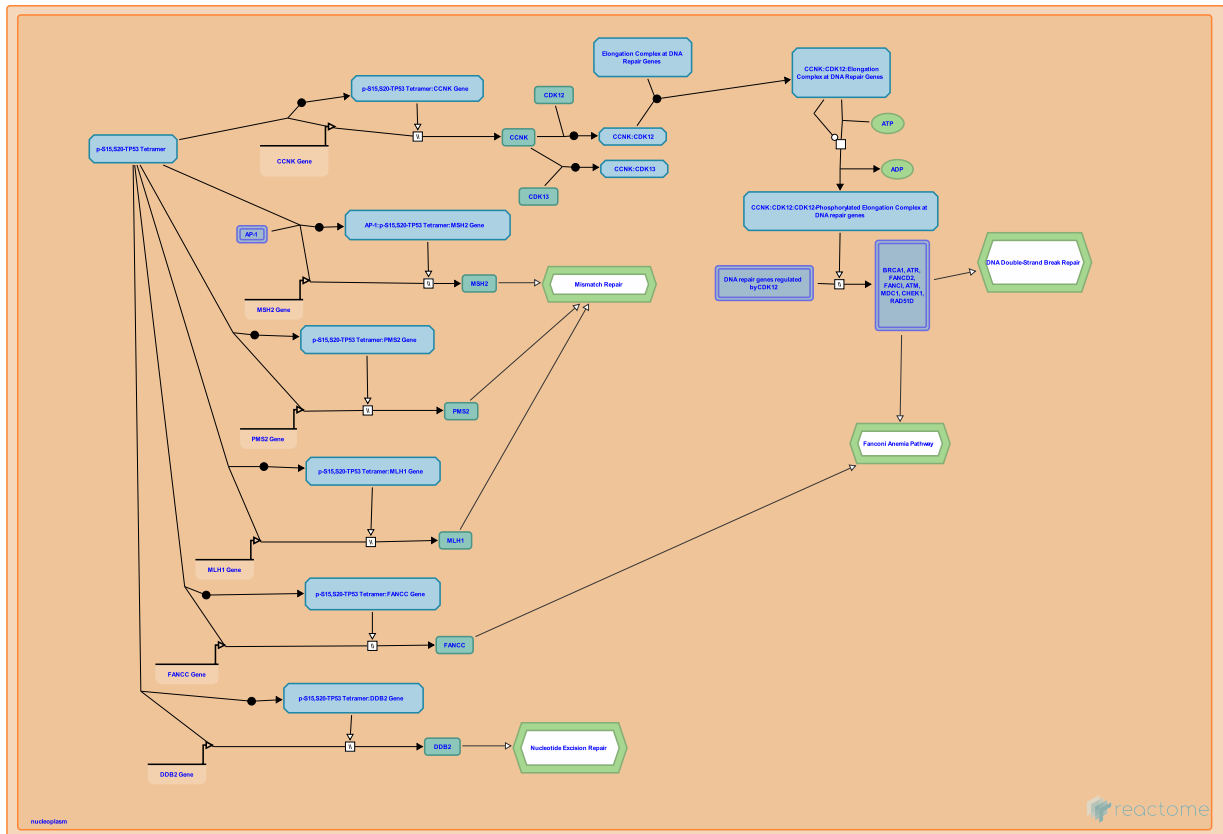


TP53 Regulates Transcription of DNA Repair Genes



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.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of [Creative Commons Attribution 4.0 International \(CC BY 4.0\) License](https://creativecommons.org/licenses/by/4.0/). For more information see our [license](#).

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](#).

26/04/2024

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

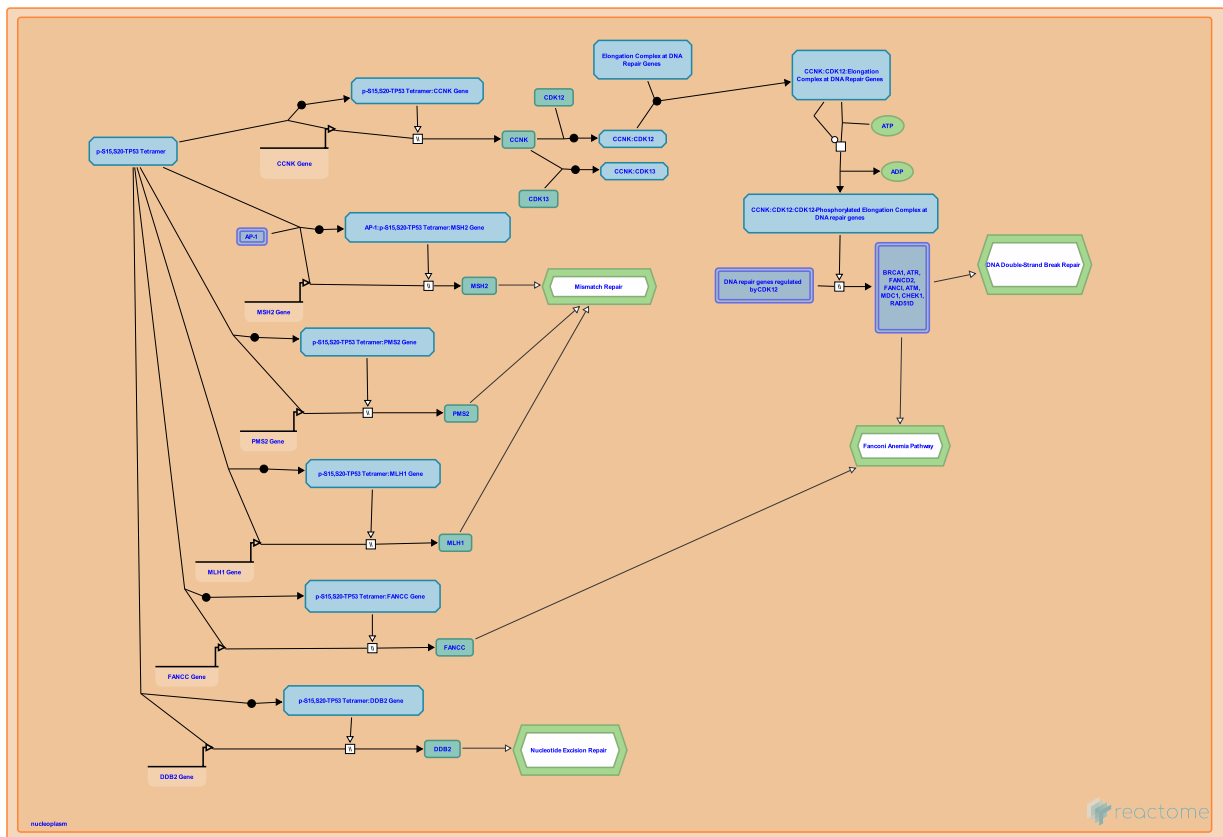
- Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics*, 18, 142. [↗](#)
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). 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. [↗](#)

Reactome database release: 88

This document contains 1 pathway and 17 reactions ([see Table of Contents](#))

TP53 Regulates Transcription of DNA Repair Genes ↗

Stable identifier: R-HSA-6796648



Several DNA repair genes contain p53 response elements and their transcription is positively regulated by TP53 (p53). TP53-mediated regulation probably ensures increased protein level of DNA repair genes under genotoxic stress.

TP53 directly stimulates transcription of several genes involved in DNA mismatch repair, including MSH2 (Scherer et al. 2000, Warnick et al. 2001), PMS2 and MLH1 (Chen and Sadowski 2005). TP53 also directly stimulates transcription of DDB2, involved in nucleotide excision repair (Tan and Chu 2002), and FANCC, involved in the Fanconi anemia pathway that repairs DNA interstrand crosslinks (Liebetau et al. 1997). Other p53 targets that can influence DNA repair functions are RRM2B (Kuo et al. 2012), XPC (Fitch et al. 2003), GADD45A (Amundson et al. 2002), CDKN1A (Cazzalini et al. 2010) and PCNA (Xu and Morris 1999). Interestingly, the responsiveness of some of these DNA repair genes to p53 activation has been shown in human cells but not for orthologous mouse genes (Jegga et al. 2008, Tan and Chu 2002). Contrary to the positive modulation of nucleotide excision repair (NER) and mismatch repair (MMR), p53 can negatively modulate base excision repair (BER), by down-regulating the endonuclease APEX1 (APE1), acting in concert with SP1 (Poletto et al. 2016).

Expression of several DNA repair genes is under indirect TP53 control, through TP53-mediated stimulation of cyclin K (CCNK) expression (Mori et al. 2002). CCNK is the activating cyclin for CDK12 and CDK13 (Blazek et al. 2013). The complex of CCNK and CDK12 binds and phosphorylates the C-terminal domain of the RNA polymerase II subunit POLR2A, which is necessary for efficient transcription of long DNA repair genes, including BRCA1, ATR, FANCD2, FANCI, ATM, MDC1, CHEK1 and RAD51D. Genes whose transcription is regulated by the complex of CCNK and CDK12 are mainly involved in the repair of DNA double strand breaks and/or the Fanconi anemia pathway (Blazek et al. 2011, Cheng et al. 2012, Bosken et al. 2014, Bartkowiak and Greenleaf 2015, Ekumi et al. 2015).

Literature references

- Sadowski, I., Chen, J. (2005). Identification of the mismatch repair genes PMS2 and MLH1 as p53 target genes by using serial analysis of binding elements. *Proc. Natl. Acad. Sci. U.S.A.*, 102, 4813-8. ↗
- Morris, GF., Xu, J. (1999). p53-mediated regulation of proliferating cell nuclear antigen expression in cells exposed to ionizing radiation. *Mol. Cell. Biol.*, 19, 12-20. ↗

Cimermancic, P., Johansen, E., Ule, J., Peterlin, BM., Hulinkova, P., Luo, Z. et al. (2011). The Cyclin K/Cdk12 complex maintains genomic stability via regulation of expression of DNA damage response genes. *Genes Dev.*, 25, 2158-72. [↗](#)

Fletcher, SC., Legrand, AJ., Dianov, GL., Poletto, M. (2016). p53 coordinates base excision repair to prevent genomic instability. *Nucleic Acids Res.* [↗](#)

Dabbas, B., Strait, KA., Ford, CD., Warnick, CT. (2001). Identification of a p53 response element in the promoter region of the hMSH2 gene required for expression in A2780 ovarian cancer cells. *J. Biol. Chem.*, 276, 27363-70. [↗](#)

Editions

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

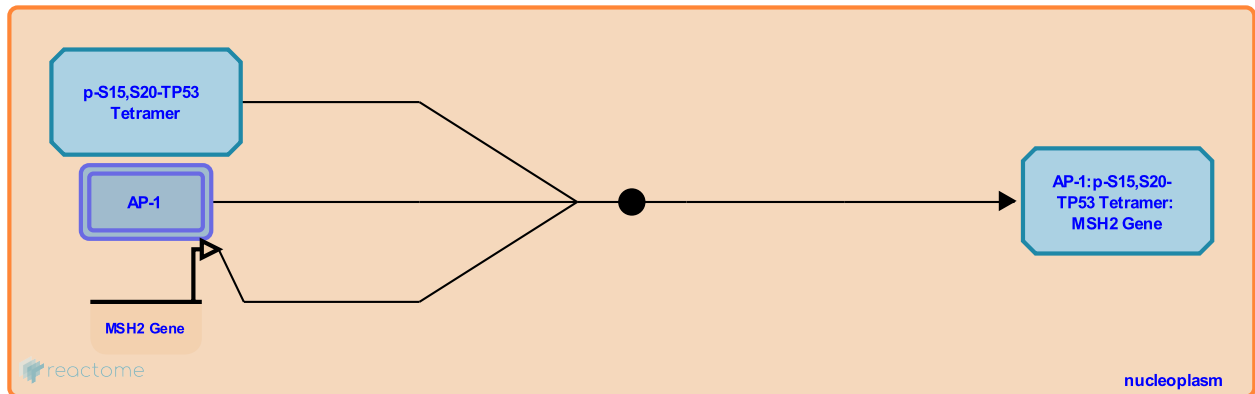
TP53 and AP-1 bind the MSH2 promoter ↗

Location: [TP53 Regulates Transcription of DNA Repair Genes](#)

Stable identifier: R-HSA-6806412

Type: binding

Compartments: nucleoplasm



TP53 (p53) binds to the p53 response element in the promoter of the MSH2 gene. The p53 response element is flanked by two AP-1 sites. The AP-1 transcription factor complex binds the MSH2 promoter cooperatively with TP53 (Scherer et al. 2000). An additional p53 response element in closer proximity to the MSH2 transcription start site has been reported that does not involve a nearby AP-1 binding site (Warnick et al. 2001).

Followed by: [TP53 and AP-1 stimulate MSH2 expression](#)

Literature references

Maier, SM., Seifert, M., Angel, P., Scherer, SJ., Zang, KD., Müller-Hermelink, HK. et al. (2000). p53 and c-Jun functionally synergize in the regulation of the DNA repair gene hMSH2 in response to UV. *J. Biol. Chem.*, 275, 37469-73 . ↗

Dabbas, B., Strait, KA., Ford, CD., Warnick, CT. (2001). Identification of a p53 response element in the promoter region of the hMSH2 gene required for expression in A2780 ovarian cancer cells. *J. Biol. Chem.*, 276, 27363-70. ↗

Editions

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

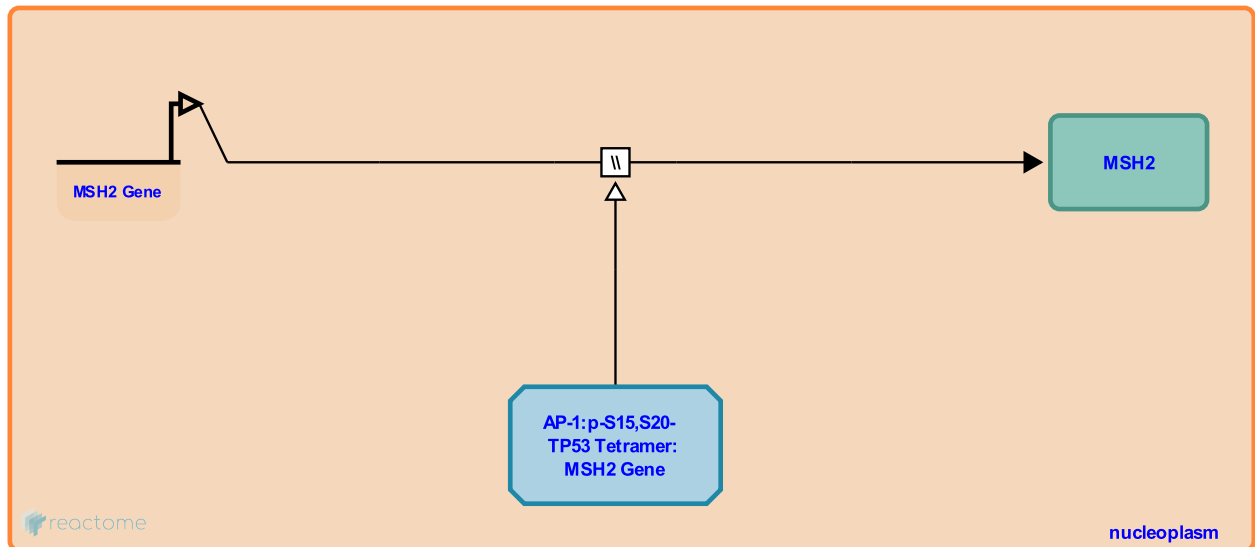
TP53 and AP-1 stimulate MSH2 expression ↗

Location: [TP53 Regulates Transcription of DNA Repair Genes](#)

Stable identifier: R-HSA-6806394

Type: omitted

Compartments: nucleoplasm



TP53 and the AP-1 transcription factor complex cooperatively stimulate transcription of the MSH2 gene, involved in DNA mismatch repair, by binding to adjacent sites in the MSH2 promoter (Scherer et al. 2001). TP53 may stimulate transcription of MSH2 independently of the AP-1 complex when bound to a different p53 response element in the MSH2 promoter (Warnick et al. 2001).

Preceded by: [TP53 and AP-1 bind the MSH2 promoter](#)

Literature references

Maier, SM., Seifert, M., Angel, P., Scherer, SJ., Zang, KD., Müller-Hermelink, HK. et al. (2000). p53 and c-Jun functionally synergize in the regulation of the DNA repair gene hMSH2 in response to UV. *J. Biol. Chem.*, 275, 37469-73 . ↗

Dabbas, B., Strait, KA., Ford, CD., Warnick, CT. (2001). Identification of a p53 response element in the promoter region of the hMSH2 gene required for expression in A2780 ovarian cancer cells. *J. Biol. Chem.*, 276, 27363-70. ↗

Editions

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

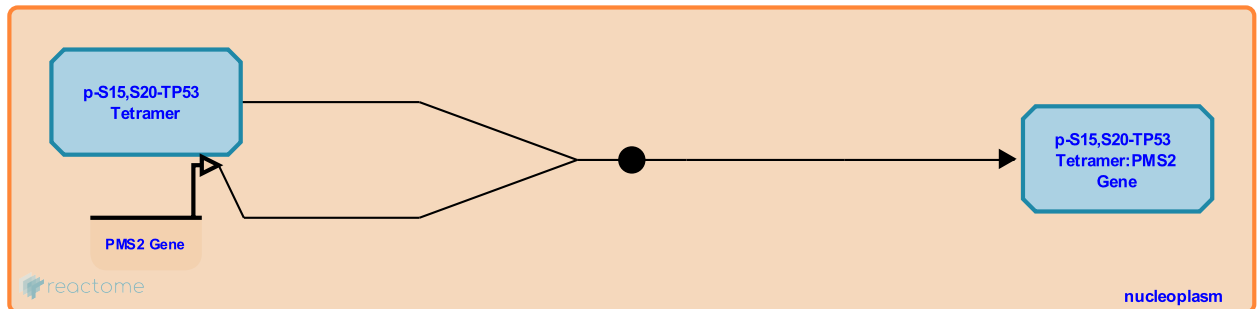
TP53 binds the PMS2 gene ↗

Location: [TP53 Regulates Transcription of DNA Repair Genes](#)

Stable identifier: R-HSA-6806408

Type: binding

Compartments: nucleoplasm



TP53 (p53) binds the p53 response element in the first intron of the PMS2 gene (Chen and Sadowski 2005).

Followed by: [TP53 stimulates PMS2 expression](#)

Literature references

Sadowski, I., Chen, J. (2005). Identification of the mismatch repair genes PMS2 and MLH1 as p53 target genes by using serial analysis of binding elements. *Proc. Natl. Acad. Sci. U.S.A.*, 102, 4813-8. ↗

Editions

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

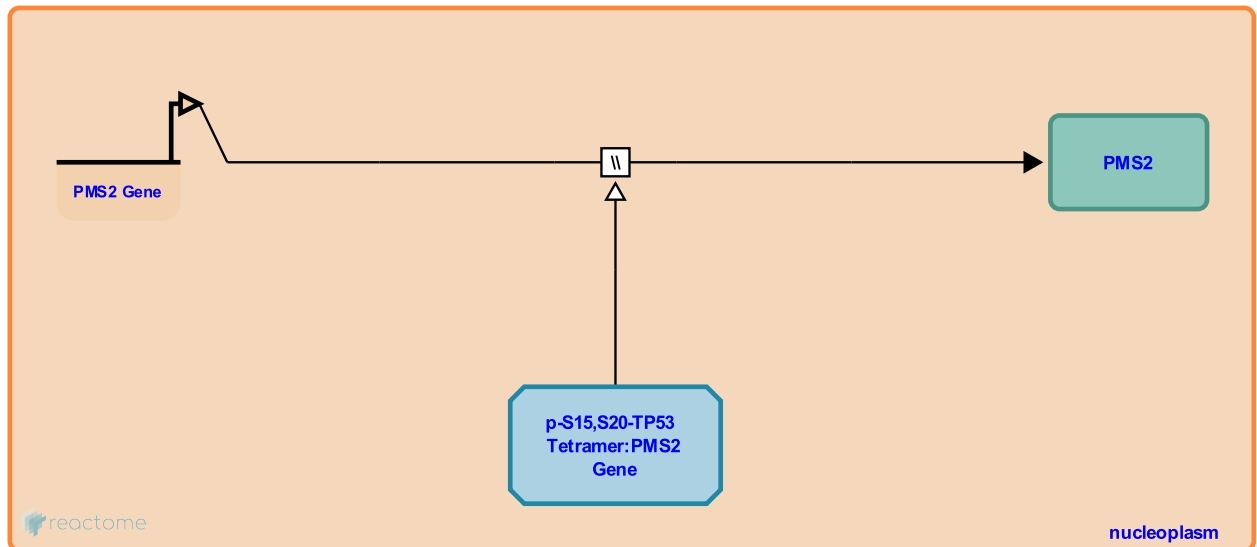
TP53 stimulates PMS2 expression ↗

Location: TP53 Regulates Transcription of DNA Repair Genes

Stable identifier: R-HSA-6806405

Type: omitted

Compartments: nucleoplasm



TP53 (p53) stimulates transcription of PMS2, involved in DNA mismatch repair, by binding to the p53 response element in the first intron of the PMS2 gene (Chen and Sadowski 2005).

Preceded by: TP53 binds the PMS2 gene

Literature references

Sadowski, I., Chen, J. (2005). Identification of the mismatch repair genes PMS2 and MLH1 as p53 target genes by using serial analysis of binding elements. *Proc. Natl. Acad. Sci. U.S.A.*, 102, 4813-8. ↗

Editions

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

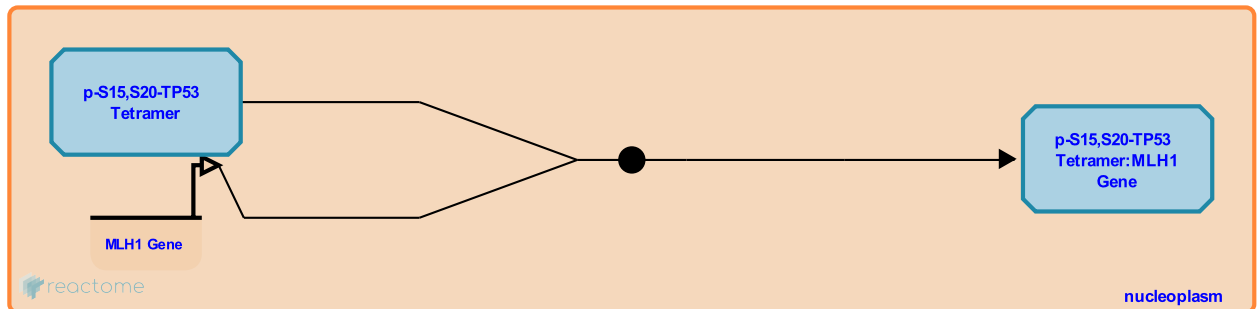
TP53 binds the MLH1 gene ↗

Location: TP53 Regulates Transcription of DNA Repair Genes

Stable identifier: R-HSA-6806413

Type: binding

Compartments: nucleoplasm



TP53 (p53) binds the p53 response element in the first intron of the MLH1 gene (Chen and Sadowski 2005).

Followed by: TP53 stimulates MLH1 expression

Literature references

Sadowski, I., Chen, J. (2005). Identification of the mismatch repair genes PMS2 and MLH1 as p53 target genes by using serial analysis of binding elements. *Proc. Natl. Acad. Sci. U.S.A.*, 102, 4813-8. ↗

Editions

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

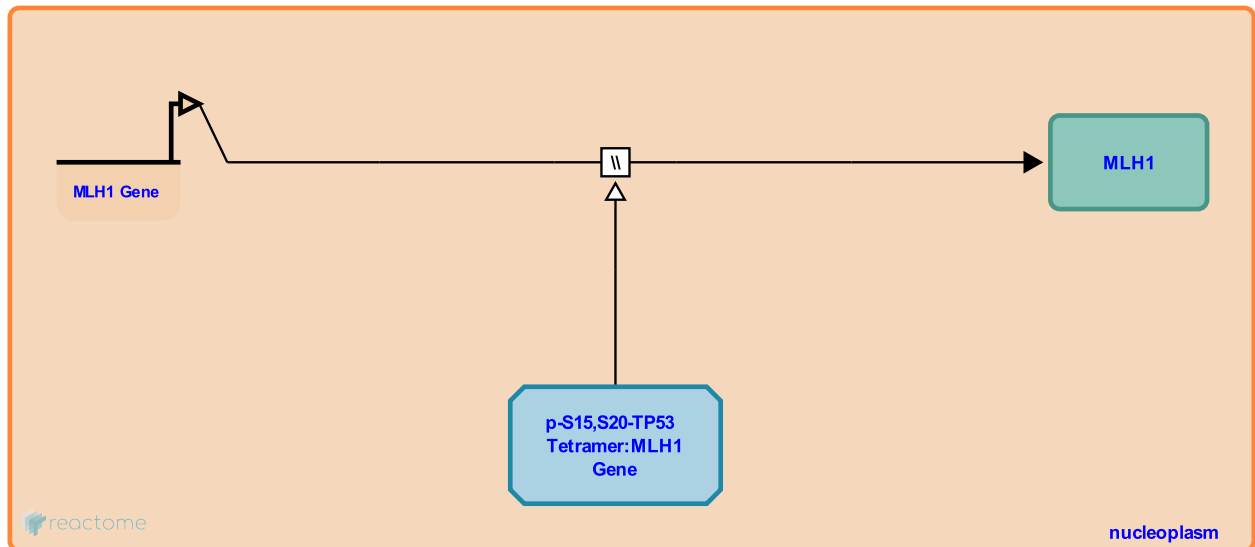
TP53 stimulates MLH1 expression ↗

Location: [TP53 Regulates Transcription of DNA Repair Genes](#)

Stable identifier: R-HSA-6806392

Type: omitted

Compartments: nucleoplasm



TP53 (p53) stimulates transcription of the MLH1 gene, involved in DNA mismatch repair, by binding to the p53 response element in the first intron of the MLH1 gene (Chen and Sadowski 2005).

Preceded by: [TP53 binds the MLH1 gene](#)

Literature references

Sadowski, I., Chen, J. (2005). Identification of the mismatch repair genes PMS2 and MLH1 as p53 target genes by using serial analysis of binding elements. *Proc. Natl. Acad. Sci. U.S.A.*, 102, 4813-8. ↗

Editions

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

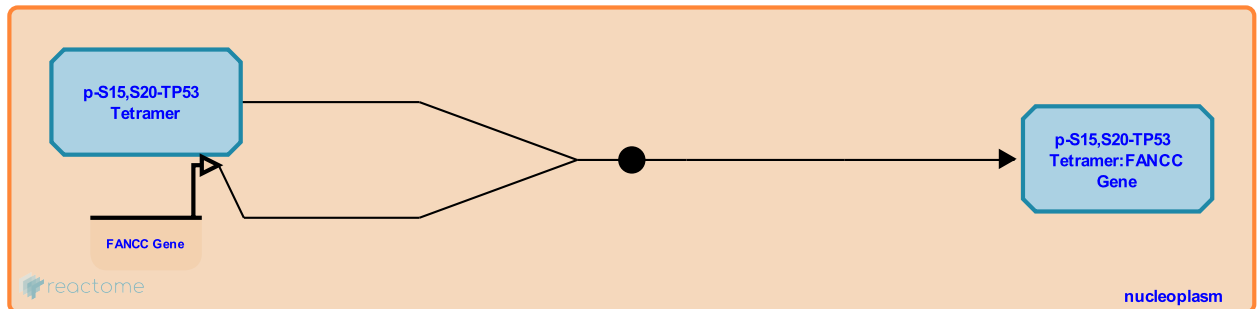
TP53 binds the FANCC gene ↗

Location: [TP53 Regulates Transcription of DNA Repair Genes](#)

Stable identifier: R-HSA-6806419

Type: binding

Compartments: nucleoplasm



TP53 (p53) binds the p53 response element in the promoter of the FANCC (Fanconi anemia group C) gene (Liebetrau et al. 1997).

Followed by: [TP53 stimulates FANCC expression](#)

Literature references

Grummt, F., Hoehn, H., Savoia, A., Liebetrau, W., Budde, A. (1997). p53 activates Fanconi anemia group C gene expression. *Hum. Mol. Genet.*, 6, 277-83. ↗

Editions

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

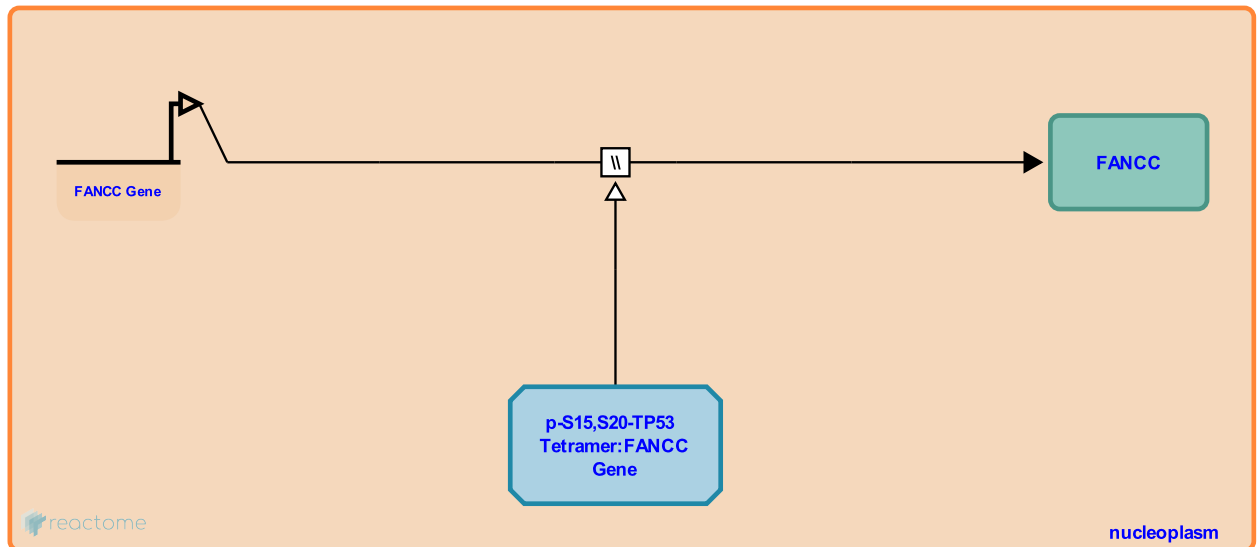
TP53 stimulates FANCC expression ↗

Location: [TP53 Regulates Transcription of DNA Repair Genes](#)

Stable identifier: R-HSA-6806425

Type: omitted

Compartments: nucleoplasm



TP53 (p53) stimulates transcription of the FANCC (Fanconi anemia group C) gene, involved in the Fanconi anemia pathway that repairs DNA interstrand crosslinks, by binding to the p53 response element in the FANCC promoter (Liebetrau et al. 1997).

Preceded by: [TP53 binds the FANCC gene](#)

Literature references

Grummt, F., Hoehn, H., Savoia, A., Liebetrau, W., Budde, A. (1997). p53 activates Fanconi anemia group C gene expression. *Hum. Mol. Genet.*, 6, 277-83. ↗

Editions

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

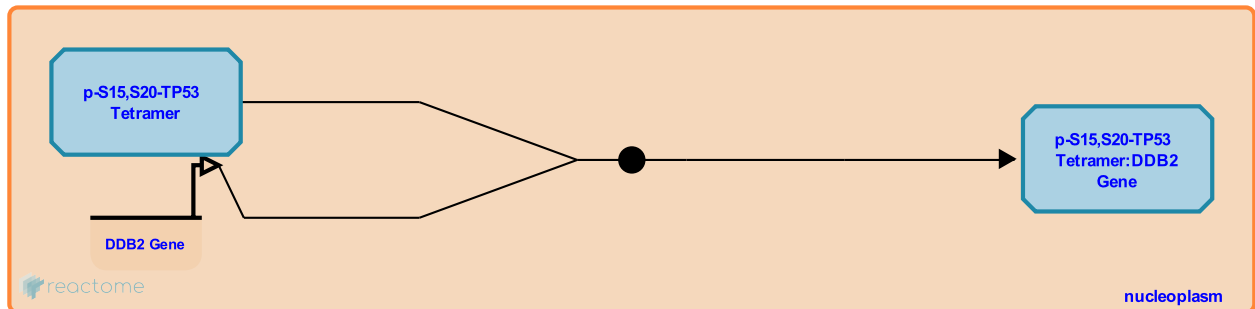
TP53 binds the DDB2 gene ↗

Location: [TP53 Regulates Transcription of DNA Repair Genes](#)

Stable identifier: R-HSA-6806417

Type: binding

Compartments: nucleoplasm



TP53 (p53) binds the p53 response element in the 5'UTR-encoding region of the DDB2 gene. The p53 response element is present in the human DDB2 gene, but absent from the mouse Ddb2 gene (Tan and Chu 2002).

Followed by: [TP53 stimulates DDB2 expression](#)

Literature references

Tan, T., Chu, G. (2002). p53 Binds and activates the xeroderma pigmentosum DDB2 gene in humans but not mice. *Mol. Cell. Biol.*, 22, 3247-54. ↗

Editions

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

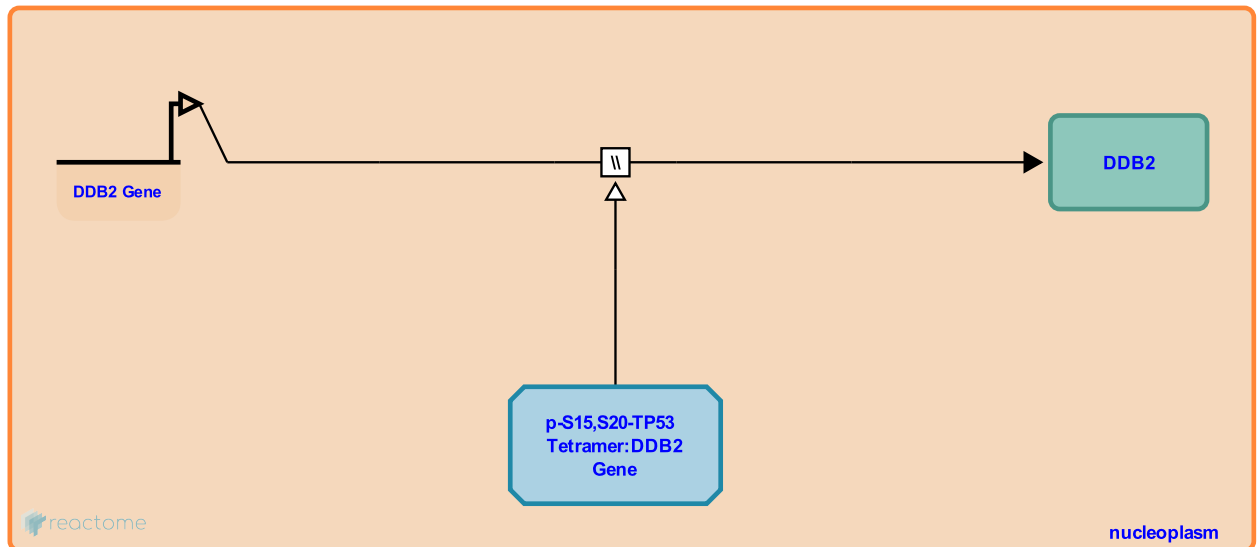
TP53 stimulates DDB2 expression ↗

Location: TP53 Regulates Transcription of DNA Repair Genes

Stable identifier: R-HSA-6806423

Type: omitted

Compartments: nucleoplasm



TP53 (p53) stimulates transcription of the DDB2 gene, involved in nucleotide excision repair, by binding to the p53 response element in the 5'UTR-encoding region of the DDB2 gene (Tan and Chu 2002).

Preceded by: TP53 binds the DDB2 gene

Literature references

Tan, T., Chu, G. (2002). p53 Binds and activates the xeroderma pigmentosum DDB2 gene in humans but not mice. *Mol. Cell. Biol.*, 22, 3247-54. ↗

Editions

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

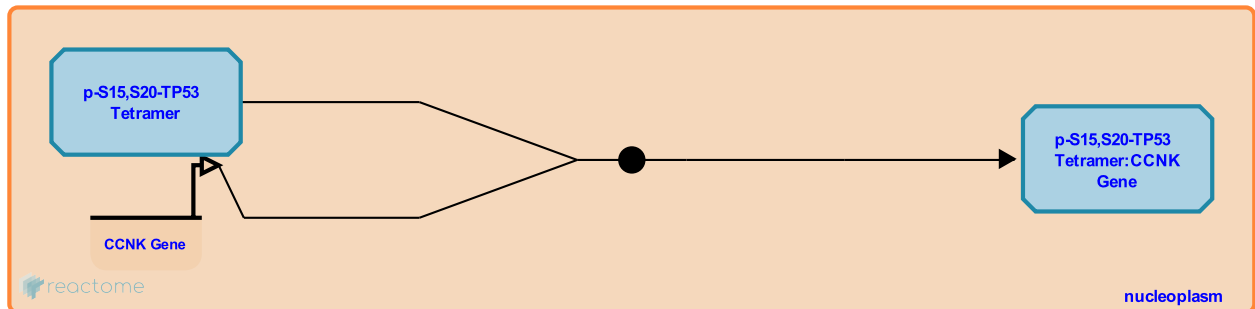
TP53 binds the CCNK gene ↗

Location: [TP53 Regulates Transcription of DNA Repair Genes](#)

Stable identifier: R-HSA-6796649

Type: binding

Compartments: nucleoplasm



TP53 (p53) binds p53 response element located in the first intron of the CCNK (cyclin K) gene (Mori et al. 2002).

Followed by: [TP53 stimulates CCNK expression](#)

Literature references

Arakawa, H., Nakamura, Y., Anazawa, Y., Mori, T., Matsui, K., Fukuda, S. (2002). Cyclin K as a direct transcriptional target of the p53 tumor suppressor. *Neoplasia*, 4, 268-74. ↗

Editions

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

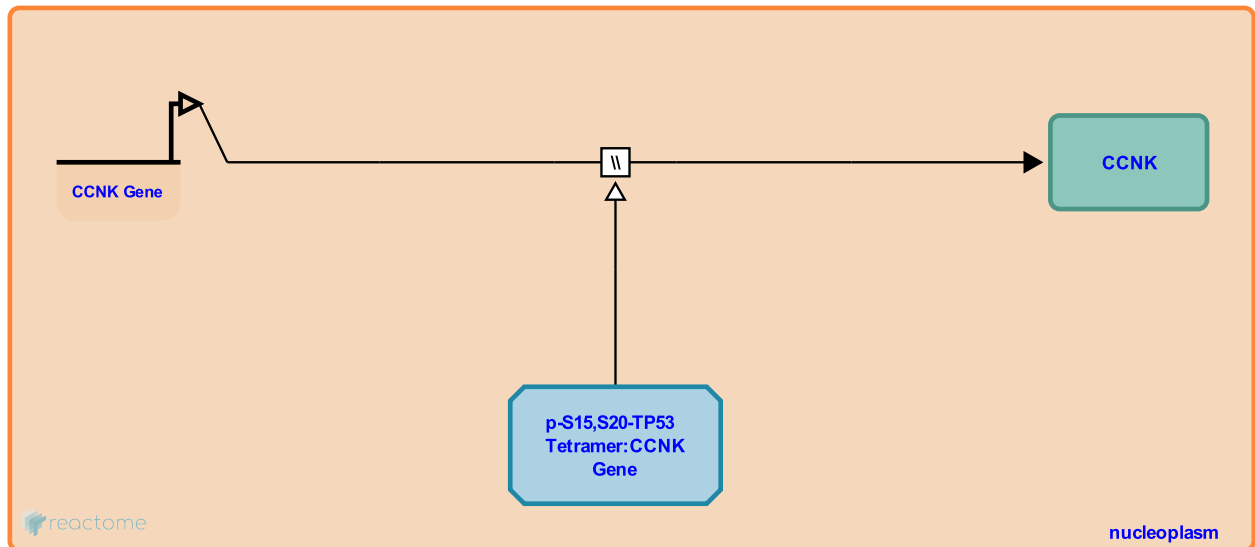
TP53 stimulates CCNK expression ↗

Location: TP53 Regulates Transcription of DNA Repair Genes

Stable identifier: R-HSA-6796647

Type: omitted

Compartments: nucleoplasm



TP53 (p53) binding to the p53 response element in the first intron of the CCNK (cyclin K) gene stimulates CCNK transcription (Mori et al. 2002).

Preceded by: TP53 binds the CCNK gene

Followed by: CCNK binds CDK13, CCNK binds CDK12

Literature references

Arakawa, H., Nakamura, Y., Anazawa, Y., Mori, T., Matsui, K., Fukuda, S. (2002). Cyclin K as a direct transcriptional target of the p53 tumor suppressor. *Neoplasia*, 4, 268-74. ↗

Editions

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

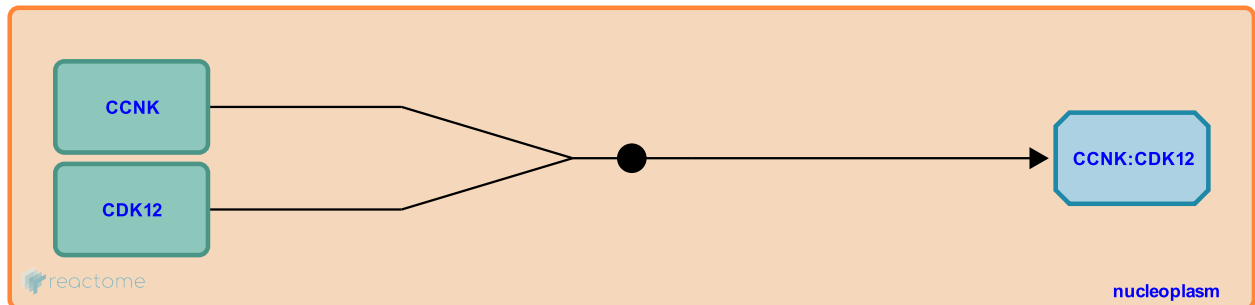
CCNK binds CDK12 [↗](#)

Location: [TP53 Regulates Transcription of DNA Repair Genes](#)

Stable identifier: R-HSA-6797090

Type: binding

Compartments: nucleoplasm



Cyclin K (CCNK) forms a complex with CDK12 (Blazek et al. 2011).

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

Followed by: [CCNK:CDK12 binds RNA Pol II at DNA repair genes](#)

Literature references

Cimermancic, P., Johansen, E., Ule, J., Peterlin, BM., Hulinkova, P., Luo, Z. et al. (2011). The Cyclin K/Cdk12 complex maintains genomic stability via regulation of expression of DNA damage response genes. *Genes Dev.*, 25, 2158-72. [↗](#)

Editions

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

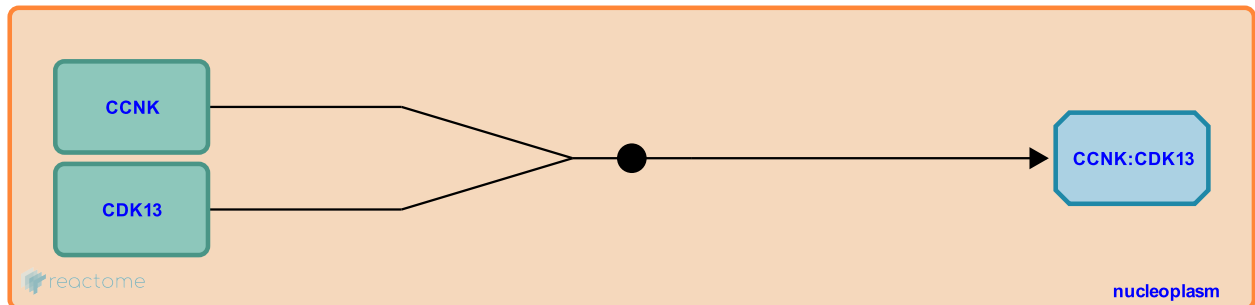
CCNK binds CDK13 [↗](#)

Location: [TP53 Regulates Transcription of DNA Repair Genes](#)

Stable identifier: R-HSA-6797100

Type: binding

Compartments: nucleoplasm



Cyclin K (CCNK) forms a complex with CDK13 (Blazek et al. 2011).

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

Literature references

Cimermancic, P., Johansen, E., Ule, J., Peterlin, BM., Hulinkova, P., Luo, Z. et al. (2011). The Cyclin K/Cdk12 complex maintains genomic stability via regulation of expression of DNA damage response genes. *Genes Dev.*, 25, 2158-72. [↗](#)

Editions

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

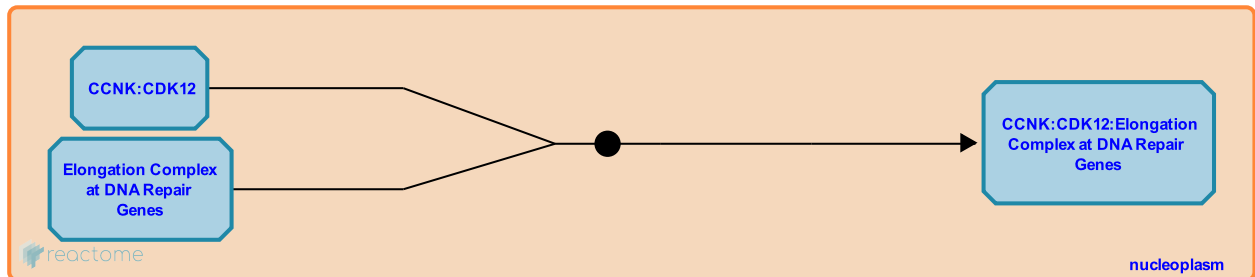
CCNK:CDK12 binds RNA Pol II at DNA repair genes ↗

Location: [TP53 Regulates Transcription of DNA Repair Genes](#)

Stable identifier: R-HSA-6797616

Type: binding

Compartments: nucleoplasm



The complex of CDK12 and CCNK (cyclin K) associates with the RNA polymerase II (RNA Pol II) elongation complex at DNA repair genes encoding long primary transcripts, such as BRCA1, ATR, FANCI, FANCD2, ATM, MDC1, CHEK1, RAD51D and APEX1 (Blazek et al. 2011, Bartkowiak and Greenleaf 2015, Ekumi et al. 2015, Liang et al. 2015).

Preceded by: [CCNK binds CDK12](#)

Followed by: [CDK12 phosphorylates RNA Pol II CTD at DNA repair genes](#)

Literature references

- Bartkowiak, B., Greenleaf, AL. (2015). Expression, purification, and identification of associated proteins of the full-length hCDK12/CyclinK complex. *J. Biol. Chem.*, 290, 1786-95. ↗
- Ekumi, KM., Paculova, H., Barboric, M., Bryja, V., Geyer, M., Rybarikova, J. et al. (2015). Ovarian carcinoma CDK12 mutations misregulate expression of DNA repair genes via deficient formation and function of the Cdk12/CycK complex. *Nucleic Acids Res.*, 43, 2575-89. ↗
- Liang, K., Smith, E., Florens, LA., Shilatifard, A., Gilmore, JM., Gao, X. et al. (2015). Characterization of human cyclin-dependent kinase 12 (CDK12) and CDK13 complexes in C-terminal domain phosphorylation, gene transcription, and RNA processing. *Mol. Cell. Biol.*, 35, 928-38. ↗
- Cimermancic, P., Johansen, E., Ule, J., Peterlin, BM., Hulinkova, P., Luo, Z. et al. (2011). The Cyclin K/Cdk12 complex maintains genomic stability via regulation of expression of DNA damage response genes. *Genes Dev.*, 25, 2158-72. ↗

Editions

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

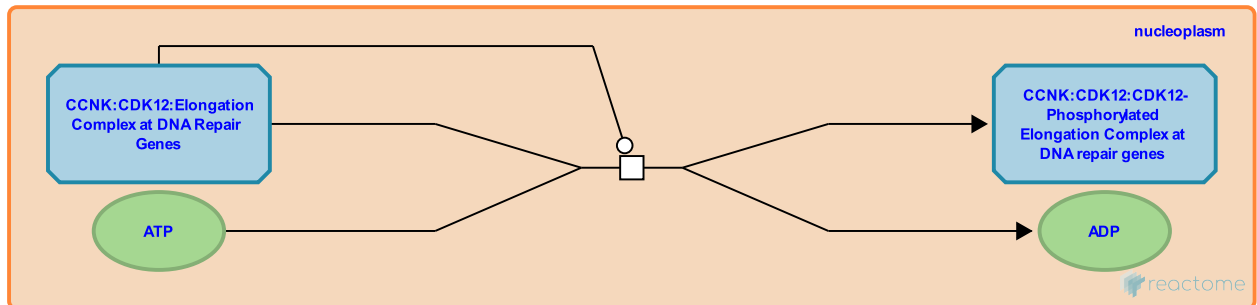
CDK12 phosphorylates RNA Pol II CTD at DNA repair genes ↗

Location: TP53 Regulates Transcription of DNA Repair Genes

Stable identifier: R-HSA-6797606

Type: transition

Compartments: nucleoplasm



CDK12, in complex with CCNK (cyclin K), phosphorylates heptapeptide repeats in the C-terminal domain (CTD) of the RNA polymerase II (RNA Pol II) subunit POLR2A. CDK12 may require phosphorylation of its threonine residue T893 to achieve full catalytic activity, but the activating kinase is not known. CDK12-mediated phosphorylation of the CTD of POLR2A occurs after the heptapeptide repeats in the CTD of POLR2A undergo phosphorylation by the CDK9-containing P-TEFb complex. It is unclear whether CDK12 acts on the second serine or the fifth serine or both in the YSPTSPS repeats. The mammalian POLR2A contains 52 heptapeptide repeats that start at amino acid position 1615. The exact localization of CDK9 and CDK12 target sites relative to the full-length POLR2A is not known. CDK12-mediated phosphorylation of the pre-phosphorylated RNA Pol II complex is important for the transcription of a group of genes with long and complex structures, involved in DNA repair (Blazek et al. 2011, Cheng et al. 2012, Bosken et al. 2014, Bartkowiak and Greenleaf 2015, Liang et al. 2015).

Preceded by: CCNK:CDK12 binds RNA Pol II at DNA repair genes

Followed by: CDK12 stimulates expression of DNA repair genes

Literature references

- Bartkowiak, B., Greenleaf, AL. (2015). Expression, purification, and identification of associated proteins of the full-length hCDK12/CyclinK complex. *J. Biol. Chem.*, 290, 1786-95. ↗
- Merzel Schachter, M., Geyer, M., Eick, D., Vogel-Bachmayr, K., Blazek, D., Farnung, L. et al. (2014). The structure and substrate specificity of human Cdk12/Cyclin K. *Nat Commun*, 5, 3505. ↗
- Liang, K., Smith, E., Florens, LA., Shilatifard, A., Gilmore, JM., Gao, X. et al. (2015). Characterization of human cyclin-dependent kinase 12 (CDK12) and CDK13 complexes in C-terminal domain phosphorylation, gene transcription, and RNA processing. *Mol. Cell. Biol.*, 35, 928-38. ↗
- Kuzyk, MA., Vollett, SE., Tien, JF., Ichu, TA., Cheng, SW., Chang, VC. et al. (2012). Interaction of cyclin-dependent kinase 12/CrkRS with cyclin K1 is required for the phosphorylation of the C-terminal domain of RNA polymerase II. *Mol. Cell. Biol.*, 32, 4691-704. ↗
- Cimermancic, P., Johansen, E., Ule, J., Peterlin, BM., Hulinkova, P., Luo, Z. et al. (2011). The Cyclin K/Cdk12 complex maintains genomic stability via regulation of expression of DNA damage response genes. *Genes Dev.*, 25, 2158-72. ↗

Editions

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

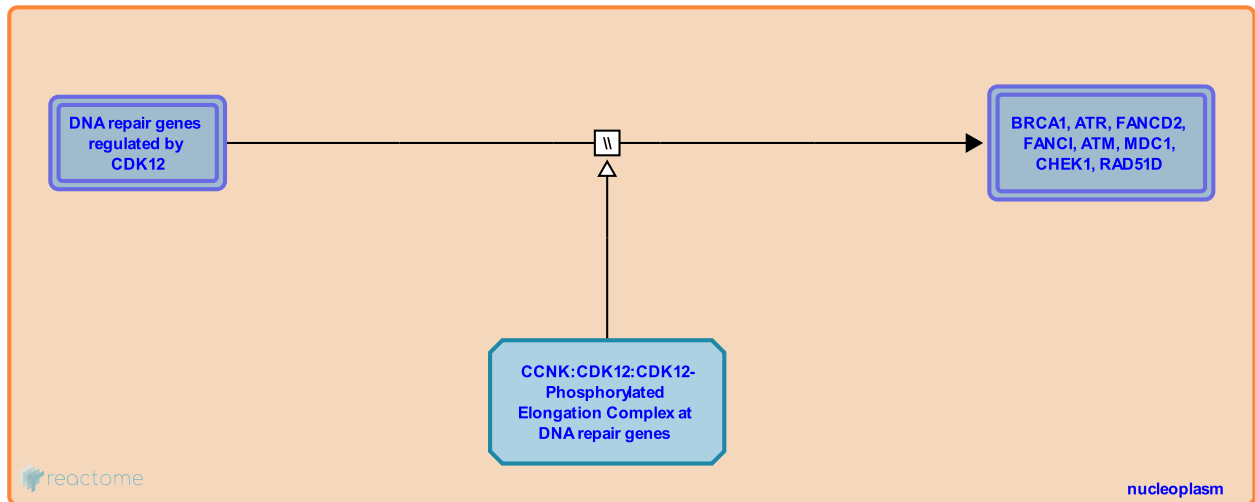
CDK12 stimulates expression of DNA repair genes ↗

Location: TP53 Regulates Transcription of DNA Repair Genes

Stable identifier: R-HSA-6797712

Type: omitted

Compartments: nucleoplasm



CDK12-mediated phosphorylation of the C-terminal domain (CTD) of the RNA polymerase II (RNA Pol II) subunit POLR2A (Rpb1) positively regulates transcription and, hence, expression of a set of DNA repair genes that encode long primary transcripts. CDK12, in complex with the TP53-regulated CCNK (cyclin K), phosphorylates POLR2A that was pre-phosphorylated by the CDK9-containing complex P-TEFb. CDK12-mediated phosphorylation of POLR2A is thought to increase the processivity of the RNA Pol II, enabling efficient transcription of long DNA repair genes (Blazek et al. 2011, Cheng et al. 2012, Bosken et al. 2014, Bartkowiak and Greenleaf 2015). CDK12 was shown to colocalize with the RNA Pol II complex at FANCD2, FANCI, ATM, CHEK1, MDC1, RAD51D and ATR gene loci (Ekumi et al. 2015) and to be necessary for achieving sufficient BRCA1 expression (Blazek et al. 2011). CDK12 positively regulates the expression of APEX1, involved in base excision repair (Liang et al. 2015). Recurrent CDK12 mutations are found in ovarian cancer. These mutations affect either the catalytic cleft of CDK12 or disable the interaction of CDK12 with CCNK, resulting in the loss of CDK12 function. Ovarian tumors that harbour inactivating CDK12 mutations exhibit decreased BRCA1 levels, defective homologous recombination repair, increased sensitivity to DNA crosslinking agents, and sensitivity to PARP inhibitors (Joshi et al. 2014, Ekumi et al. 2015).

Preceded by: CDK12 phosphorylates RNA Pol II CTD at DNA repair genes

Literature references

- Ekumi, KM., Paculova, H., Barboric, M., Bryja, V., Geyer, M., Rybarikova, J. et al. (2015). Ovarian carcinoma CDK12 mutations misregulate expression of DNA repair genes via deficient formation and function of the Cdk12/CycK complex. *Nucleic Acids Res.*, 43, 2575-89. ↗
- Bartkowiak, B., Greenleaf, AL. (2015). Expression, purification, and identification of associated proteins of the full-length hCDK12/CyclinK complex. *J. Biol. Chem.*, 290, 1786-95. ↗
- Merzel Schachter, M., Geyer, M., Eick, D., Vogel-Bachmayr, K., Blazek, D., Farnung, L. et al. (2014). The structure and substrate specificity of human Cdk12/Cyclin K. *Nat Commun*, 5, 3505. ↗
- Liang, K., Smith, E., Florens, LA., Shilatifard, A., Gilmore, JM., Gao, X. et al. (2015). Characterization of human cyclin-dependent kinase 12 (CDK12) and CDK13 complexes in C-terminal domain phosphorylation, gene transcription, and RNA processing. *Mol. Cell. Biol.*, 35, 928-38. ↗
- Karnitz, LM., Huntoon, CJ., Sutor, SL., Joshi, PM. (2014). Ovarian cancer-associated mutations disable catalytic activity of CDK12, a kinase that promotes homologous recombination repair and resistance to cisplatin and poly(ADP-ribose) polymerase inhibitors. *J. Biol. Chem.*, 289, 9247-53. ↗

Editions

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

Table of Contents

Introduction	1
☰ TP53 Regulates Transcription of DNA Repair Genes	2
↳ TP53 and AP-1 bind the MSH2 promoter	4
↳ TP53 and AP-1 stimulate MSH2 expression	5
↳ TP53 binds the PMS2 gene	6
↳ TP53 stimulates PMS2 expression	7
↳ TP53 binds the MLH1 gene	8
↳ TP53 stimulates MLH1 expression	9
↳ TP53 binds the FANCC gene	10
↳ TP53 stimulates FANCC expression	11
↳ TP53 binds the DDB2 gene	12
↳ TP53 stimulates DDB2 expression	13
↳ TP53 binds the CCNK gene	14
↳ TP53 stimulates CCNK expression	15
↳ CCNK binds CDK12	16
↳ CCNK binds CDK13	17
↳ CCNK:CDK12 binds RNA Pol II at DNA repair genes	18
↳ CDK12 phosphorylates RNA Pol II CTD at DNA repair genes	19
↳ CDK12 stimulates expression of DNA repair genes	20
Table of Contents	22