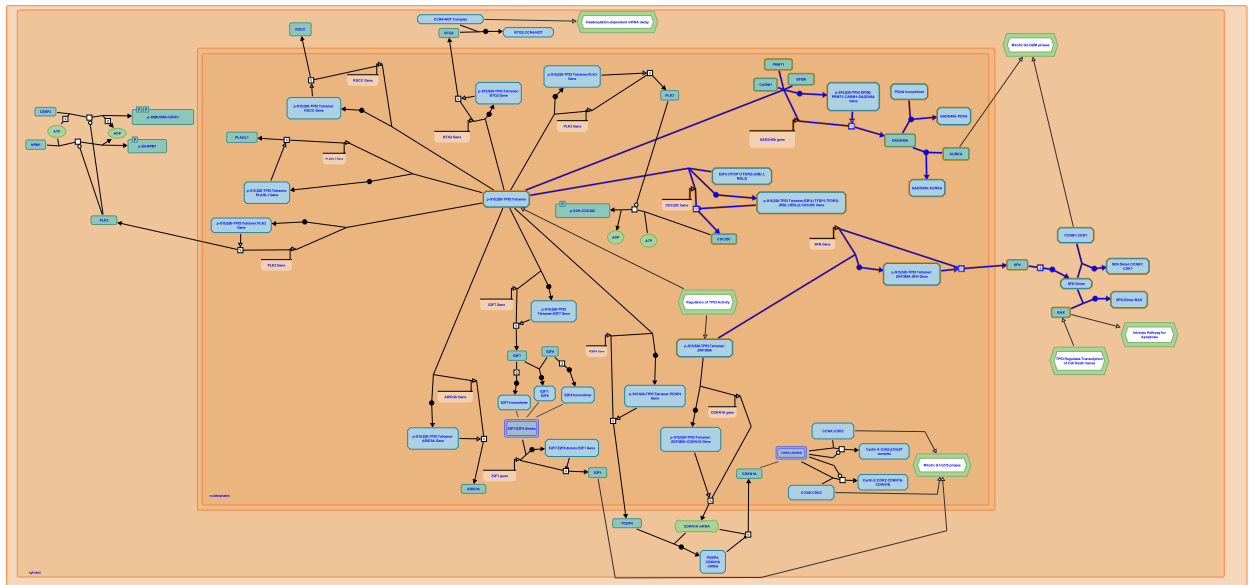


TP53 Regulates Transcription of Genes Involved in G2 Cell Cycle Arrest



Inga, A., Orlic-Milacic, M., 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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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

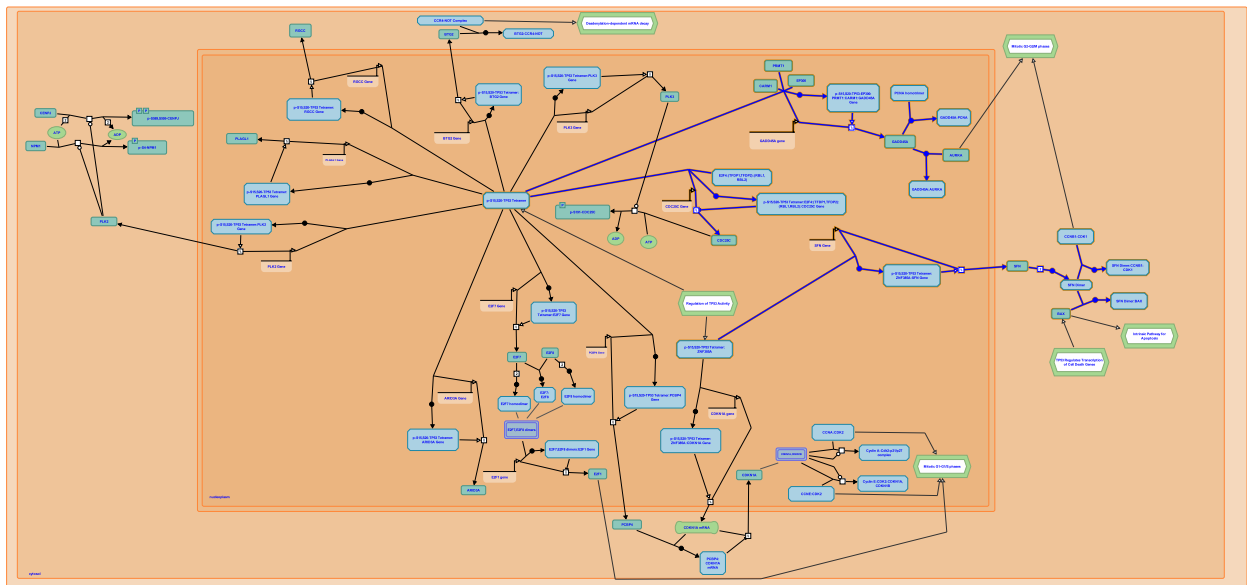
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Reactome database release: 70

This document contains 1 pathway and 11 reactions ([see Table of Contents](#))

TP53 Regulates Transcription of Genes Involved in G2 Cell Cycle Arrest ↗

Stable identifier: R-HSA-6804114



reactome

TP53 contributes to the establishment of G2 arrest by inducing transcription of GADD45A and SFN, and by inhibiting transcription of CDC25C. TP53 induces GADD45A transcription in cooperation with chromatin modifying enzymes EP300, PRMT1 and CARM1 (An et al. 2004). GADD45A binds Aurora kinase A (AURKA), inhibiting its catalytic activity and preventing AURKA-mediated G2/M transition (Shao et al. 2006, Sanchez et al. 2010). GADD45A also forms a complex with PCNA. PCNA is involved in both normal and repair DNA synthesis. The effect of GADD45 interaction with PCNA, if any, on S phase progression, G2 arrest and DNA repair is not known (Smith et al. 1994, Hall et al. 1995, Sanchez et al. 2010, Kim et al. 2013). SFN (14-3-3-sigma) is induced by TP53 (Hermeking et al. 1997) and contributes to G2 arrest by binding to the complex of CDK1 and CCNB1 (cyclin B1) and preventing its translocation to the nucleus. Phosphorylation of a number of nuclear proteins by the complex of CDK1 and CCNB1 is needed for G2/M transition (Chan et al. 1999). While promoting G2 arrest, SFN can simultaneously inhibit apoptosis by binding to BAX and preventing its translocation to mitochondria, a step involved in cytochrome C release (Samuel et al. 2001). TP53 binds the promoter of the CDC25C gene in cooperation with the transcriptional repressor E2F4 and represses CDC25C transcription, thus maintaining G2 arrest (St Clair et al. 2004, Benson et al. 2014). 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 SFN transcription (Das et al. 2007).

Literature references

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- Shao, S., Wang, Y., Jin, S., Song, Y., Wang, X., Fan, W. et al. (2006). Gadd45a interacts with aurora-A and inhibits its kinase activity. *J. Biol. Chem.*, 281, 28943-50. ↗
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- An, W., Kim, J., Roeder, RG. (2004). Ordered cooperative functions of PRMT1, p300, and CARM1 in transcriptional activation by p53. *Cell*, 117, 735-48. ↗

Editions

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

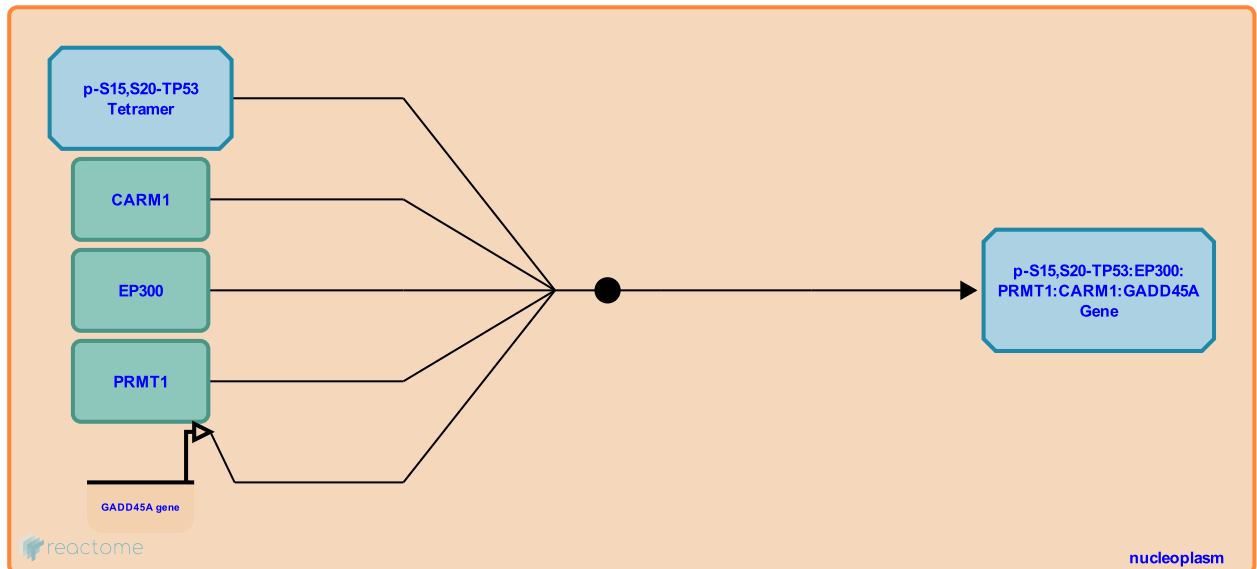
TP53 in complex with EP300, PRMT1 and CARM1 binds the GADD45A promoter ↗

Location: TP53 Regulates Transcription of Genes Involved in G2 Cell Cycle Arrest

Stable identifier: R-HSA-3215152

Type: binding

Compartments: nucleoplasm



TP53, together with chromatin modifying enzymes EP300, PRMT1 and CARM1, binds the p53 response element in the third intron of the GADD45A gene (An et al. 2004).

Followed by: TP53 in complex with EP300, PRMT1 and CARM1 stimulates GADD45A transcription

Literature references

An, W., Kim, J., Roeder, RG. (2004). Ordered cooperative functions of PRMT1, p300, and CARM1 in transcriptional activation by p53. *Cell*, 117, 735-48. ↗

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TP53 in complex with EP300, PRMT1 and CARM1 stimulates GADD45A transcription

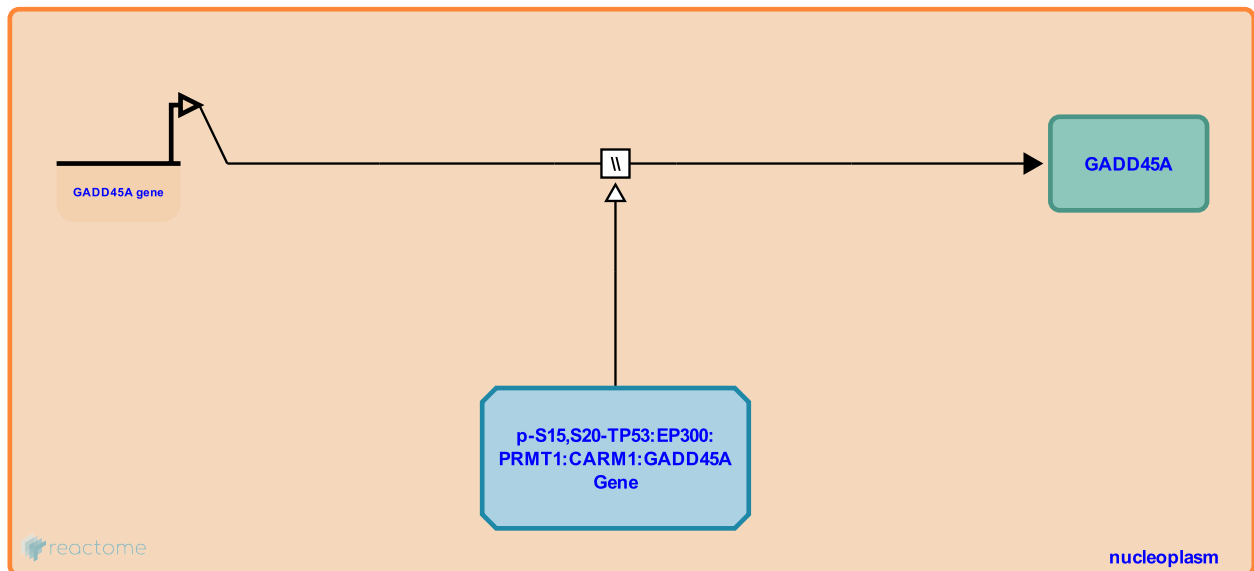


Location: TP53 Regulates Transcription of Genes Involved in G2 Cell Cycle Arrest

Stable identifier: R-HSA-3215144

Type: omitted

Compartments: nucleoplasm



Binding of TP53 (p53) to the p53 response element in the third intron of the GADD45A gene, together with chromatin modification mediated by TP53-associated proteins CARM1, PRMT1 and EP300, stimulates GADD45A transcription (An et al. 2004).

Preceded by: TP53 in complex with EP300, PRMT1 and CARM1 binds the GADD45A promoter

Followed by: GADD45A binds PCNA, GADD45A binds AURKA

Literature references

An, W., Kim, J., Roeder, RG. (2004). Ordered cooperative functions of PRMT1, p300, and CARM1 in transcriptional activation by p53. *Cell*, 117, 735-48. [↗](#)

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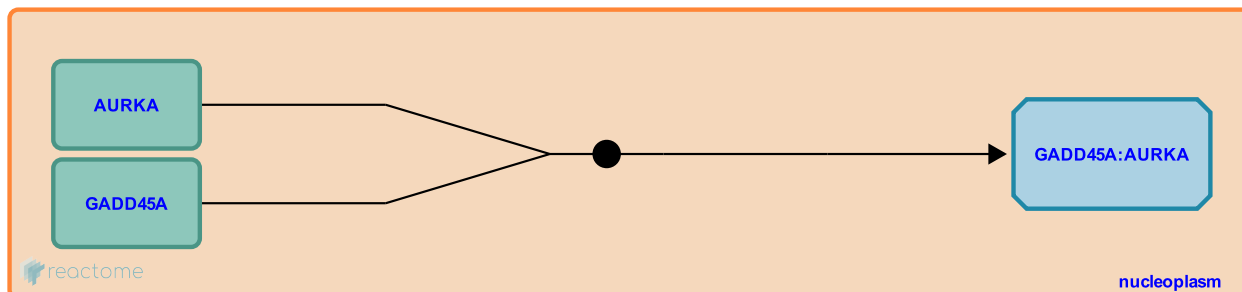
GADD45A binds AURKA ↗

Location: [TP53 Regulates Transcription of Genes Involved in G2 Cell Cycle Arrest](#)

Stable identifier: R-HSA-6791235

Type: binding

Compartments: nucleoplasm



GADD45A binds Aurora-A protein kinase (AURKA). GADD45A inhibits the kinase activity of AURKA and AURKA-induced centrosome amplification, thus interfering with the G2/M transition (Shao et al. 2006, Sanchez et al. 2010).

Preceded by: [TP53 in complex with EP300, PRMT1 and CARM1 stimulates GADD45A transcription](#)

Literature references

Sánchez, R., Pantoja-Uceda, D., Prieto, J., Diercks, T., Marcaida, MJ., Montoya, G. et al. (2010). Solution structure of human growth arrest and DNA damage 45alpha (Gadd45alpha) and its interactions with proliferating cell nuclear antigen (PCNA) and Aurora A kinase. *J. Biol. Chem.*, 285, 22196-201. ↗

Shao, S., Wang, Y., Jin, S., Song, Y., Wang, X., Fan, W. et al. (2006). Gadd45a interacts with aurora-A and inhibits its kinase activity. *J. Biol. Chem.*, 281, 28943-50. ↗

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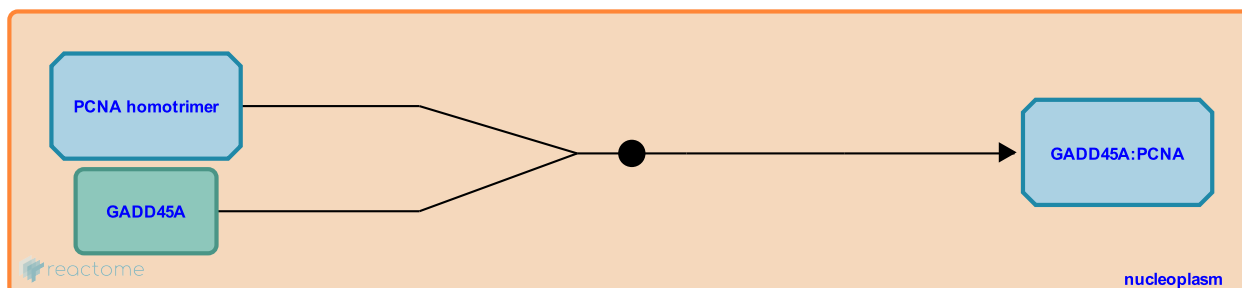
GADD45A binds PCNA [↗](#)

Location: [TP53 Regulates Transcription of Genes Involved in G2 Cell Cycle Arrest](#)

Stable identifier: R-HSA-6791109

Type: binding

Compartments: nucleoplasm



GADD45A binds PCNA homotrimer (Smith et al. 1994, Hall et al. 1995, Sanchez et al. 2010). The consequences of this interaction are not clear. Binding to GADD45A may negatively regulate PCNA-mediated DNA synthesis during S phase of the cell cycle or it may promote PCNA-mediated DNA repair synthesis (Smith et al. 1994, Kim et al. 2013).

Preceded by: [TP53 in complex with EP300, PRMT1 and CARM1 stimulates GADD45A transcription](#)

Literature references

- Smith, ML., Chen, IT., Zhan, Q., Bae, I., Chen, CY., Gilmer, TM. et al. (1994). Interaction of the p53-regulated protein Gadd45 with proliferating cell nuclear antigen. *Science*, 266, 1376-80. [↗](#)
- Sánchez, R., Pantoja-Uceda, D., Prieto, J., Diercks, T., Marcaida, MJ., Montoya, G. et al. (2010). Solution structure of human growth arrest and DNA damage 45alpha (Gadd45alpha) and its interactions with proliferating cell nuclear antigen (PCNA) and Aurora A kinase. *J. Biol. Chem.*, 285, 22196-201. [↗](#)
- Hall, PA., Kearsley, JM., Coates, PJ., Norman, DG., Warbrick, E., Cox, LS. (1995). Characterisation of the interaction between PCNA and Gadd45. *Oncogene*, 10, 2427-33. [↗](#)
- Kim, HL., Kim, SU., Seo, YR. (2013). A novel role for Gadd45a in base excision repair: modulation of APE1 activity by the direct interaction of Gadd45a with PCNA. *Biochem. Biophys. Res. Commun.*, 434, 185-90. [↗](#)

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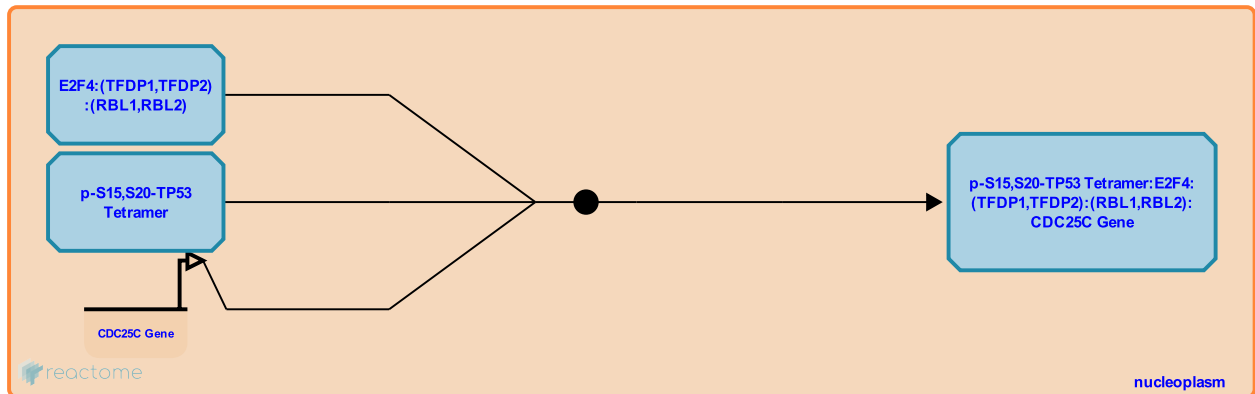
TP53 and E2F4 bind the CDC25C gene ↗

Location: TP53 Regulates Transcription of Genes Involved in G2 Cell Cycle Arrest

Stable identifier: R-HSA-6798282

Type: binding

Compartments: nucleoplasm



The promoter of the CDC25C gene contains p53 response elements as well as E2F binding sites and can bind both TP53 (St Clair et al. 2004) and E2F4 (Benson et al. 2014). E2F4 transcription repressor complex consists of E2F4, a transcriptional co-factor TFDP1 (DP1) or TFDP2 (DP2), and a retinoblastoma family protein RBL1 (p107) or RBL2 (p130). The CDK inhibitor p21 (CDKN1A), induced by TP53, positively affects E2F4 recruitment to the CDC25C promoter, probably by upregulating RBL2 (Helmbold et al. 2009, Benson et al. 2014).

Followed by: TP53 and E2F4 inhibit CDC25C expression

Literature references

St Clair, S., Giono, L., Varmeh-Ziaie, S., Resnick-Silverman, L., Liu, WJ., Padi, A. et al. (2004). DNA damage-induced downregulation of Cdc25C is mediated by p53 via two independent mechanisms: one involves direct binding to the cdc25C promoter. *Mol. Cell*, 16, 725-36. ↗

Benson, EK., Mungamuri, SK., Attie, O., Kracikova, M., Sachidanandam, R., Manfredi, JJ. et al. (2014). p53-dependent gene repression through p21 is mediated by recruitment of E2F4 repression complexes. *Oncogene*, 33, 3959-69. ↗

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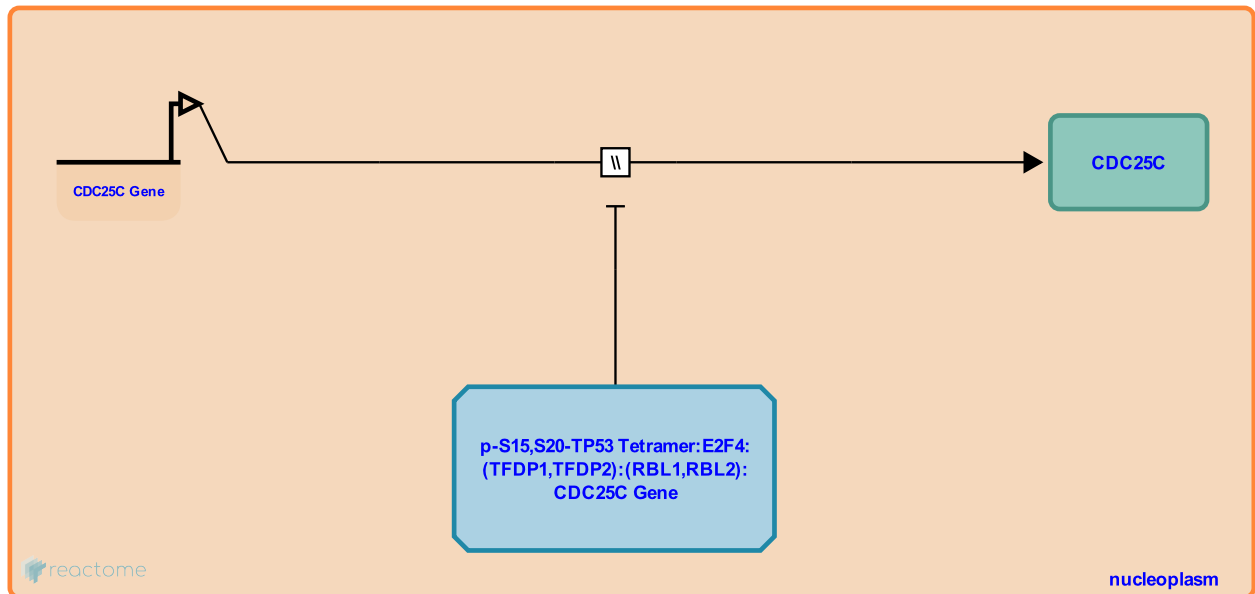
TP53 and E2F4 inhibit CDC25C expression ↗

Location: TP53 Regulates Transcription of Genes Involved in G2 Cell Cycle Arrest

Stable identifier: R-HSA-6798268

Type: omitted

Compartments: nucleoplasm



Binding of TP53 and the E2F4 repressor complex to the promoter of the CDC25C gene results in the inhibition of CDC25C transcription, an important step in the maintenance of the G2 cell cycle checkpoint (St. Clair et al. 2004, Benson et al. 2014).

Preceded by: TP53 and E2F4 bind the CDC25C gene

Literature references

Benson, EK., Mungamuri, SK., Attie, O., Kracikova, M., Sachidanandam, R., Manfredi, JJ. et al. (2014). p53-dependent gene repression through p21 is mediated by recruitment of E2F4 repression complexes. *Oncogene*, 33, 3959-69. ↗

St Clair, S., Giono, L., Varmeh-Ziaie, S., Resnick-Silverman, L., Liu, WJ., Padi, A. et al. (2004). DNA damage-induced downregulation of Cdc25C is mediated by p53 via two independent mechanisms: one involves direct binding to the cdc25C promoter. *Mol. Cell*, 16, 725-36. ↗

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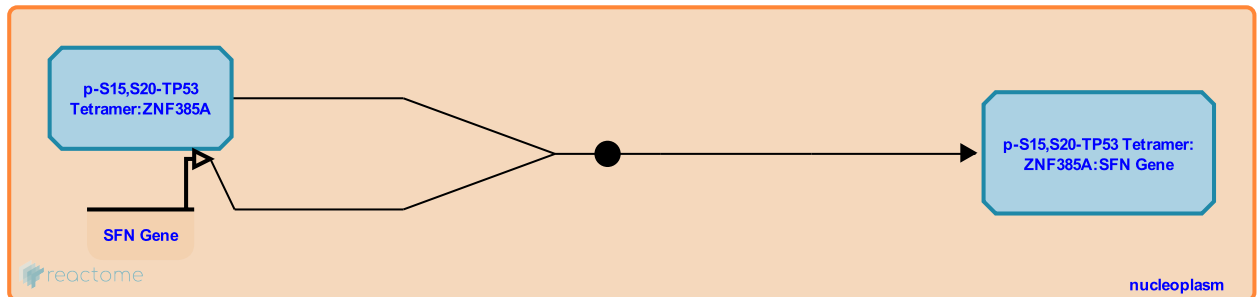
TP53 binds the SFN gene ↗

Location: TP53 Regulates Transcription of Genes Involved in G2 Cell Cycle Arrest

Stable identifier: R-HSA-6803858

Type: binding

Compartments: nucleoplasm



TP53 (p53) binds the p53 response element in the promoter region of the SFN (14-3-3 sigma) gene (Hermeking et al. 1997). Interaction between ZNF385A (HZF) and TP53 facilitates TP53 binding to the promoter of the SFN gene (Das et al. 2007).

Followed by: TP53 stimulates SFN expression

Literature references

Hermeking, H., Lengauer, C., Polyak, K., He, TC., Zhang, L., Thiagalingam, S. et al. (1997). 14-3-3 sigma is a p53-regulated inhibitor of G2/M progression. *Mol. Cell*, 1, 3-11. ↗

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. ↗

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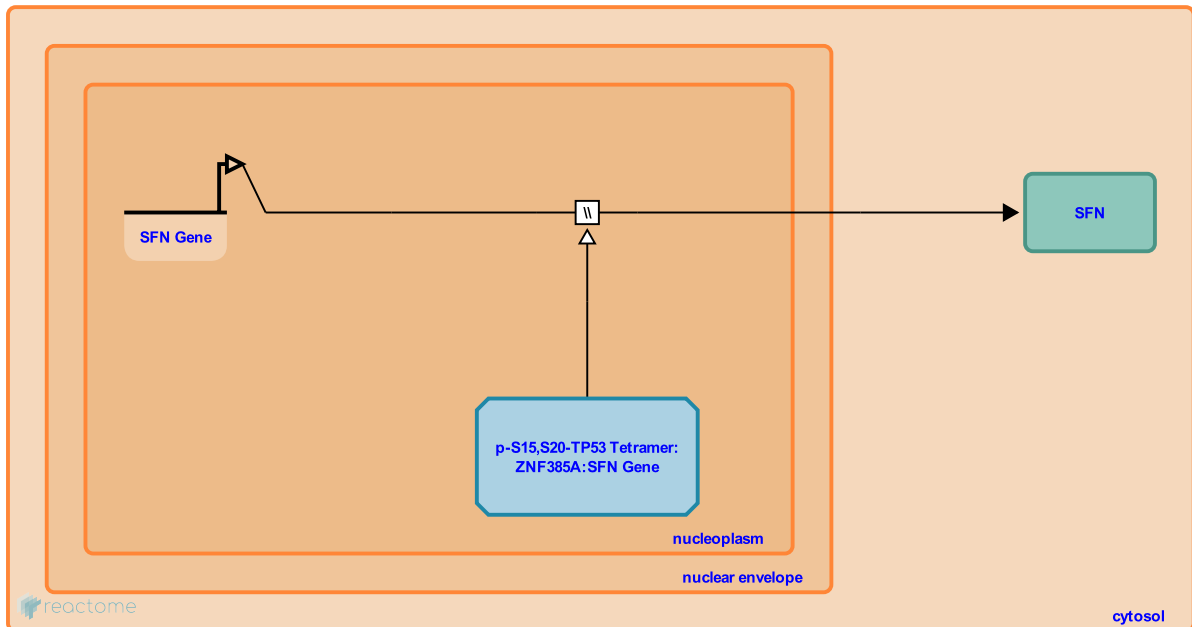
TP53 stimulates SFN expression ↗

Location: TP53 Regulates Transcription of Genes Involved in G2 Cell Cycle Arrest

Stable identifier: R-HSA-6803871

Type: omitted

Compartments: nucleoplasm, cytosol



Binding of TP53 (p53) to the p53 response element in the promoter region of the SFN (14-3-3 sigma) gene stimulates SFN transcription. SFN expression triggers G2 arrest in response to genotoxic agents by sequestering proteins involved in cell cycle progression in the cytosol (Hermeking et al. 1997, Chan et al. 1999). Formation of the complex of TP53 and ZNF385A (HZF) facilitates TP53-mediated induction of SFN3 (Das et al. 2007).

Preceded by: TP53 binds the SFN gene

Followed by: SFN dimerizes

Literature references

- Hermeking, H., Lengauer, C., Polyak, K., He, TC., Zhang, L., Thiagalingam, S. et al. (1997). 14-3-3 sigma is a p53-regulated inhibitor of G2/M progression. *Mol. Cell*, 1, 3-11. ↗
- Chan, TA., Hermeking, H., Lengauer, C., Kinzler, KW., Vogelstein, B. (1999). 14-3-3Sigma is required to prevent mitotic catastrophe after DNA damage. *Nature*, 401, 616-20. ↗
- 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. ↗

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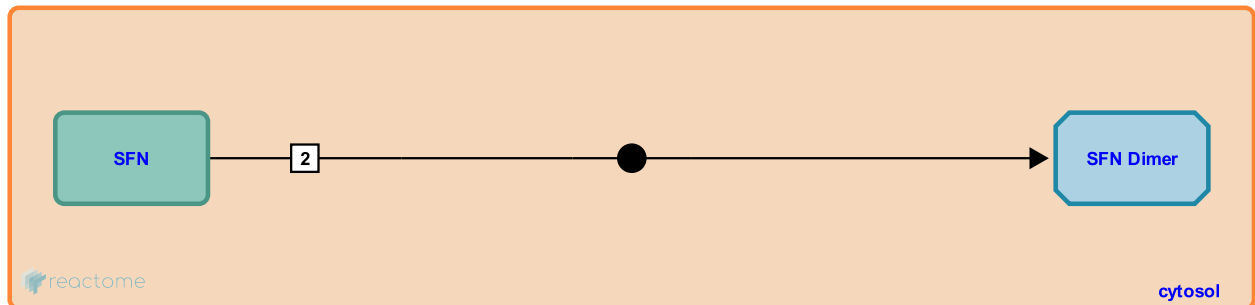
SFN dimerizes ↗

Location: [TP53 Regulates Transcription of Genes Involved in G2 Cell Cycle Arrest](#)

Stable identifier: R-HSA-6803890

Type: binding

Compartments: cytosol



SFN functions as a homodimer (Verdoodt et al. 2006).

Preceded by: [TP53 stimulates SFN expression](#)

Followed by: [SFN dimer binds BAX](#), [SFN dimer binds CDK1 and CCNB1](#)

Literature references

Verdoodt, B., Benzinger, A., Popowicz, GM., Holak, TA., Hermeking, H. (2006). Characterization of 14-3-3sigma dimerization determinants: requirement of homodimerization for inhibition of cell proliferation. *Cell Cycle*, 5, 2920-6. ↗

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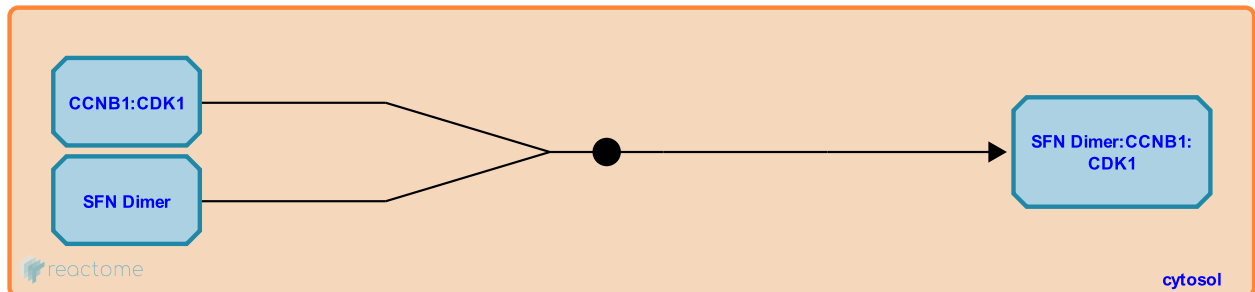
SFN dimer binds CDK1 and CCNB1 ↗

Location: [TP53 Regulates Transcription of Genes Involved in G2 Cell Cycle Arrest](#)

Stable identifier: R-HSA-6803875

Type: binding

Compartments: cytosol



SFN (14-3-3-sigma) dimer binds the complex of CCNB1 (cyclin B1) and CDK1 (Cdc2) in the cytosol and prevents the translocation of the CCNB1:CDK1 complex into the nucleus. This induces G2 cell cycle arrest as nuclear localization of the CCNB1:CDK1 complex is necessary for phosphorylation of nuclear target proteins that are needed for the G2/M transition (Chan et al. 1999).

Preceded by: [SFN dimerizes](#)

Literature references

Chan, TA., Hermeking, H., Lengauer, C., Kinzler, KW., Vogelstein, B. (1999). 14-3-3Sigma is required to prevent mitotic catastrophe after DNA damage. *Nature*, 401, 616-20. ↗

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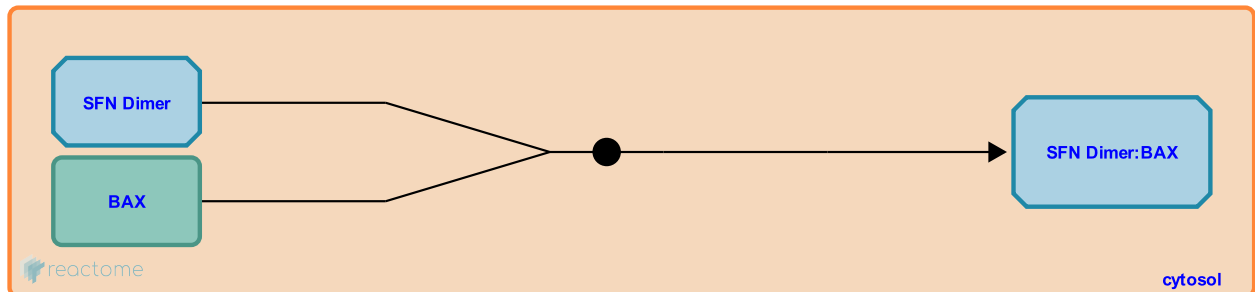
SFN dimer binds BAX [↗](#)

Location: [TP53 Regulates Transcription of Genes Involved in G2 Cell Cycle Arrest](#)

Stable identifier: R-HSA-6803892

Type: binding

Compartments: cytosol



SFN (14-3-3-sigma) dimer forms a complex with BAX. Binding of SFN to BAX prevents BAX translocation from cytosol to mitochondria, thus inhibiting cytochrome C release and apoptosis. SFN therefore promotes G2 cell cycle arrest while simultaneously preventing apoptosis (Samuel et al. 2001).

Preceded by: [SFN dimerizes](#)

Literature references

Samuel, T., Weber, HO., Rauch, P., Verdoodt, B., Eppel, JT., McShea, A. et al. (2001). The G2/M regulator 14-3-3sigma prevents apoptosis through sequestration of Bax. *J. Biol. Chem.*, 276, 45201-6. [↗](#)

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