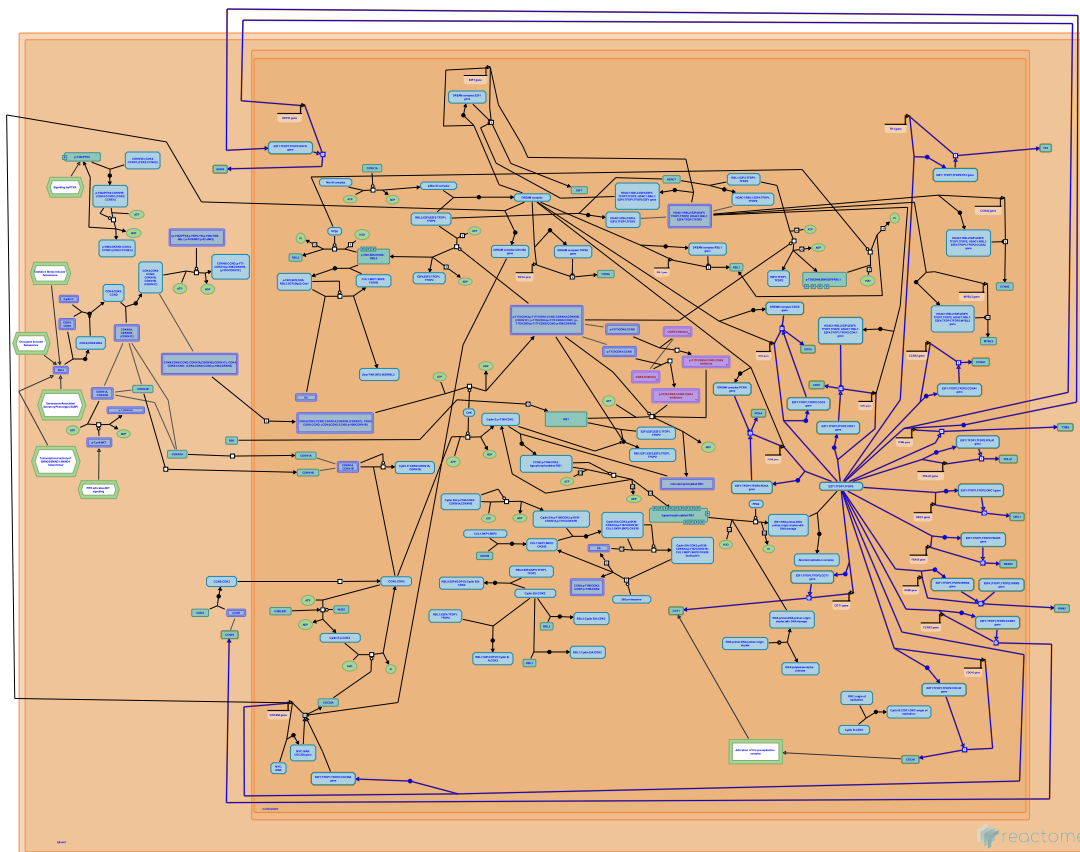


G1/S-Specific Transcription



Bosco, G., Gopinathrao, G., Herlihy, A., MacPherson, D., Matthews, L., Orlic-Milacic, M.

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

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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](https://reactome.org/textbook).

05/05/2024

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. [↗](#)

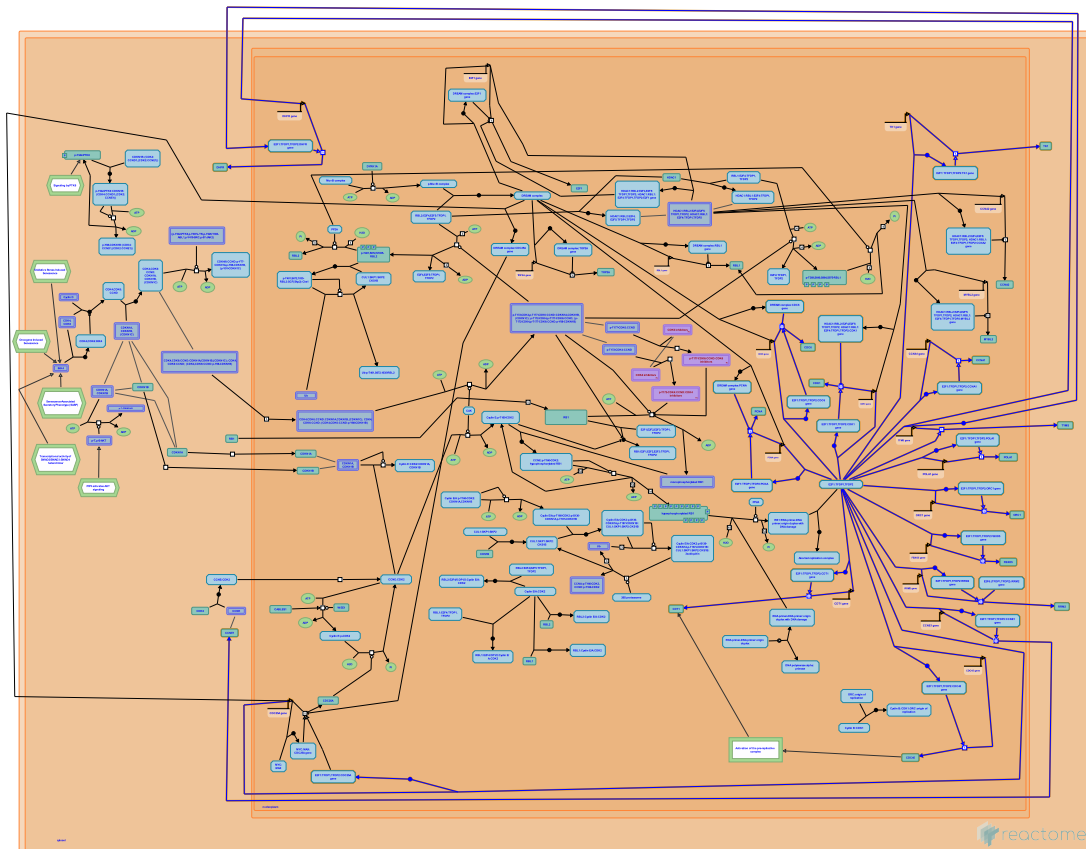
Reactome database release: 88

This document contains 1 pathway and 28 reactions ([see Table of Contents](#))

G1/S-Specific Transcription [↗](#)

Stable identifier: R-HSA-69205

Compartments: nucleoplasm



The E2F family of transcription factors regulate the transition from the G1 to the S phase in the cell cycle. E2F activity is regulated by members of the retinoblastoma protein (pRb) family, resulting in the tight control of the expression of E2F-responsive genes. Phosphorylation of pRb by cyclin D:CDK complexes releases pRb from E2F, inducing E2F-targeted genes such as cyclin E.

E2F1 binds to E2F binding sites on the genome activating the synthesis of the target proteins. For annotation purposes, the reactions regulated by E2F1 are grouped under this pathway and information about the target genes alone are displayed for annotation purposes.

Cellular targets for activation by E2F1 include thymidylate synthase (TYMS) (DeGregori et al. 1995), Rir2 (RRM2) (DeGregori et al. 1995, Giangrande et al. 2004), Dihydrofolate reductase (DHFR) (DeGregori et al. 1995, Wells et al. 1997, Darbinian et al. 1999), Cdc2 (CDK1) (Furukawa et al. 1994, DeGregori et al. 1995, Zhu et al. 2004), Cyclin A1 (CCNA1) (DeGregori et al. 1995, Liu et al. 1998), CDC6 (DeGregori et al. 1995, Yan et al. 1998; Ohtani et al. 1998), CDT1 (Yoshida and Inoue 2004), CDC45 (Arata et al. 2000), Cyclin E (CCNE1) (Ohtani et al. 1995), Emi1 (FBXO5) (Hsu et al. 2002), and ORC1 (Ohtani et al. 1996, Ohtani et al. 1998). The activation of TK1 (Dnk1) (Dou et al. 1994, DeGregori et al. 1995, Giangrande et al. 2004) and CDC25A (DeGregori et al. 1995, Vigo et al. 1999) by E2F1 is conserved in *Drosophila* (Duronio and O'Farrell 1994, Reis and Edgar 2004).

RRM2 protein is involved in dNTP level regulation and activation of this enzyme results in higher levels of dNTPs in anticipation of S phase. E2F activation of RRM2 has been shown also in *Drosophila* by Duronio and O'Farrell (1994). E2F1 activation of CDC45 is shown in mouse cells by using human E2F1 construct (Arata et al. 2000). Cyclin E is also transcriptionally regulated by E2F1. Cyclin E protein plays important role in the transition of G1 in S phase by associating with CDK2 (Ohtani et al. 1996). E2F1-mediated activation of PCNA has been demonstrated in *Drosophila* (Duronio and O'Farrell 1994) and in some human cells by using recombinant adenovirus constructs (DeGregori et al. 1995). E2F1-mediated activation of the DNA polymerase alpha subunit p180 (POLA1) has been demonstrated in some human cells. It has also been demonstrated in *Drosophila* by Ohtani and Nevins (1994). It has been observed in *Drosophila* that E2F1 induced expression of Orc1 stimulates ORC1 6 complex formation and binding to the origin of replication (Asano and Wharton 1999). ORC1 6 recruit CDC6 and CDT1 that are required to recruit the MCM2 7 replication helicases. E2F1 regulation incorporates a feedback mechanism wherein Geminin (GMNN) can inhibit MCM2 7 recruitment of ORC1 6 complex by interacting with CDC6/CDT1. The activation of CDC25A and TK1 (Dnk1) by E2F1 has been inferred from similar events in *Drosophila* (Duronio RJ and O'Farrell

1994; Reis and Edgar 2004). E2F1 activates string (CDC25) that in turn activates the complex of Cyclin B and CDK1. A similar phenomenon has been observed in mouse NIH 3T3 cells and in Rat1 cells.

Literature references

- Ohtani, K., Ikeda, M., Nakamura, M., Tsujimoto, A. (1998). Regulation of cell growth-dependent expression of mammalian CDC6 gene by the cell cycle transcription factor E2F. *Oncogene*, *17*, 1777-85. [↗](#)
- Wang, J., Dou, QP., Pardee, AB., Zhao, S., Helin, K., Levin, AH. (1994). G1/S-regulated E2F-containing protein complexes bind to the mouse thymidine kinase gene promoter. *J. Biol. Chem.*, *269*, 1306-13. [↗](#)
- Hateboer, G., Vigo, E., Helin, K., Prosperini, E., Cartwright, P., Moroni, MC. et al. (1999). CDC25A phosphatase is a target of E2F and is required for efficient E2F-induced S phase. *Mol Cell Biol*, *19*, 6379-95. [↗](#)
- Tretiakova, A., Kundu, M., Gallia, GL., Khalili, K., Giordano, A., Shcherbik, N. et al. (1999). Association of Pur alpha and E2F-1 suppresses transcriptional activity of E2F-1. *Oncogene*, *18*, 6398-402. [↗](#)
- Kijima, S., Ohtani, K., Fujita, M., Arata, Y., Kato, JY. (2000). Cdk2-dependent and -independent pathways in E2F-mediated S phase induction. *J Biol Chem*, *275*, 6337-45. [↗](#)

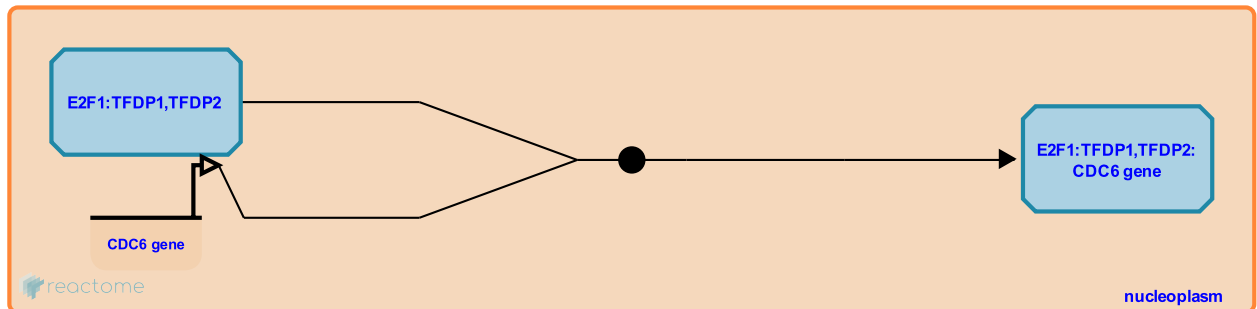
E2F1 binds the CDC6 gene promoter ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961620

Type: binding

Compartments: nucleoplasm



E2F1 binds to E2F binding sites in the promoter of the CDC6 gene (Yan et al., 1998; Ohtani et al., 1998). CDC6 is required to recruit the MCM2-7 replication helicases.

Followed by: CDC6 gene expression is stimulated by E2F1 and repressed by the DREAM complex

Literature references

Ohtani, K., Ikeda, M., Nakamura, M., Tsujimoto, A. (1998). Regulation of cell growth-dependent expression of mammalian CDC6 gene by the cell cycle transcription factor E2F. *Oncogene*, 17, 1777-85. ↗

Leone, G., Williams, RS., Nevins, JR., DeGregori, J., Stillman, B., Shohet, R. et al. (1998). Cdc6 is regulated by E2F and is essential for DNA replication in mammalian cells. *Proc Natl Acad Sci U S A*, 95, 3603-8. ↗

Editions

| | | |
|------------|----------|-------------------|
| 2004-06-16 | Reviewed | Bosco, G. |
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| 2010-04-21 | Revised | Matthews, L. |
| 2017-02-06 | Edited | Orlic-Milacic, M. |

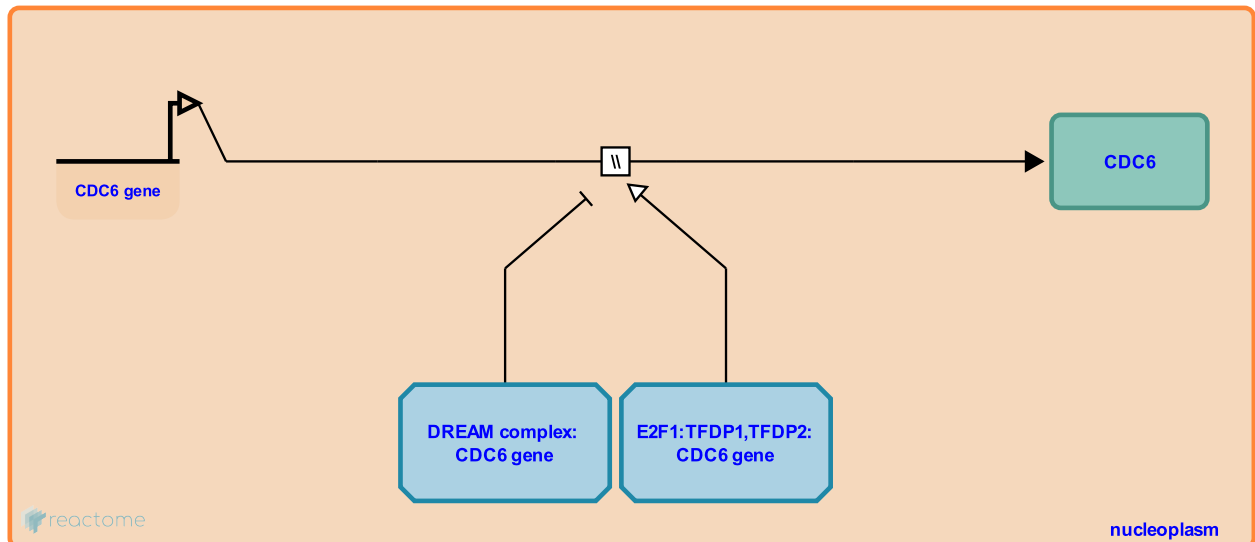
CDC6 gene expression is stimulated by E2F1 and repressed by the DREAM complex ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961619

Type: omitted

Compartments: nucleoplasm



E2F1 directly stimulates transcription of the CDC6 gene (Yan et al., 1998; Ohtani et al., 1998). CDC6 is required to recruit the MCM2-7 replication helicases.

Transcription of the CDC6 gene is directly repressed by the DREAM complex (Litovchick et al. 2007).

Preceded by: E2F1 binds the CDC6 gene promoter

Literature references

Ohtani, K., Ikeda, M., Nakamura, M., Tsujimoto, A. (1998). Regulation of cell growth-dependent expression of mammalian CDC6 gene by the cell cycle transcription factor E2F. *Oncogene*, 17, 1777-85. ↗

Leone, G., Williams, RS., Nevins, JR., DeGregori, J., Stillman, B., Shohet, R. et al. (1998). Cdc6 is regulated by E2F and is essential for DNA replication in mammalian cells. *Proc Natl Acad Sci U S A*, 95, 3603-8. ↗

DeCaprio, JA., Washburn, MP., Swanson, SK., Zhu, X., Florens, LA., Chen, R. et al. (2007). Evolutionarily conserved multisubunit RBL2/p130 and E2F4 protein complex represses human cell cycle-dependent genes in quiescence. *Mol Cell*, 26, 539-51. ↗

Editions

| | | |
|------------|----------|-------------------|
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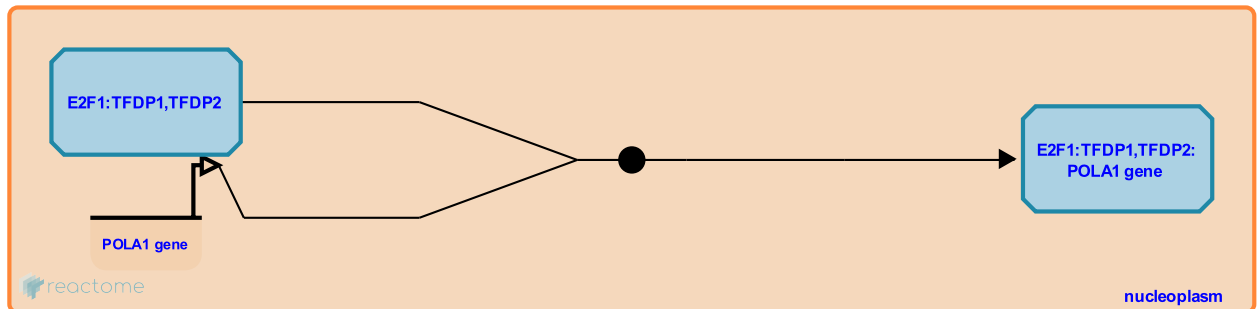
E2F1 binds the POLA1 gene promoter ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961636

Type: binding

Compartments: nucleoplasm



E2F1 binds to E2F binding sites in the promoter of the POLA1 gene, encoding the DNA polymerase alpha catalytic subunit p180 (DeGregori et al. 1995, Giangrande et al. 2004).

Followed by: POLA1 gene transcription is stimulated by E2F1

Literature references

Laakso, N., Nevins, JR., Rempel, RE., Zhu, W., Giangrande, PH. (2004). Combinatorial gene control involving E2F and E Box family members. *EMBO J.*, 23, 1336-47. ↗

Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. ↗

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|------------|----------|-------------------|
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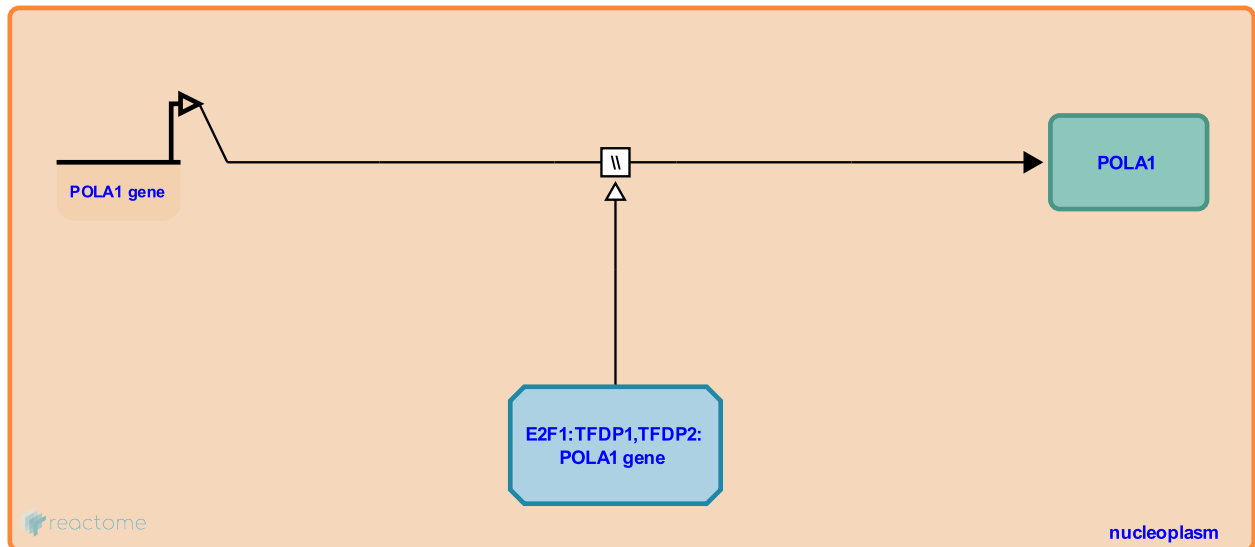
POLA1 gene transcription is stimulated by E2F1 [↗](#)

Location: [G1/S-Specific Transcription](#)

Stable identifier: R-HSA-8961632

Type: omitted

Compartments: nucleoplasm



E2F1 binds to E2F binding sites in the promoter of the POLA1 gene, stimulating POLA1 transcription. POLA1 encodes the catalytic subunit p180 of the DNA polymerase alpha (DeGregori et al. 1995, Giangrande et al. 2004). Activation of POLA1 by E2F1 has also been demonstrated in *Drosophila* (Ohtani and Nevins 1994).

Preceded by: [E2F1 binds the POLA1 gene promoter](#)

Literature references

Laakso, N., Nevins, JR., Rempel, RE., Zhu, W., Giangrande, PH. (2004). Combinatorial gene control involving E2F and E Box family members. *EMBO J.*, 23, 1336-47. [↗](#)

Nevins, JR., Ohtani, K. (1994). Functional properties of a *Drosophila* homolog of the E2F1 gene. *Mol Cell Biol*, 14, 1603-12. [↗](#)

Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. [↗](#)

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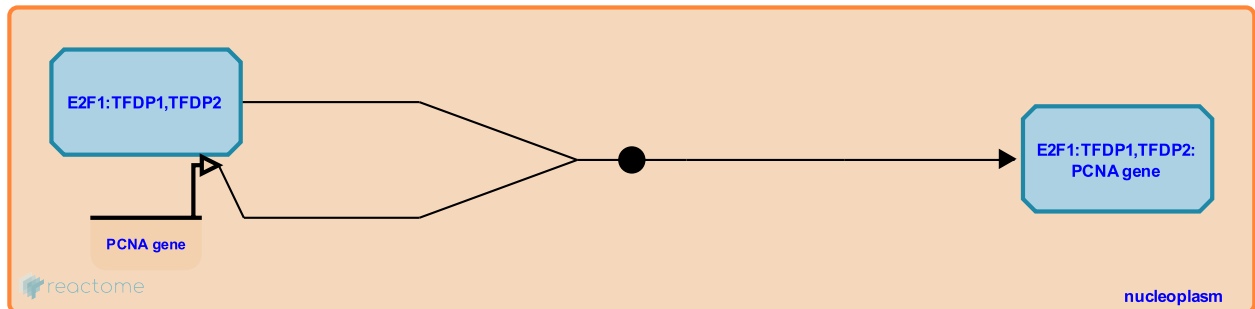
E2F1 binds the PCNA gene promoter ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961651

Type: binding

Compartments: nucleoplasm



E2F1 binds to E2F binding sites in the promoter of the PCNA gene, encoding the proliferating cell nuclear antigen, a component of the DNA polymerase complex involved in eukaryotic DNA replication (DeGregori et al. 1995, Li et al. 2003).

Followed by: PCNA gene expression is stimulated by E2F1 and repressed by the DREAM complex

Literature references

Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. ↗

Lu, CD., Li, YY., Wang, L. (2003). An E2F site in the 5'-promoter region contributes to serum-dependent up-regulation of the human proliferating cell nuclear antigen gene. *FEBS Lett.*, 544, 112-8. ↗

Editions

| | | |
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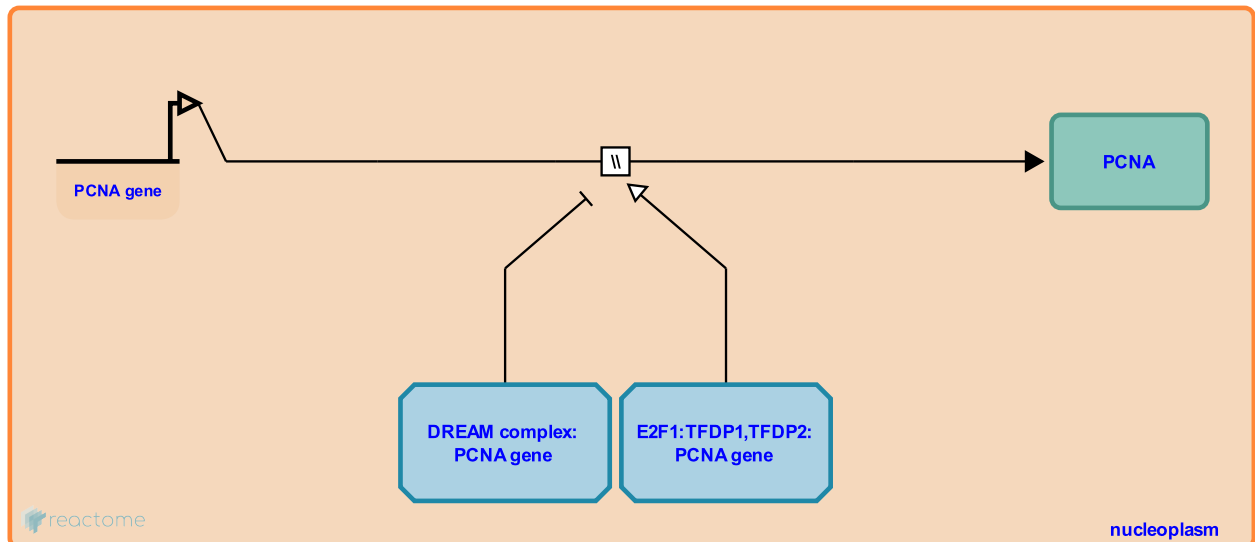
PCNA gene expression is stimulated by E2F1 and repressed by the DREAM complex ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961665

Type: omitted

Compartments: nucleoplasm



E2F1 directly stimulates transcription of the PCNA gene, which encodes the proliferating cell nuclear antigen, a component of the DNA polymerase complex involved in eukaryotic DNA replication (DeGregori et al. 1995, Li et al. 2003).

The PCNA gene transcription is directly repressed by the DREAM complex (Litovchick et al. 2007).

Preceded by: E2F1 binds the PCNA gene promoter

Literature references

Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. ↗

O'Farrell, PH., Duronio, RJ. (1994). Developmental control of a G1-S transcriptional program in *Drosophila*. *Development*, 120, 1503-15. ↗

Lu, CD., Li, YY., Wang, L. (2003). An E2F site in the 5'-promoter region contributes to serum-dependent up-regulation of the human proliferating cell nuclear antigen gene. *FEBS Lett.*, 544, 112-8. ↗

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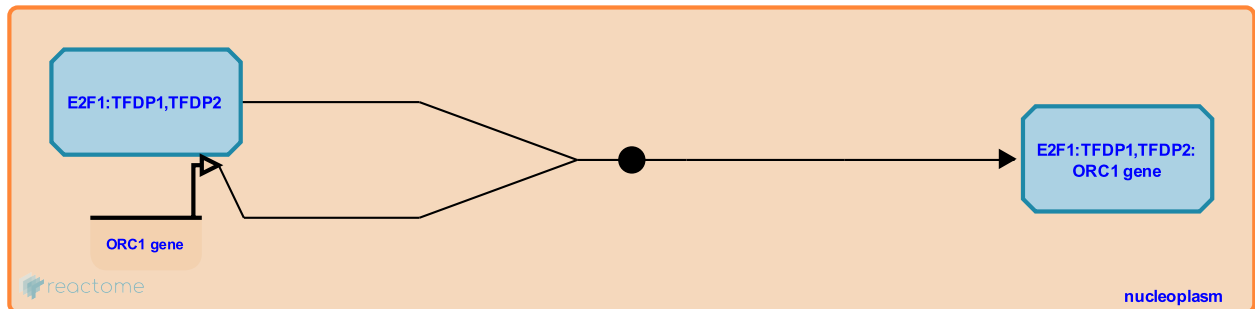
E2F1 binds the ORC1 gene promoter ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961671

Type: binding

Compartments: nucleoplasm



E2F1 binds to E2F binding sites in the promoter of the ORC1 gene (Ohtani et al. 1996, Ohtani et al. 1998). It has been observed in *Drosophila* that E2F1 regulated expression of *Orc1* stimulates ORC1-6 complex formation and binding to the origin of replication (Asano and Wharton, 1999).

Followed by: [ORC1 gene expression is stimulated by E2F1](#)

Literature references

Ohtani, K., Ikeda, M., Nakamura, M., Tsujimoto, A. (1998). Regulation of cell growth-dependent expression of mammalian CDC6 gene by the cell cycle transcription factor E2F. *Oncogene*, 17, 1777-85. ↗

Leone, G., Nevins, JR., DeGregori, J., Ohtani, K., Herendeen, DR., Kelly, TJ. (1996). Expression of the HsOrc1 gene, a human ORC1 homolog, is regulated by cell proliferation via the E2F transcription factor. *Mol Cell Biol*, 16, 6977-84. ↗

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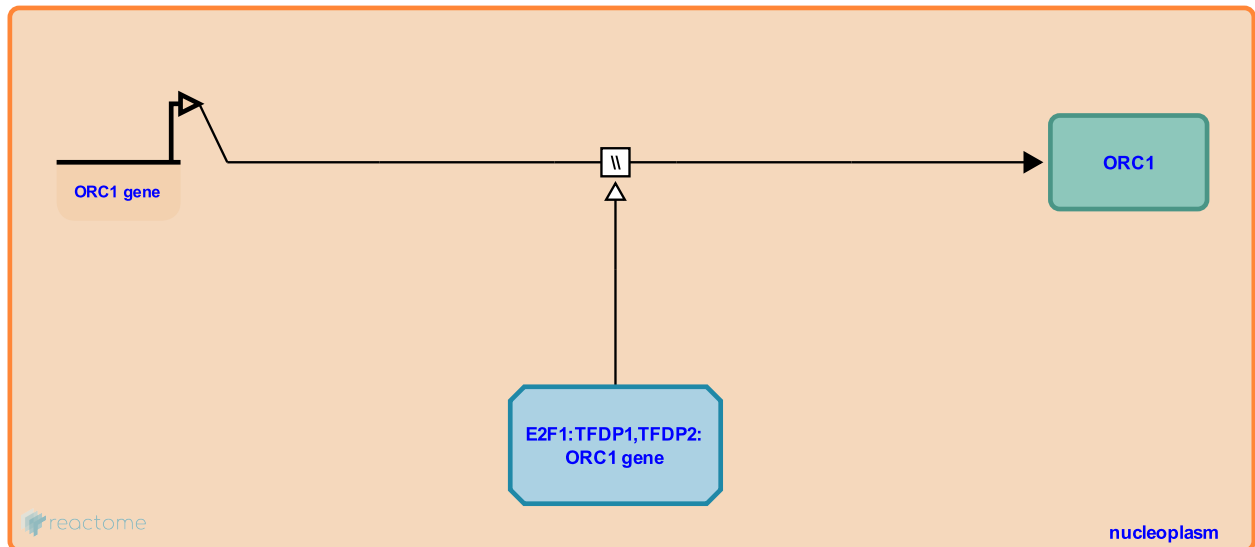
ORC1 gene expression is stimulated by E2F1 ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961678

Type: omitted

Compartments: nucleoplasm



E2F1 directly stimulates transcription of the ORC1 gene (Ohtani et al. 1996, Ohtani et al. 1998). E2F1 regulated expression of Orc1 stimulates ORC1-6 complex formation and binding to the origin of replication in *Drosophila* (Asano and Wharton, 1999).

Preceded by: [E2F1 binds the ORC1 gene promoter](#)

Literature references

Ohtani, K., Ikeda, M., Nakamura, M., Tsujimoto, A. (1998). Regulation of cell growth-dependent expression of mammalian CDC6 gene by the cell cycle transcription factor E2F. *Oncogene*, *17*, 1777-85. ↗

Leone, G., Nevins, JR., DeGregori, J., Ohtani, K., Herendeen, DR., Kelly, TJ. (1996). Expression of the HsOrc1 gene, a human ORC1 homolog, is regulated by cell proliferation via the E2F transcription factor. *Mol Cell Biol*, *16*, 6977-84. ↗

Asano, M., Wharton, RP. (1999). E2F mediates developmental and cell cycle regulation of ORC1 in *Drosophila*. *EMBO J*, *18*, 2435-48. ↗

Editions

| | | |
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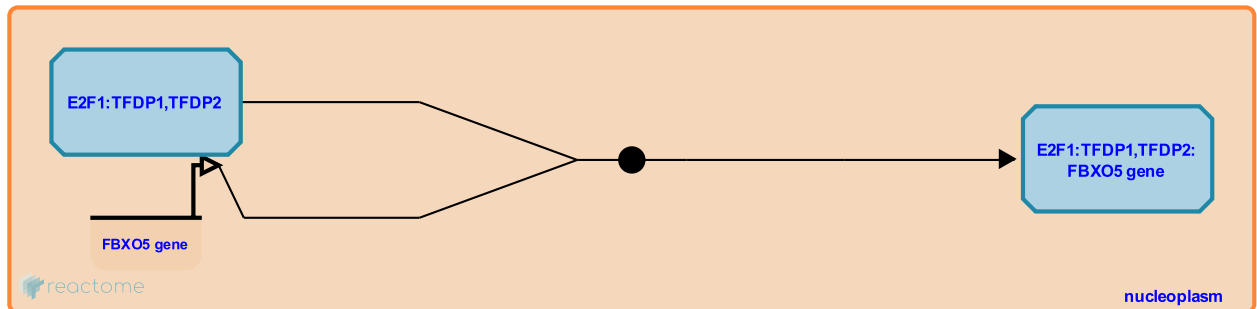
E2F1 binds the FBXO5 gene promoter ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961688

Type: binding

Compartments: nucleoplasm



E2F1 binds to E2F binding sites in the promoter of the FBXO5 (Emi1) gene (Hsu et al. 2002).

Followed by: FBXO5 gene expression is stimulated by E2F1

Literature references

Reimann, JD., Lukas, J., Hsu, JY., Sorensen, CS., Jackson, PK. (2002). E2F-dependent accumulation of hEmi1 regulates S phase entry by inhibiting APC(Cdh1). *Nat Cell Biol*, 4, 358-66. ↗

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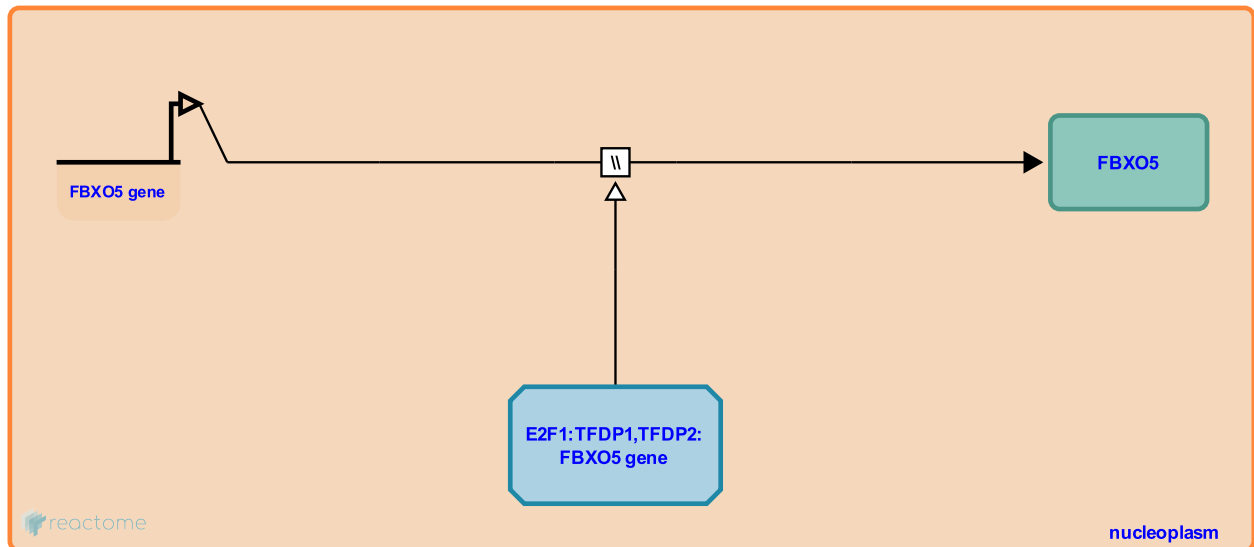
FBXO5 gene expression is stimulated by E2F1 [↗](#)

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961699

Type: omitted

Compartments: nucleoplasm



E2F1 directly stimulates transcription of the FBXO5 (Emi1) gene (Hsu et al. 2002).

Preceded by: [E2F1 binds the FBXO5 gene promoter](#)

Literature references

Reimann, JD., Lukas, J., Hsu, JY., Sorensen, CS., Jackson, PK. (2002). E2F-dependent accumulation of hEmi1 regulates S phase entry by inhibiting APC(Cdh1). *Nat Cell Biol*, 4, 358-66. [↗](#)

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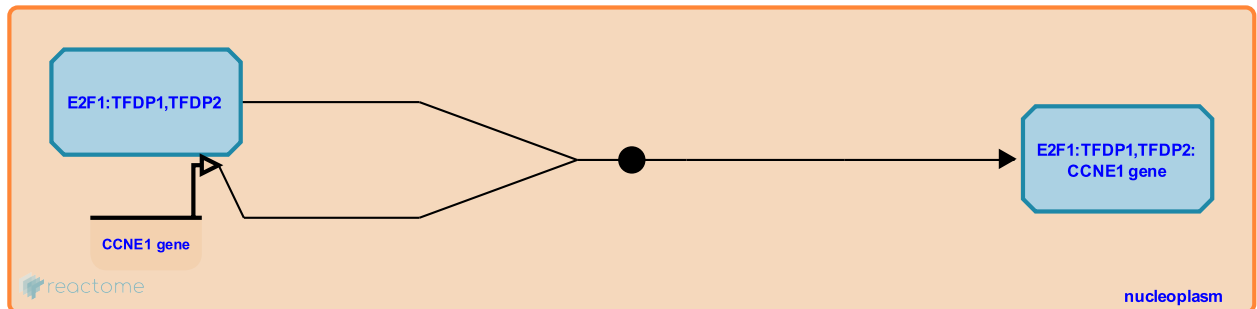
E2F1 binds the CCNE1 gene promoter ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961840

Type: binding

Compartments: nucleoplasm



E2F1 binds to E2F binding sites in the promoter of the CCNE1 gene, encoding cyclin E1 (DeGregori et al. 1995, Ohtani et al. 1995).

Followed by: CCNE1 gene transcription is stimulated by E2F1

Literature references

Nevins, JR., DeGregori, J., Ohtani, K. (1995). Regulation of the cyclin E gene by transcription factor E2F1. *Proc Natl Acad Sci U S A*, 92, 12146-50. ↗

Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. ↗

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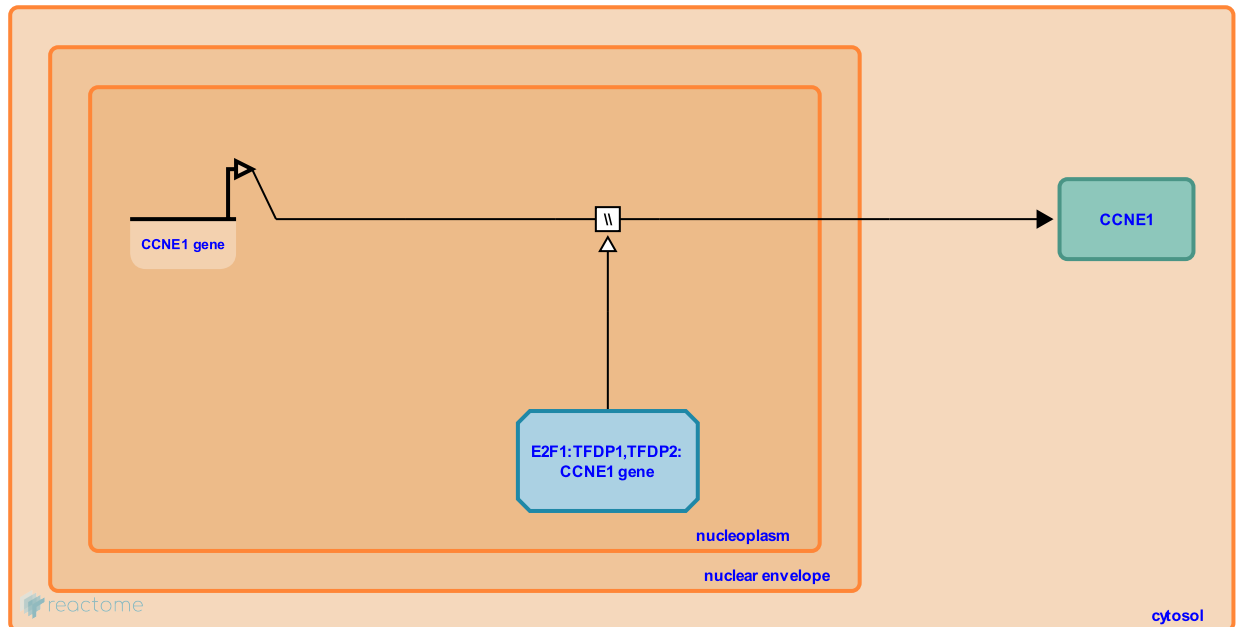
CCNE1 gene transcription is stimulated by E2F1 [↗](#)

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961846

Type: omitted

Compartments: nucleoplasm



E2F1 directly stimulates transcription of the CCNE1 gene, encoding cyclin E1 (DeGregori et al. 1995, Ohtani et al. 1995). Cyclin E proteins play an important role in the transition from G1 to S-phase by associating with CDK2.

Preceded by: E2F1 binds the CCNE1 gene promoter

Literature references

Nevins, JR., DeGregori, J., Ohtani, K. (1995). Regulation of the cyclin E gene by transcription factor E2F1. *Proc Natl Acad Sci U S A*, 92, 12146-50. [↗](#)

Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. [↗](#)

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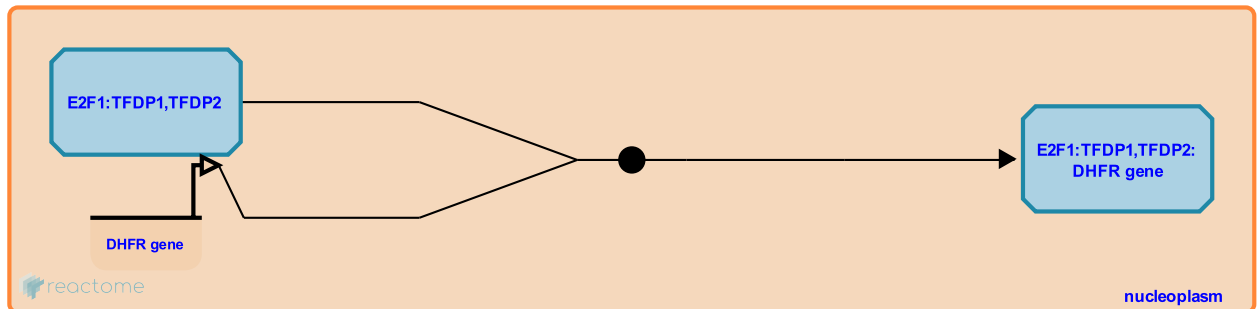
E2F1 binds the DHFR gene promoter ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961863

Type: binding

Compartments: nucleoplasm



E2F1 binds to E2F binding sites in the promoter of the DHFR gene, encoding dihydrofolate reductase. DHFR is involved in folate metabolism and synthesis of DNA bases (DeGregori et al. 1995, Wells et al. 1997, Darbinian et al. 1999).

Followed by: DHFR gene expression is stimulated by E2F1

Literature references

Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. ↗

Wu, CL., Magae, J., Illenye, S., Heintz, NH., Wells, JM. (1997). Accumulation of E2F-4.DP-1 DNA binding complexes correlates with induction of dhfr gene expression during the G1 to S phase transition. *J. Biol. Chem.*, 272, 4483-92. ↗

Tretiakova, A., Kundu, M., Gallia, GL., Khalili, K., Giordano, A., Shcherbik, N. et al. (1999). Association of Pur alpha and E2F-1 suppresses transcriptional activity of E2F-1. *Oncogene*, 18, 6398-402. ↗

Editions

| | | |
|------------|----------|-------------------|
| 2004-06-16 | Reviewed | Bosco, G. |
| 2004-06-16 | Authored | Gopinathrao, G. |
| 2010-04-21 | Revised | Matthews, L. |
| 2017-02-06 | Edited | Orlic-Milacic, M. |

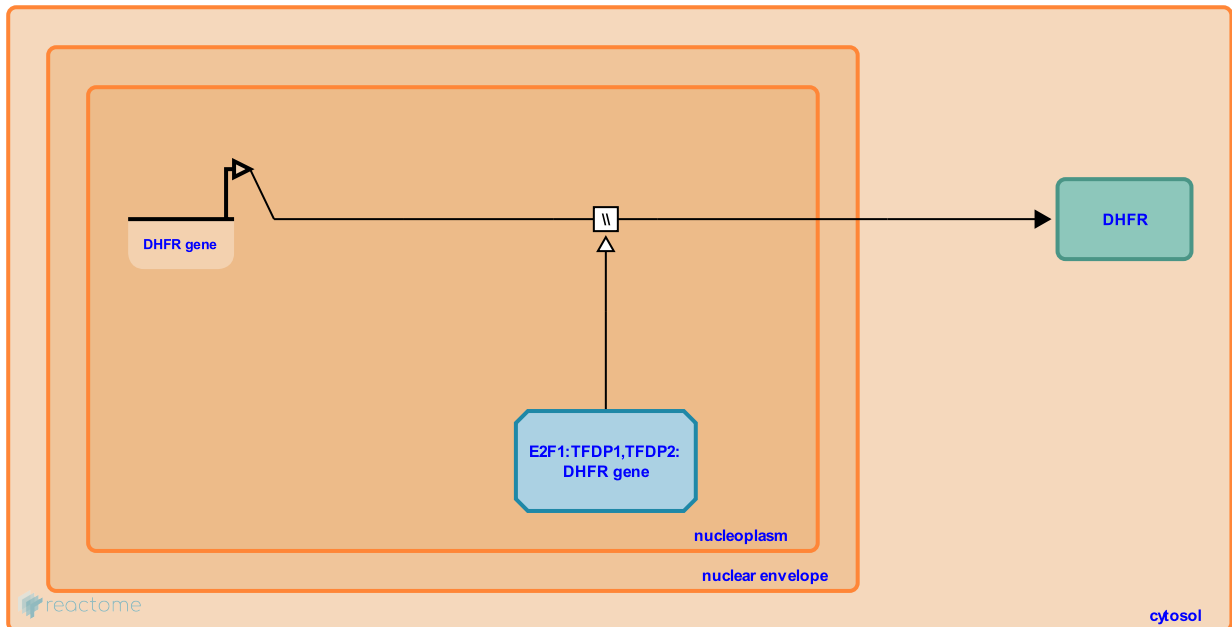
DHFR gene expression is stimulated by E2F1 [↗](#)

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961874

Type: omitted

Compartments: nucleoplasm



E2F1 directly stimulates transcription of the DHFR gene, encoding dihydrofolate reductase. DHFR is involved in folate metabolism and synthesis of DNA bases (DeGregori et al. 1995, Wells et al. 1997, Darbinian et al. 1999).

Preceded by: E2F1 binds the DHFR gene promoter

Literature references

- Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. [↗](#)
- Wu, CL., Magae, J., Illenye, S., Heintz, NH., Wells, JM. (1997). Accumulation of E2F-4.DP-1 DNA binding complexes correlates with induction of dhfr gene expression during the G1 to S phase transition. *J. Biol. Chem.*, 272, 4483-92. [↗](#)
- Tretiakova, A., Kundu, M., Gallia, GL., Khalili, K., Giordano, A., Shcherbik, N. et al. (1999). Association of Pur alpha and E2F-1 suppresses transcriptional activity of E2F-1. *Oncogene*, 18, 6398-402. [↗](#)

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| 2017-02-06 | Edited | Orlic-Milacic, M. |

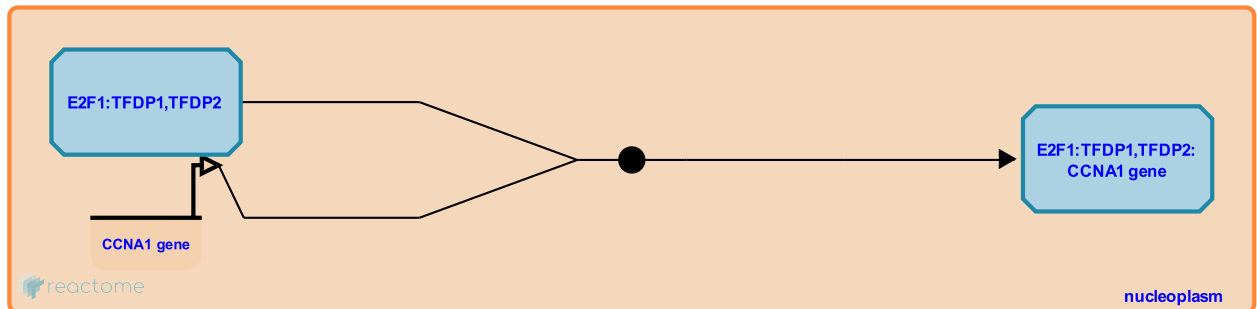
E2F1 binds the CCNA1 gene promoter ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961888

Type: binding

Compartments: nucleoplasm



E2F1 binds to E2F binding sites in the promoter of the CCNA1 gene, encoding cyclin A1 (DeGregori et al. 1995, Liu et al. 1998).

Followed by: CCNA1 gene expression is stimulated by E2F1

Literature references

Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. ↗

Müller, R., England, K., Lucibello, FC., Liu, N. (1998). A new model of cell cycle-regulated transcription: repression of the cyclin A promoter by CDF-1 and anti-repression by E2F. *Oncogene*, 16, 2957-63. ↗

Editions

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| 2004-06-16 | Reviewed | Bosco, G. |
| 2004-06-16 | Authored | Gopinathrao, G. |
| 2010-04-21 | Revised | Matthews, L. |
| 2017-02-06 | Edited | Orlic-Milacic, M. |

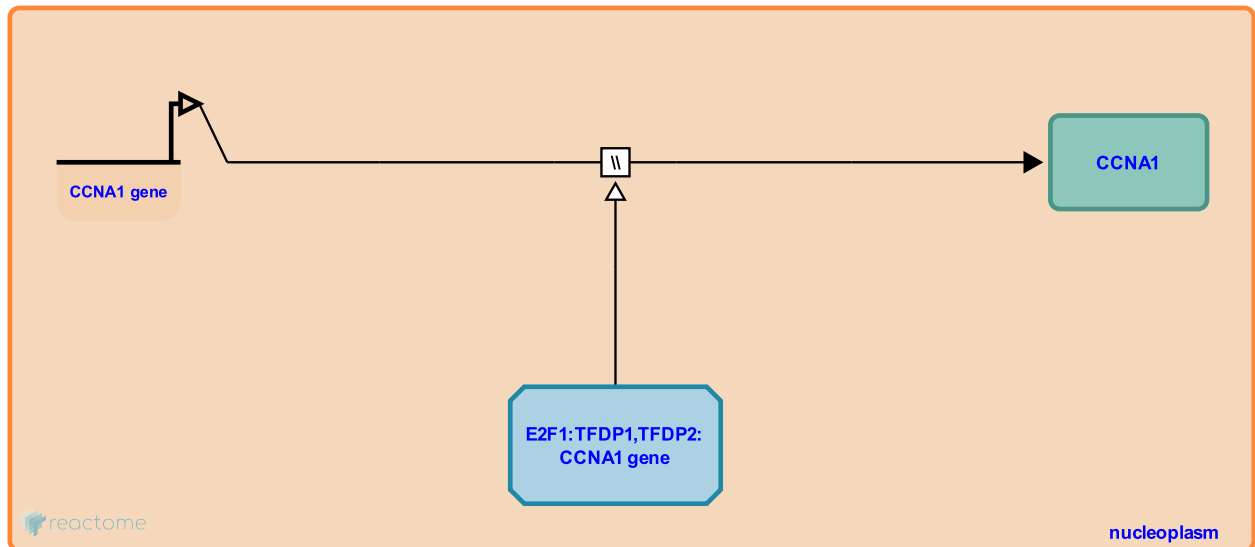
CCNA1 gene expression is stimulated by E2F1 [↗](#)

Location: [G1/S-Specific Transcription](#)

Stable identifier: R-HSA-8961895

Type: omitted

Compartments: nucleoplasm



E2F1 directly stimulates transcription of the CCNA1 gene, encoding cyclin A1 (DeGregori et al. 1995, Liu et al. 1998).

Preceded by: [E2F1 binds the CCNA1 gene promoter](#)

Literature references

Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. [↗](#)

Müller, R., Engeland, K., Lucibello, FC., Liu, N. (1998). A new model of cell cycle-regulated transcription: repression of the cyclin A promoter by CDF-1 and anti-repression by E2F. *Oncogene*, 16, 2957-63. [↗](#)

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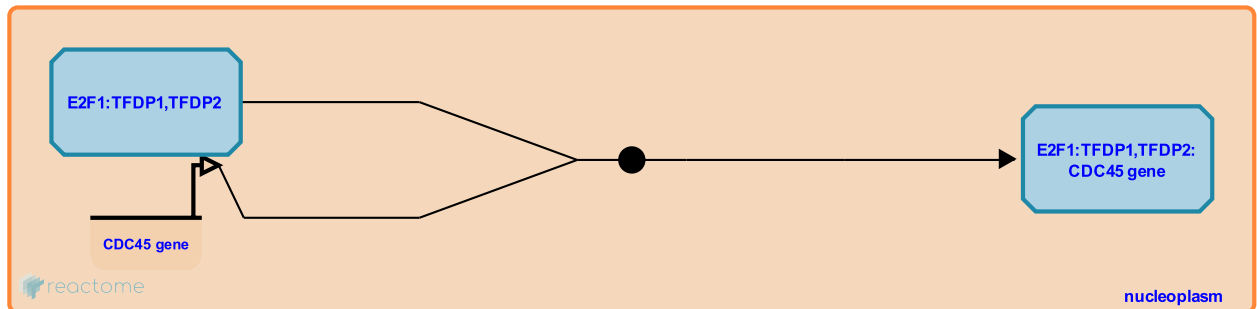
E2F1 binds the CDC45 gene promoter ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961907

Type: binding

Compartments: nucleoplasm



E2F1 binds to E2F binding sites in the promoter of the CDC45 gene (Arata et al. 2000).

Followed by: CDC45 gene expression is stimulated by E2F1

Literature references

Kijima, S., Ohtani, K., Fujita, M., Arata, Y., Kato, JY. (2000). Cdk2-dependent and -independent pathways in E2F-mediated S phase induction. *J Biol Chem*, 275, 6337-45. ↗

Editions

| | | |
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| 2004-06-16 | Authored | Gopinathrao, G. |
| 2010-04-21 | Revised | Matthews, L. |
| 2017-02-06 | Edited | Orlic-Milacic, M. |

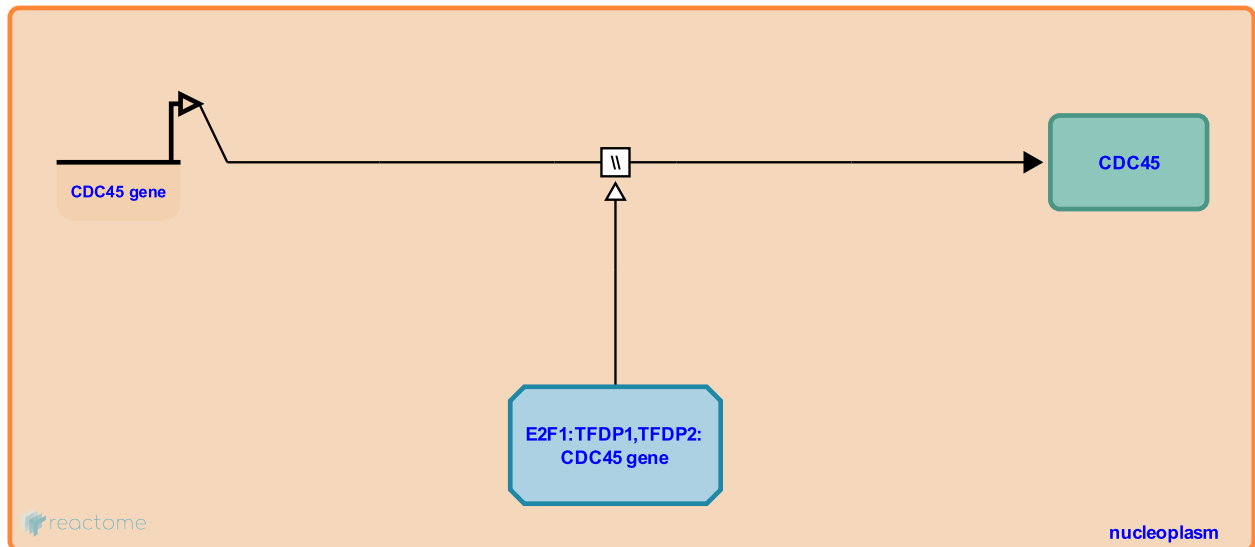
CDC45 gene expression is stimulated by E2F1 ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961915

Type: omitted

Compartments: nucleoplasm



E2F1 directly stimulates transcription of the CDC45 gene (Arata et al. 2000), encoding Cell division control protein 45 homolog, which is required for initiation of DNA replication.

Preceded by: [E2F1 binds the CDC45 gene promoter](#)

Literature references

Kijima, S., Ohtani, K., Fujita, M., Arata, Y., Kato, JY. (2000). Cdk2-dependent and -independent pathways in E2F-mediated S phase induction. *J Biol Chem*, 275, 6337-45. ↗

Editions

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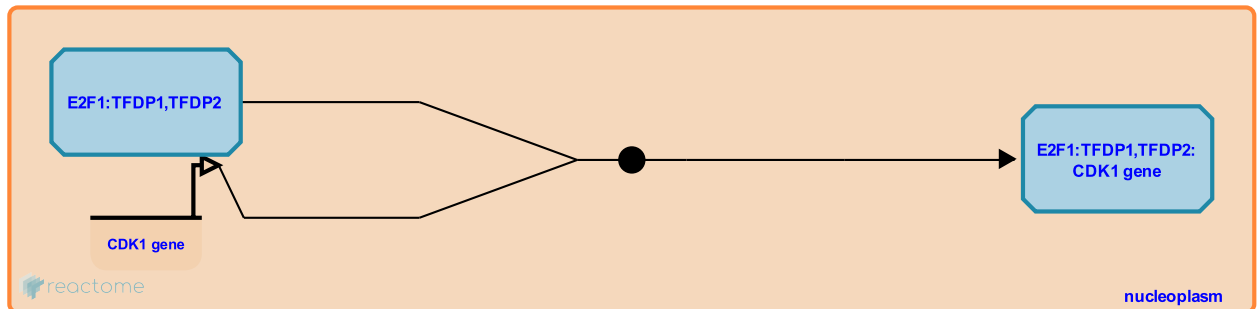
E2F1 binds the CDK1 gene promoter ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961920

Type: binding

Compartments: nucleoplasm



E2F1 binds to E2F binding sites in the promoter of the CDK1 gene, encoding cyclin-dependent kinase 1 (Cdc2) (Furukawa et al. 1994, DeGregori et al. 1995, Zhu et al. 2004).

Followed by: CDK1 gene expression is stimulated by E2F1 and repressed by RBL1 and RBL2

Literature references

Nevins, JR., Zhu, W., Giangrande, PH. (2004). E2Fs link the control of G1/S and G2/M transcription. *EMBO J.*, 23, 4615-26. ↗

Saito, M., Furukawa, Y., Sakoe, K., Ohta, M., Terui, Y. (1994). The role of cellular transcription factor E2F in the regulation of cdc2 mRNA expression and cell cycle control of human hematopoietic cells. *J. Biol. Chem.*, 269, 26249-58. ↗

Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. ↗

Editions

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| 2004-06-16 | Reviewed | Bosco, G. |
| 2004-06-16 | Authored | Gopinathrao, G. |
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| 2017-02-06 | Edited | Orlic-Milacic, M. |

CDK1 gene expression is stimulated by E2F1 and repressed by RBL1 and RBL2 ↗

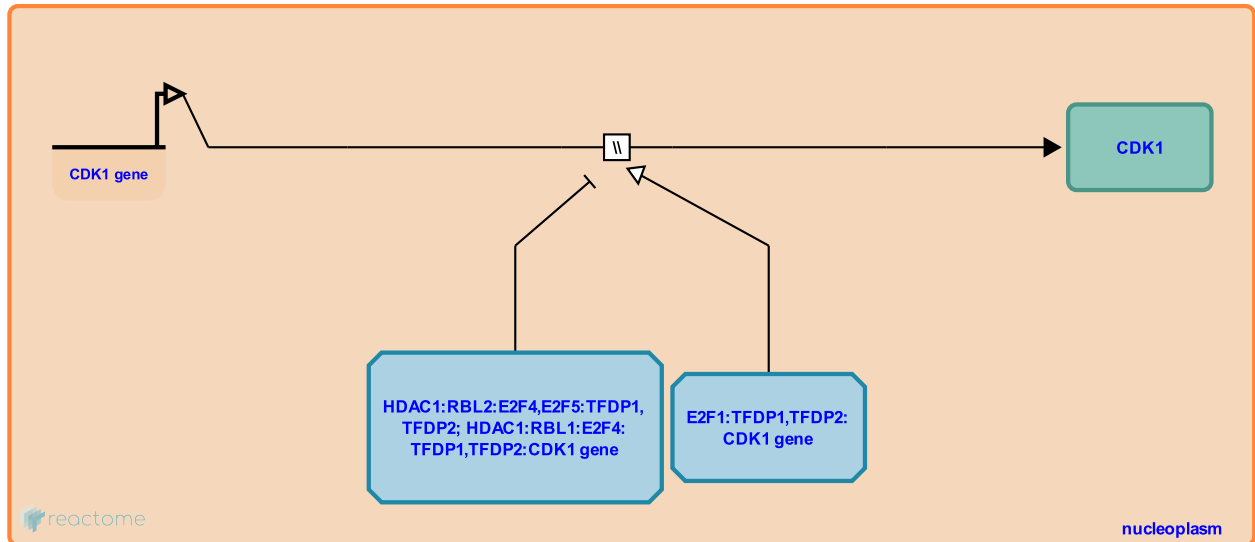
Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961934

Type: omitted

Compartments: nucleoplasm

Inferred from: Cdk1 gene expression is inhibited by Rbl1 or Rbl2 in complex with Hdac1 (Mus musculus)



E2F1 directly stimulates transcription of the CDK1 gene, encoding cyclin-dependent kinase 1 (Cdc2) (Furukawa et al. 1994, DeGregori et al. 1995, Zhu et al. 2004). Transcription of the CDK1 gene is directly inhibited by complexes of HDAC1 and RBL1 (p107) or RBL2 (p130) in G1 and G0, respectively (Rayman et al. 2002).

Preceded by: E2F1 binds the CDK1 gene promoter

Literature references

Nevins, JR., Zhu, W., Giangrande, PH. (2004). E2Fs link the control of G1/S and G2/M transcription. *EMBO J.*, 23, 4615-26. ↗

Catchpole, S., Dynlacht, BD., te Riele, H., Dannenberg, JH., Watson, RJ., Rayman, JB. et al. (2002). E2F mediates cell cycle-dependent transcriptional repression in vivo by recruitment of an HDAC1/mSin3B corepressor complex. *Genes Dev*, 16, 933-47. ↗

Saito, M., Furukawa, Y., Sakoe, K., Ohta, M., Terui, Y. (1994). The role of cellular transcription factor E2F in the regulation of cdc2 mRNA expression and cell cycle control of human hematopoietic cells. *J. Biol. Chem.*, 269, 26249-58. ↗

Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. ↗

Editions

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| 2004-06-16 | Reviewed | Bosco, G. |
| 2004-06-16 | Authored | Gopinathrao, G. |
| 2010-04-21 | Revised | Matthews, L. |
| 2017-02-06 | Edited | Orlic-Milacic, M. |

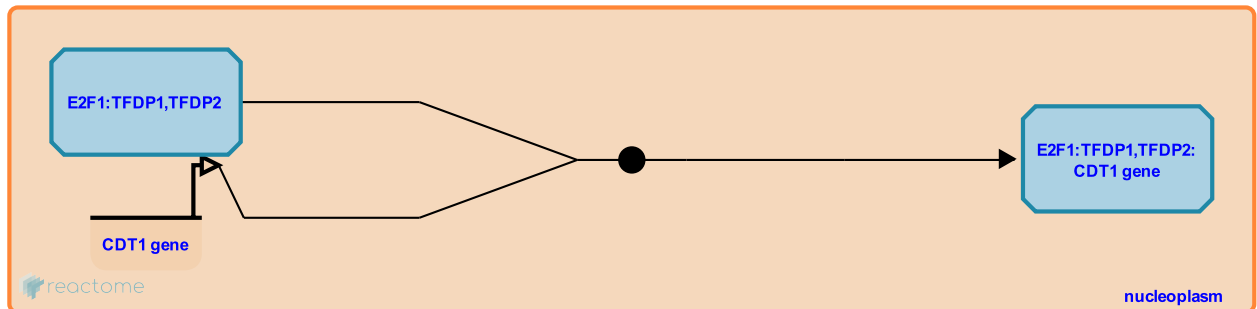
E2F1 binds the CDT1 gene promoter ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961946

Type: binding

Compartments: nucleoplasm



E2F1 binds to E2F binding sites in the promoter of the CDT1 gene, encoding DNA replication factor Cdt1 (Yoshida and Inoue 2004).

Followed by: CDT1 gene expression is stimulated by E2F1

Literature references

Inoue, I., Yoshida, K. (2004). Regulation of Geminin and Cdt1 expression by E2F transcription factors. *Oncogene*, 23, 3802-12. ↗

Editions

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| 2004-06-16 | Reviewed | Bosco, G. |
| 2004-06-16 | Authored | Gopinathrao, G. |
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| 2017-02-06 | Edited | Orlic-Milacic, M. |

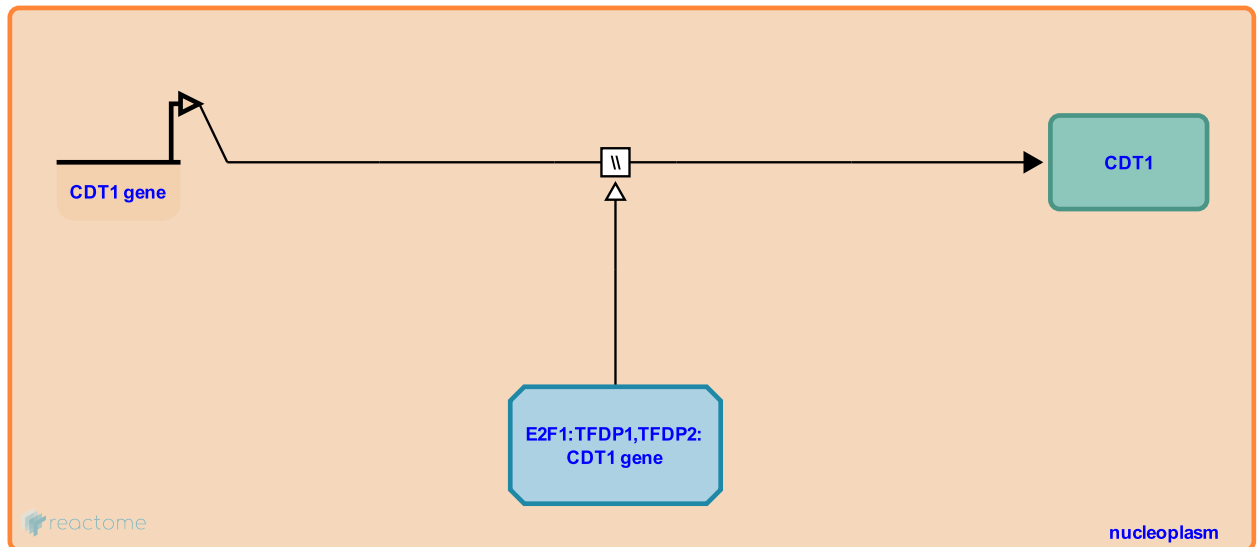
CDT1 gene expression is stimulated by E2F1 [↗](#)

Location: [G1/S-Specific Transcription](#)

Stable identifier: R-HSA-8961952

Type: omitted

Compartments: nucleoplasm



E2F1 directly stimulates transcription of the CDT1 gene, encoding DNA replication factor Cdt1 (Yoshida and Inoue 2004).

Preceded by: [E2F1 binds the CDT1 gene promoter](#)

Literature references

Inoue, I., Yoshida, K. (2004). Regulation of Geminin and Cdt1 expression by E2F transcription factors. *Oncogene*, 23, 3802-12. [↗](#)

Editions

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| 2004-06-16 | Reviewed | Bosco, G. |
| 2004-06-16 | Authored | Gopinathrao, G. |
| 2010-04-21 | Revised | Matthews, L. |
| 2017-02-06 | Edited | Orlic-Milacic, M. |

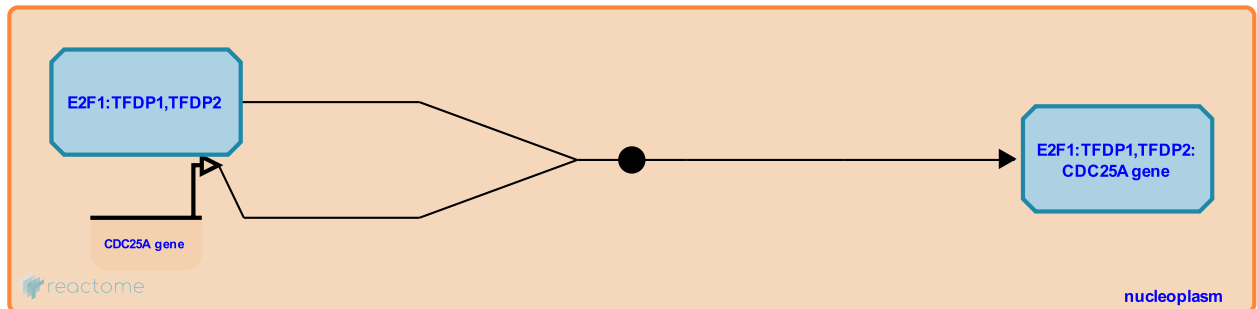
E2F1 binds the CDC25A gene promoter ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961961

Type: binding

Compartments: nucleoplasm



E2F1 binds to E2F binding sites in the promoter of the CDC25A gene, encoding M-phase inducer phosphatase 1 (DeGregori et al. 1995, Vigo et al. 1999).

Literature references

Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. ↗

Hateboer, G., Vigo, E., Helin, K., Prosperini, E., Cartwright, P., Moroni, MC. et al. (1999). CDC25A phosphatase is a target of E2F and is required for efficient E2F-induced S phase. *Mol Cell Biol*, 19, 6379-95. ↗

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| 2010-04-21 | Revised | Matthews, L. |
| 2017-02-06 | Edited | Orlic-Milacic, M. |

E2F1 binds the RRM2 gene promoter ↗

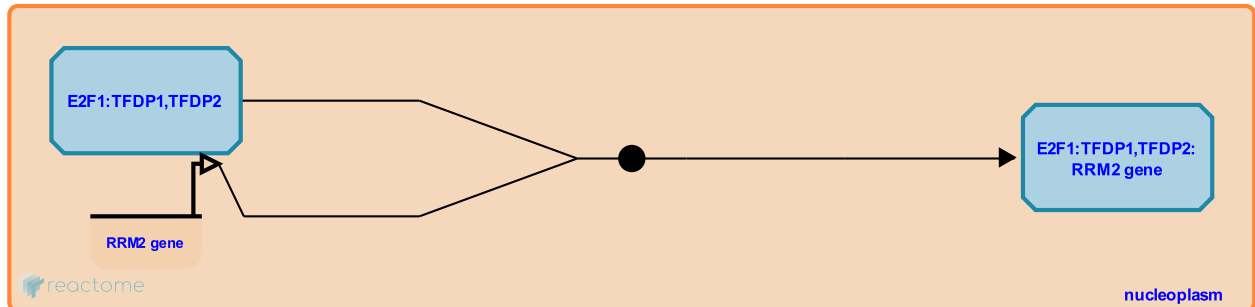
Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961972

Type: binding

Compartments: nucleoplasm

Inferred from: E2f1 binds the Rrm2 gene promoter (Mus musculus)



E2F1 binds to E2F binding sites in the promoter of the RRM2 gene, encoding Ribonucleoside-diphosphate reductase subunit M2 (DeGregori et al. 1995, Giangrande et al. 2004).

Followed by: RRM2 gene expression is stimulated by E2F1 and inhibited by E2F6

Literature references

Laakso, N., Nevins, JR., Rempel, RE., Zhu, W., Giangrande, PH. (2004). Combinatorial gene control involving E2F and E Box family members. *EMBO J.*, 23, 1336-47. ↗

Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. ↗

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| 2004-06-16 | Reviewed | Bosco, G. |
| 2004-06-16 | Authored | Gopinathrao, G. |
| 2010-04-21 | Revised | Matthews, L. |
| 2017-02-06 | Edited | Orlic-Milacic, M. |

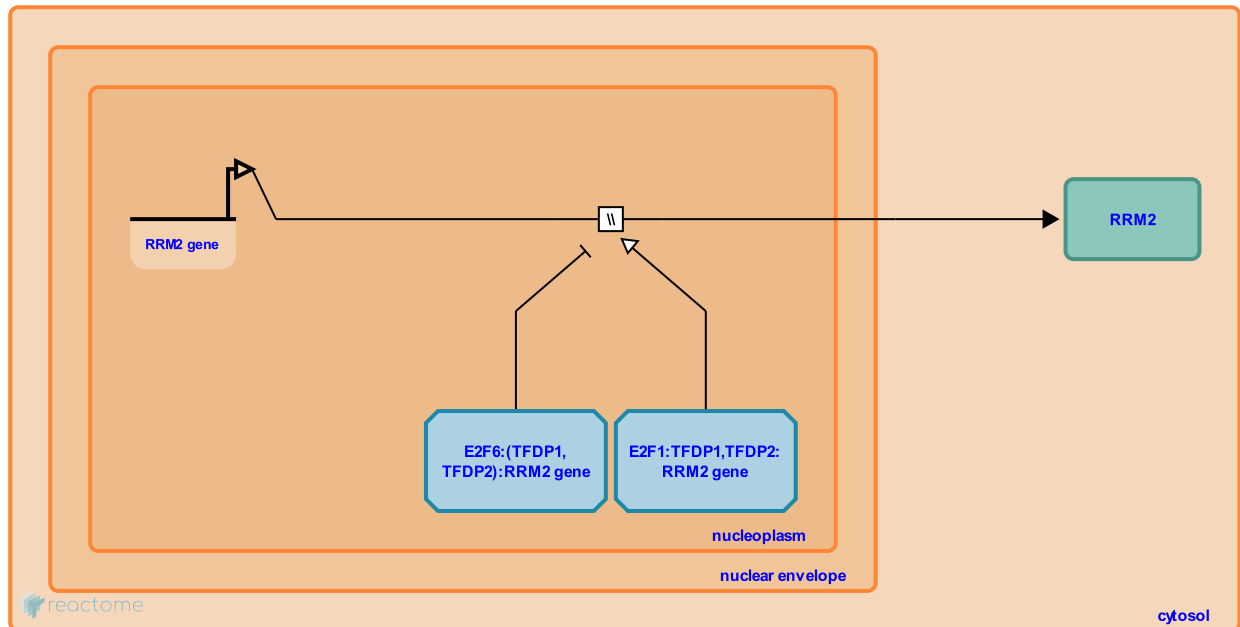
RRM2 gene expression is stimulated by E2F1 and inhibited by E2F6 ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8961982

Type: omitted

Compartments: nucleoplasm



E2F1 directly stimulates transcription of the RRM2 gene, encoding Ribonucleoside-diphosphate reductase subunit M2 (DeGregori et al. 1995, Giangrande et al. 2004). Binding of E2F6 to the RRM2 gene promoter inhibits RRM2 transcription (Bertoli et al. 2013).

Preceded by: E2F1 binds the RRM2 gene promoter

Literature references

- Laakso, N., Nevins, JR., Rempel, RE., Zhu, W., Giangrande, PH. (2004). Combinatorial gene control involving E2F and E Box family members. *EMBO J.*, 23, 1336-47. ↗
- Bertoli, C., McGowan, C., Klier, S., Wittenberg, C., de Bruin, RA. (2013). Chk1 inhibits E2F6 repressor function in response to replication stress to maintain cell-cycle transcription. *Curr. Biol.*, 23, 1629-37. ↗
- Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. ↗

Editions

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| 2004-06-16 | Reviewed | Bosco, G. |
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| 2017-05-12 | Reviewed | Herlihy, A. |
| 2017-05-31 | Revised | Orlic-Milacic, M. |

E2F1 binds the TK1 gene promoter ↗

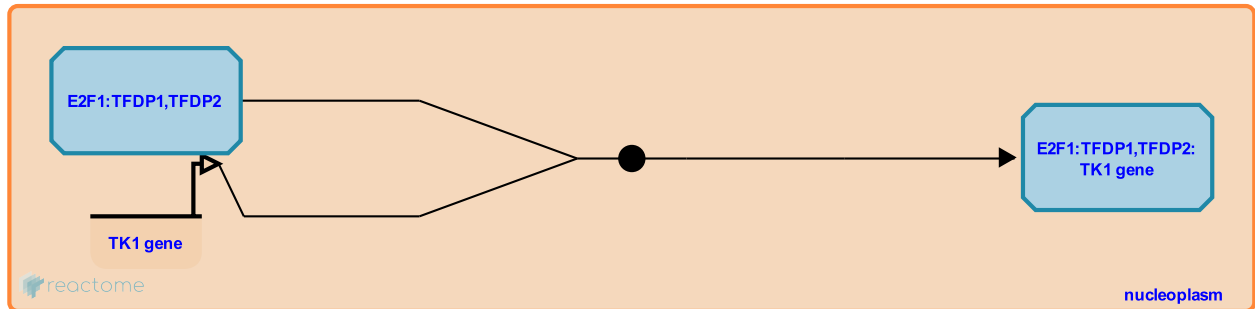
Location: [G1/S-Specific Transcription](#)

Stable identifier: R-HSA-8961991

Type: binding

Compartments: nucleoplasm

Inferred from: [E2F1 binds the Tk1 gene promoter \(Homo sapiens\)](#)



E2F1 binds to E2F binding sites in the promoter of the TK1 gene, encoding thymidine kinase (Dou et al. 1994, DeGregori et al. 1995, Giangrande et al. 2004).

Followed by: [TK1 gene expression is stimulated by E2F1](#)

Literature references

Laakso, N., Nevins, JR., Rempel, RE., Zhu, W., Giangrande, PH. (2004). Combinatorial gene control involving E2F and E Box family members. *EMBO J.*, 23, 1336-47. ↗

Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. ↗

Wang, J., Dou, QP., Pardee, AB., Zhao, S., Helin, K., Levin, AH. (1994). G1/S-regulated E2F-containing protein complexes bind to the mouse thymidine kinase gene promoter. *J. Biol. Chem.*, 269, 1306-13. ↗

Editions

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| 2004-06-16 | Reviewed | Bosco, G. |
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| 2010-04-21 | Revised | Matthews, L. |
| 2017-02-06 | Edited | Orlic-Milacic, M. |

TK1 gene expression is stimulated by E2F1 [↗](#)

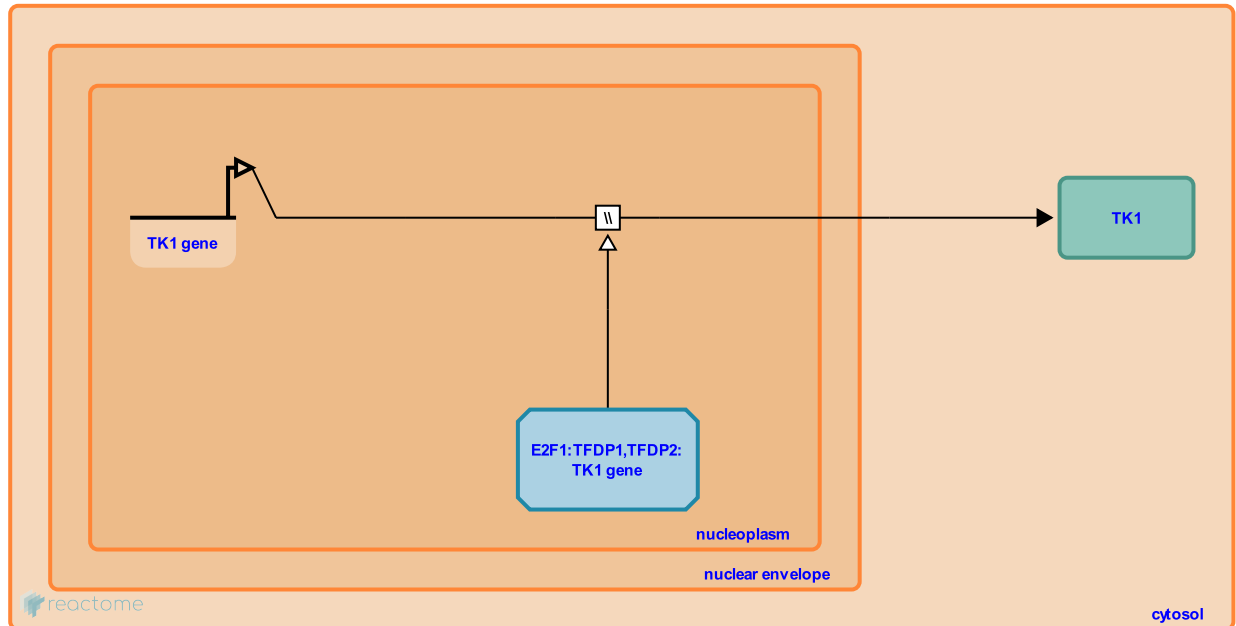
Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8962039

Type: omitted

Compartments: nucleoplasm

Inferred from: [Tk1 gene expression is stimulated by E2F1 \(Mus musculus\)](#)



E2F1 directly stimulates transcription of the TK1 gene, encoding thymidine kinase (Dou et al. 1994, DeGregori et al. 1995, Giangrande et al. 2004).

Preceded by: [E2F1 binds the TK1 gene promoter](#)

Literature references

- Laakso, N., Nevins, JR., Rempel, RE., Zhu, W., Giangrande, PH. (2004). Combinatorial gene control involving E2F and E Box family members. *EMBO J.*, 23, 1336-47. [↗](#)
- Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. [↗](#)
- Wang, J., Dou, QP., Pardee, AB., Zhao, S., Helin, K., Levin, AH. (1994). G1/S-regulated E2F-containing protein complexes bind to the mouse thymidine kinase gene promoter. *J. Biol. Chem.*, 269, 1306-13. [↗](#)

Editions

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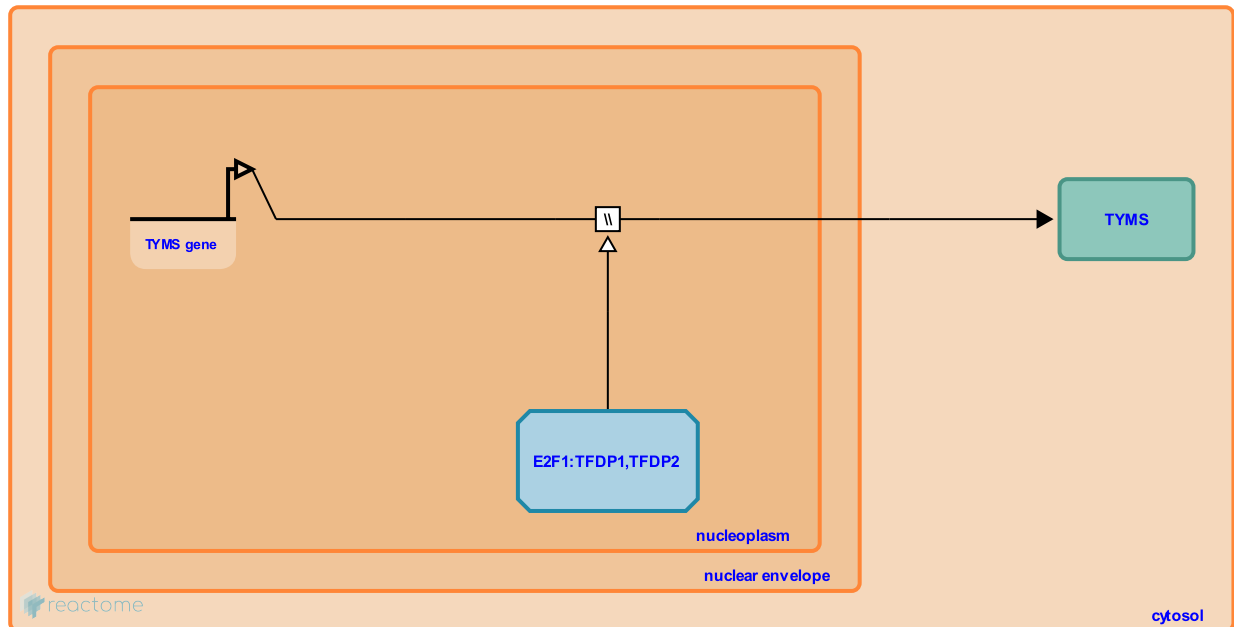
TYMS gene expression ↗

Location: G1/S-Specific Transcription

Stable identifier: R-HSA-8962050

Type: omitted

Compartments: nucleoplasm



Expression of the TYMS gene, encoding thymidylate synthase, is positively regulated by E2F1, but direct regulation has not been demonstrated (DeGregori et al. 1995).

Literature references

Nevins, JR., DeGregori, J., Kowalik, T. (1995). Cellular targets for activation by the E2F1 transcription factor include DNA synthesis- and G1/S-regulatory genes. *Mol Cell Biol*, 15, 4215-24. ↗

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