewed	Di Stefano, L.
2017-01-03	Edited	Orlic-Milacic, M.
2017-01-24	Reviewed	de Bruin, A., Westendorp, B.
2017-01-27	Edited	Orlic-Milacic, M.

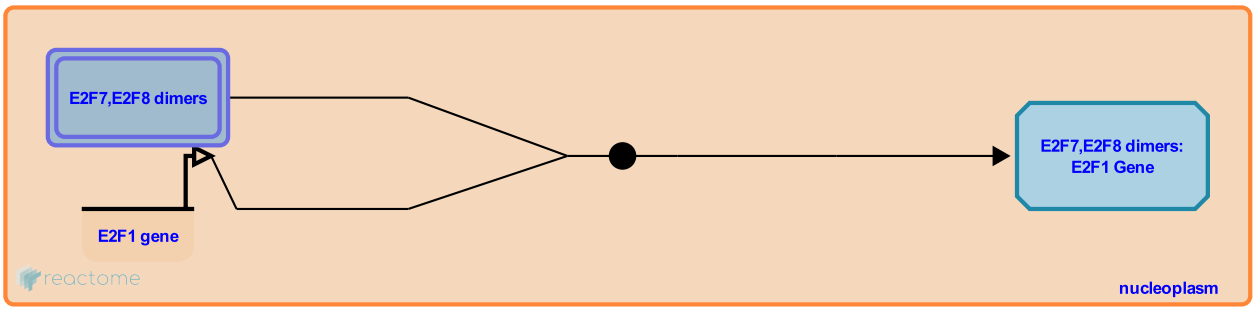
E2F7 and E2F8 homo- and heterodimers bind the E2F1 gene promoter ↗

Location: TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest

Stable identifier: R-HSA-6798347

Type: binding

Compartments: nucleoplasm



E2F7 binds to E2F sites in the promoter of the E2F1 gene to inhibit its expression (Di Stefano et al. 2003, Carvajal et al. 2012, Aksoy et al. 2012). Besides E2F7 homodimers, heterodimers of E2F7 and E2F8, as well as E2F8 homodimers, can also bind to the promoter of the E2F1 gene to inhibit its transcription (Li et al. 2008, Zalmas et al. 2008).

Preceded by: E2F7 forms homodimers, E2F7 binds E2F8, E2F8 forms homodimers

Followed by: E2F7 and E2F8 homo- and heterodimers inhibit E2F1 expression

Literature references

Carvajal, LA., Hamard, PJ., Tonnessen, C., Manfredi, JJ. (2012). E2F7, a novel target, is up-regulated by p53 and mediates DNA damage-dependent transcriptional repression. *Genes Dev., 26*, 1533-45. ↗

Aksoy, O., Chicas, A., Zeng, T., Zhao, Z., McCurrach, M., Wang, X. et al. (2012). The atypical E2F family member E2F7 couples the p53 and RB pathways during cellular senescence. *Genes Dev., 26*, 1546-57. ↗

Li, J., Ran, C., Li, E., Gordon, F., Comstock, G., Siddiqui, H. et al. (2008). Synergistic function of E2F7 and E2F8 is essential for cell survival and embryonic development. *Dev. Cell, 14*, 62-75. ↗

Zalmas, LP., Zhao, X., Graham, AL., Fisher, R., Reilly, C., Coutts, AS. et al. (2008). DNA-damage response control of E2F7 and E2F8. *EMBO Rep., 9*, 252-9. ↗

Di Stefano, L., Jensen, MR., Helin, K. (2003). E2F7, a novel E2F featuring DP-independent repression of a subset of E2F-regulated genes. *EMBO J., 22*, 6289-98. ↗

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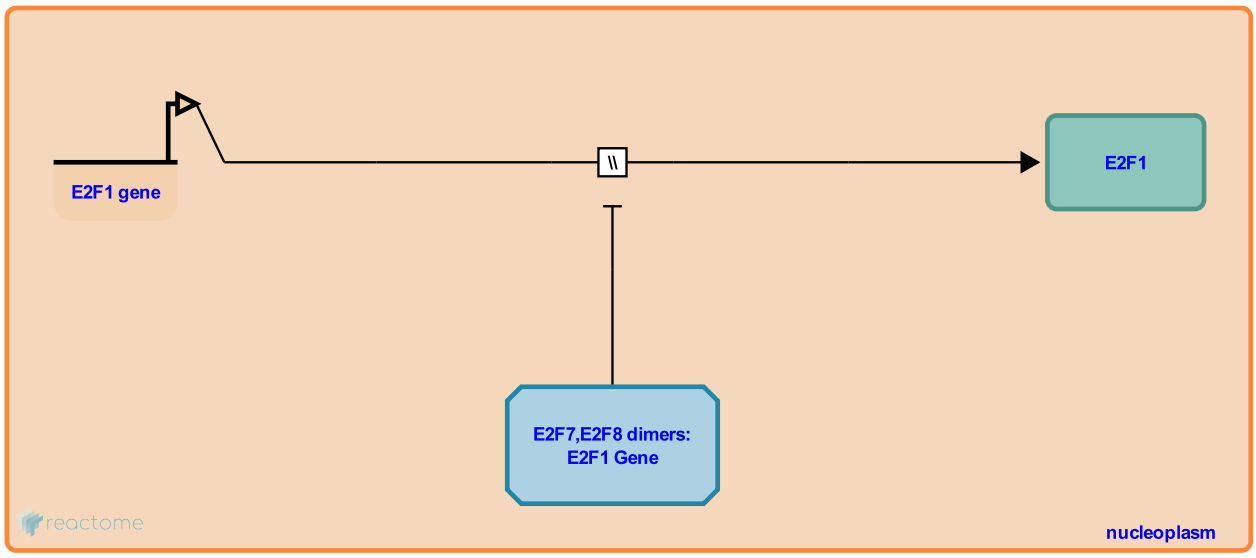
E2F7 and E2F8 homo- and heterodimers inhibit E2F1 expression ↗

Location: TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest

Stable identifier: R-HSA-6798353

Type: omitted

Compartments: nucleoplasm



Upon binding to E2F elements in the promoter of the E2F1 gene, E2F7 represses transcription of E2F1 (Di Stefano et al. 2003, Li et al. 2008, Zalmas et al. 2008, Carvajal et al. 2012). E2F1 transcription is also directly repressed by E2F8. E2F7 and E2F8 bind to the E2F1 gene promoter as homo- or heterodimers (Li et al. 2008, Zalmas et al. 2008). E2F7- and E2F8-mediated repression of E2F1 transcription is an important step in the DNA damage induced cell cycle arrest (Zalmas et al. 2008). E2F8-mediated repression of the E2F1 gene is involved in the polyploidization of hepatocytes during liver development (Pandit et al. 2012). Loss of E2F7 and E2F8 triggers apoptosis via induction of E2F1 in response to stress (Li et al. 2008, Thurlings et al. 2016).

Preceded by: E2F7 and E2F8 homo- and heterodimers bind the E2F1 gene promoter

Literature references

Carvajal, LA., Hamard, PJ., Tonnessen, C., Manfredi, JJ. (2012). E2F7, a novel target, is up-regulated by p53 and mediates DNA damage-dependent transcriptional repression. *Genes Dev., 26*, 1533-45. ↗

Li, J., Ran, C., Li, E., Gordon, F., Comstock, G., Siddiqui, H. et al. (2008). Synergistic function of E2F7 and E2F8 is essential for cell survival and embryonic development. *Dev. Cell, 14*, 62-75. ↗

Zalmas, LP., Zhao, X., Graham, AL., Fisher, R., Reilly, C., Coutts, AS. et al. (2008). DNA-damage response control of E2F7 and E2F8. *EMBO Rep., 9*, 252-9. ↗

Pandit, SK., Westendorp, B., Nantasanti, S., van Liere, E., Tooten, PC., Cornelissen, PW. et al. (2012). E2F8 is essential for polyploidization in mammalian cells. *Nat. Cell Biol., 14*, 1181-91. ↗

Thurlings, I., Martínez-López, LM., Westendorp, B., Zijp, M., Kuiper, R., Tooten, P. et al. (2016). Synergistic functions of E2F7 and E2F8 are critical to suppress stress-induced skin cancer. *Oncogene*. ↗

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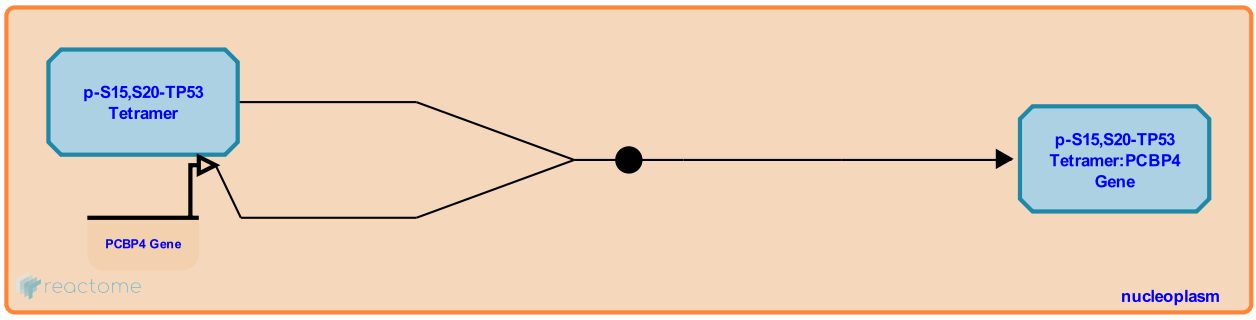
TP53 binds the PCBP4 gene ↗

Location: TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest

Stable identifier: R-HSA-6803391

Type: binding

Compartments: nucleoplasm



TP53 (p53) binds two p53 response elements in the promoter of the PCBP4 (MCG10) gene (Zhu and Chen 2000).

Followed by: TP53 stimulates PCBP4 expression

Literature references

Zhu, J., Chen, X. (2000). MCG10, a novel p53 target gene that encodes a KH domain RNA-binding protein, is capable of inducing apoptosis and cell cycle arrest in G(2)-M. *Mol. Cell. Biol., 20,* 5602-18. ↗

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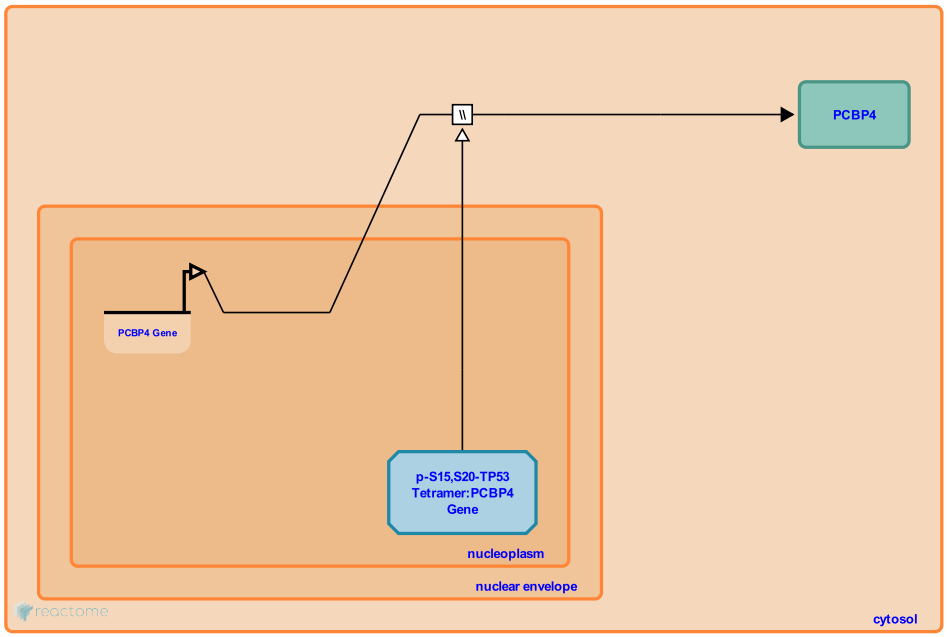
TP53 stimulates PCBP4 expression ↗

Location: TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest

Stable identifier: R-HSA-6803400

Type: omitted

Compartments: cytosol, nucleoplasm



Binding of TP53 (p53) to two p53 response elements in the promoter of the PCBP4 (MCG10) gene stimulates PCBP4 transcription. PCBP4 has three K homology (KH) domains involved in RNA binding that can interact with a poly(C) sequence. PCBP4 binding destabilizes its targets, including CDKN1A (p21), thus favouring p53-dependent apoptosis over cell cycle arrest (Zhu and Chen 2000).

Preceded by: TP53 binds the PCBP4 gene

Followed by: PCBP4 binds the CDKN1A mRNA

Literature references

Zhu, J., Chen, X. (2000). MCG10, a novel p53 target gene that encodes a KH domain RNA-binding protein, is capable of inducing apoptosis and cell cycle arrest in G(2)-M. *Mol. Cell. Biol., 20*, 5602-18. ↗

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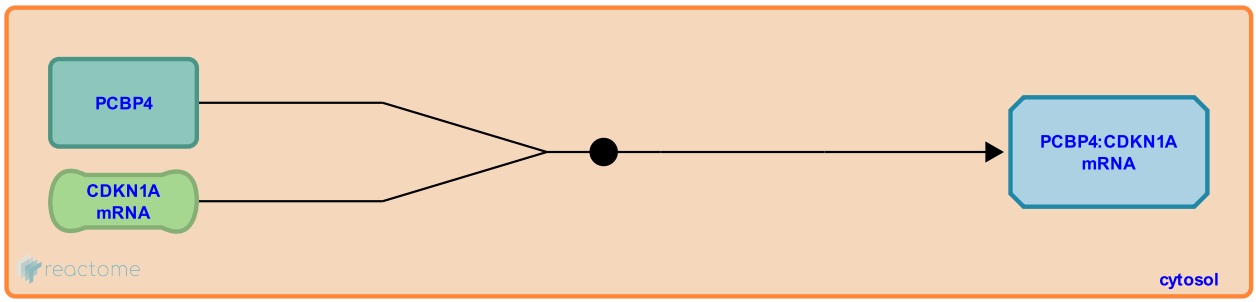
PCBP4 binds the CDKN1A mRNA ↗

Location: TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest

Stable identifier: R-HSA-6803403

Type: binding

Compartments: cytosol



PCBP4 binds the 3'-UTR of the CDKN1A (p21) mRNA and reduces its stability (Scoumanne et al. 2011).

Preceded by: TP53 stimulates CDKN1A (p21) transcription, TP53 stimulates PCBP4 expression

Followed by: PCBP4 modulates CDKN1A translation

Literature references

Scoumanne, A., Cho, SJ., Zhang, J., Chen, X. (2011). The cyclin-dependent kinase inhibitor p21 is regulated by RNA-binding protein PCBP4 via mRNA stability. *Nucleic Acids Res., 39*, 213-24. ↗

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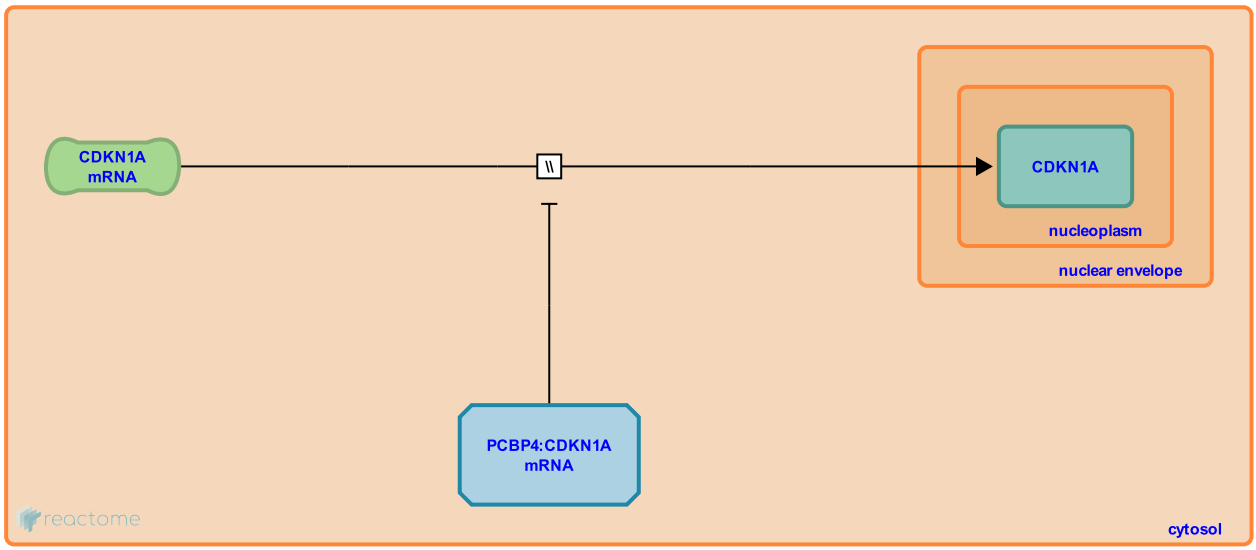
PCBP4 modulates CDKN1A translation ↗

Location: TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest

Stable identifier: R-HSA-6803411

Type: omitted

Compartments: cytosol, nucleoplasm



PCBP4 binding to the 3'-UTR of the CDKN1A (p21) mRNA reduces half-life of the CDKN1A mRNA and the amount of CDKN1A protein. Upon DNA damage, TP53-mediated induction of CDKN1A is rapid, while the induction of PCBP4 is more gradual. It is hypothesized that, under prolonged stress, PCBP4-mediated down-regulation of CDKN1A may switch from G1 cell cycle arrest to G2 arrest, which may precede apoptosis (Scoumanne et al. 2011).

Preceded by: PCBP4 binds the CDKN1A mRNA

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

Literature references

Scoumanne, A., Cho, SJ., Zhang, J., Chen, X. (2011). The cyclin-dependent kinase inhibitor p21 is regulated by RNA-binding protein PCBP4 via mRNA stability. *Nucleic Acids Res., 39*, 213-24. ↗

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Table of Contents