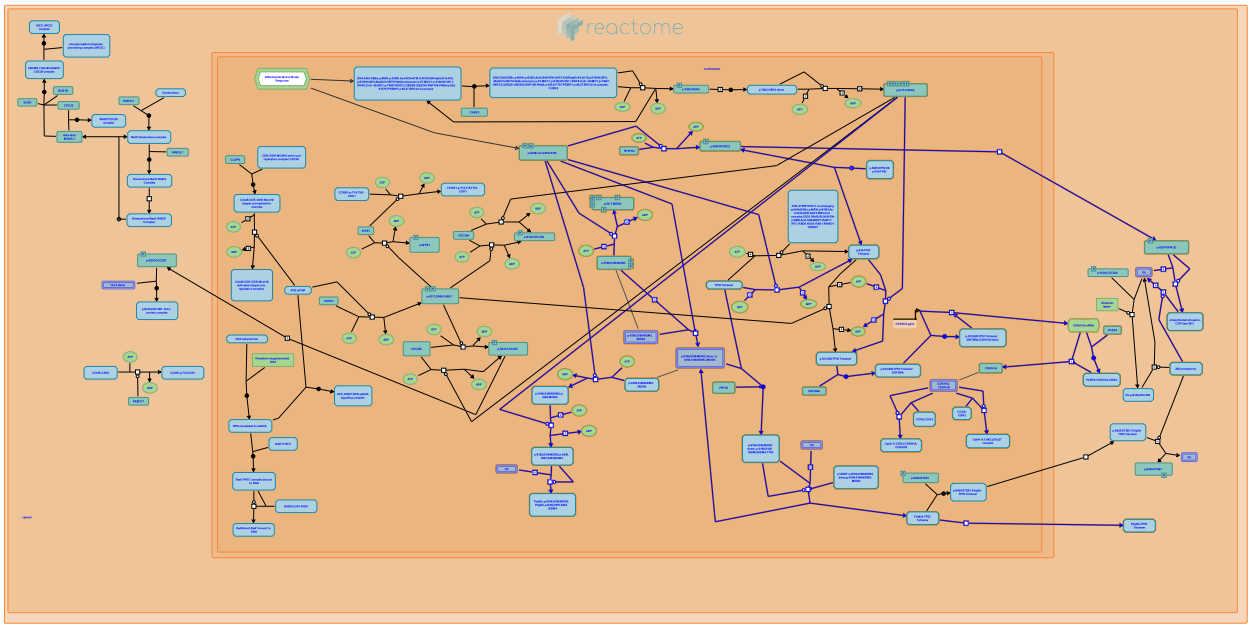
p53-Dependent G1 DNA Damage Response



Coqueret, O., Inga, A., Manfredi, JJ., Matthews, L., Orlic-Milacic, M., Pagano, M., Sanchez, Y., Zaccara, S.

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

19/05/2024

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. ↗

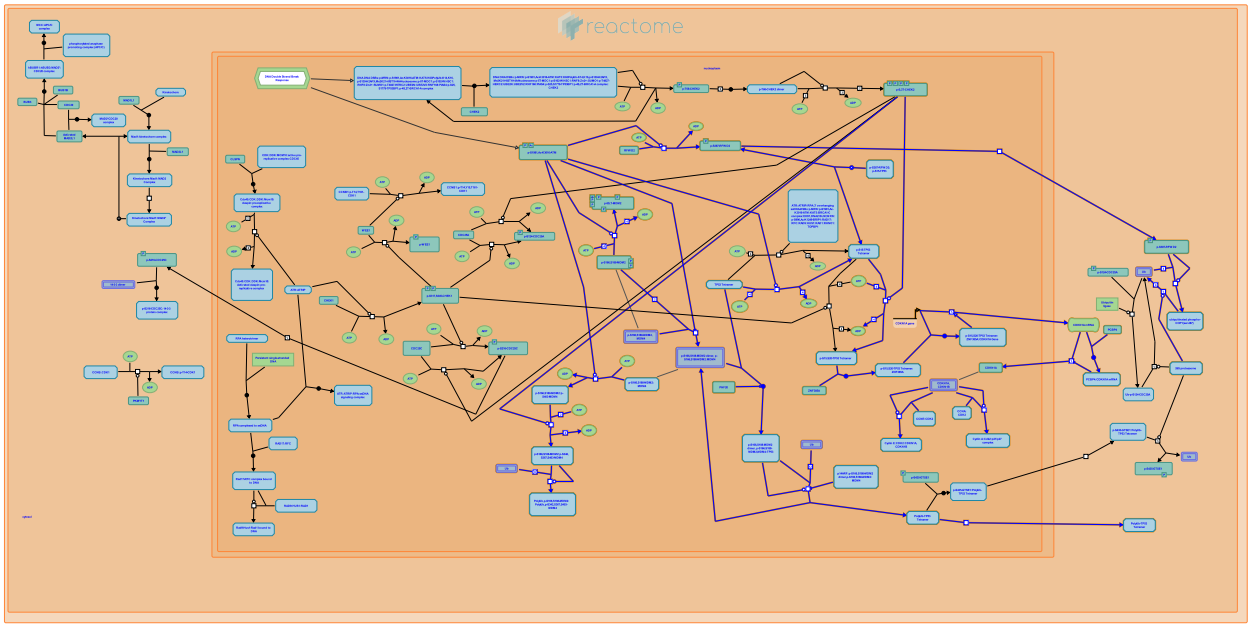
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

p53-Dependent G1 DNA Damage Response ↗

Stable identifier: R-HSA-69563



Most of the damage-induced modifications of p53 are dependent on the ATM kinase. The first link between ATM and p53 was predicted based on the earlier studies that showed that AT cells exhibit a reduced and delayed induction of p53 following exposure to IR (Kastan et al, 1992 and Khanna and Lavin, 1993).

Under normal conditions, p53 is a short-lived protein. The MDM2 protein, usually interacts with p53 (Haupt et al, 1997 and Kubbutat et al, 1997), and by virtue of its E3 ubiquitin ligase activity, shuttles p53 to the cytoplasm and mediates its degradation by the ubiquitin-proteasome machinery. Upon detection of DNA damage, the ATM kinase mediates the phosphorylation of the Mdm2 protein to block its interaction with p53. Also, phosphorylation of p53 at multiple loci, by the ATM kinase and by other kinases activated by the ATM kinase, stabilizes and activates the p53 protein.

The p53 protein activates the transcription of cyclin-dependent kinase inhibitor, p21. p21 inactivates the CyclinE:Cdk2 complexes, and prevent entry of the cell into S phase, leading to G1 arrest. Under severe conditions, the cell may undergo apoptosis.

Literature references

Vousden, KH., Kubbutat, MH., Jones, SN. (1997). Regulation of p53 stability by Mdm2. *Nature, 387*, 299-303. ↗

Kazaz, A., Haupt, Y., Maya, R., Oren, M. (1997). Mdm2 promotes the rapid degradation of p53. *Nature, 387*, 296-9. ↗

Lavin, MF., Khanna, KK. (1993). Ionizing radiation and UV induction of p53 protein by different pathways in ataxia-telangiectasia cells. *Oncogene, 8*, 3307-12. ↗

el-Deiry, WS., Kastan, MB., Plunkett, BS., Jacks, T., Vogelstein, B., Walsh, WV. et al. (1992). A mammalian cell cycle checkpoint pathway utilizing p53 and GADD45 is defective in ataxia-telangiectasia. *Cell, 71*, 587-97. ↗

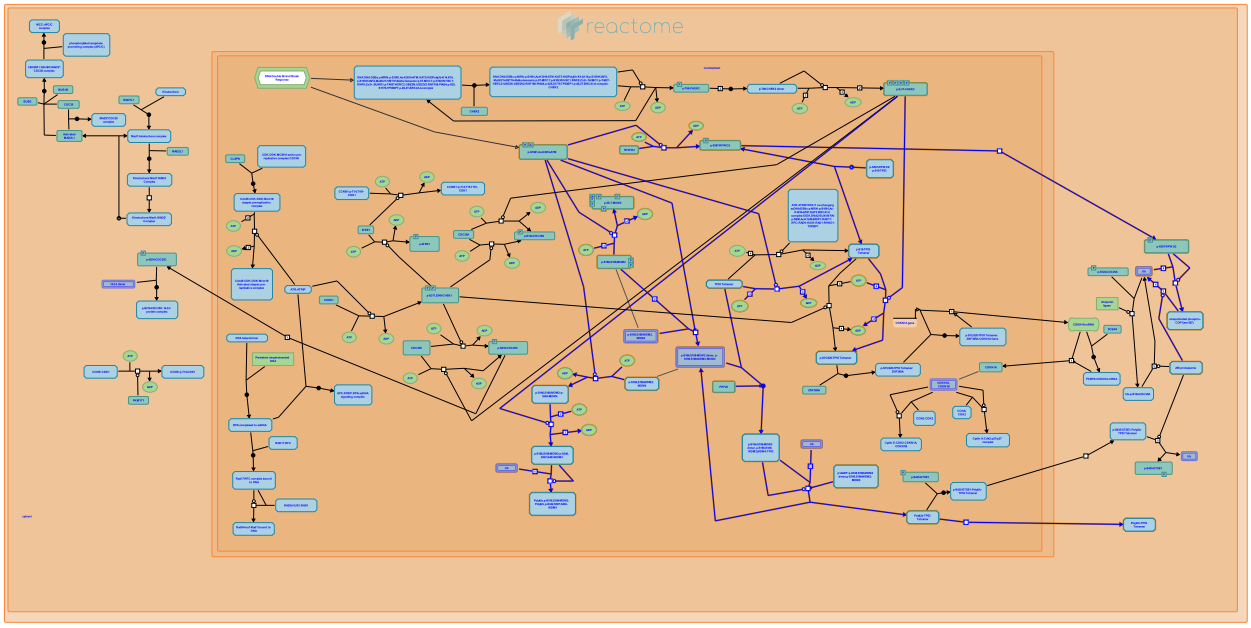
Editions

2018-07-10	Reviewed	Manfredi, JJ.

Stabilization of p53

Location: p53-Dependent G1 DNA Damage Response

Stable identifier: R-HSA-69541



Later studies pin-pointed that a single serine (Ser-15) was phosphorylated by ATM and phosphorylation of Ser-15 was rapidly-induced in IR-treated cells and this response was ATM-dependent (Canman et al, 1998; Banin et al, 1998 and Khanna et al, 1998). ATM also regulates the phosphorylation of p53 at other sites, especially Ser-20, by activating other serine/threonine kinases in response to IR (Chehab et al, 2000; Shieh et al, 2000; Hirao et al 2000). Phosphorylation of p53 at Ser-20 interferes with p53-MDM2 interaction. MDM2 is transcriptionally activated by p53 and is a negative regulator of p53 that targets it for degradation (Haupt et al, 1997; Kubbutat et al, 1997). In addition modification of MDM2 by ATM also affects p53 stabilization (Maya et al, 2001).

Literature references

Shiloh, Y., Kastan, MB., Buschmann, T., Ronai, Z., Shifman, O., Moas, M. et al. (2001). ATM-dependent phosphorylation of Mdm2 on serine 395: role in p53 activation by DNA damage. *Genes Dev, 15*, 1067-77.

Appel, M., Halazonetis, TD., Chehab, NH., Malikzay, A. (2000). Chk2/hCds1 functions as a DNA damage checkpoint in G(1) by stabilizing p53. *Genes Dev, 14*, 278-88.

Tamai, K., Taya, Y., Ahn, J., Prives, C., Shieh, SY. (2000). The human homologs of checkpoint kinases Chk1 and Cds1 (Chk2) phosphorylate p53 at multiple DNA damage-inducible sites. *Genes Dev, 14*, 289-300.

Hirao, A., Elledge, SJ., Mak, TW., Yoshida, H., Liu, D., Matsuoka, S. et al. (2000). DNA damage-induced activation of p53 by the checkpoint kinase Chk2. *Science, 287*, 1824-7.

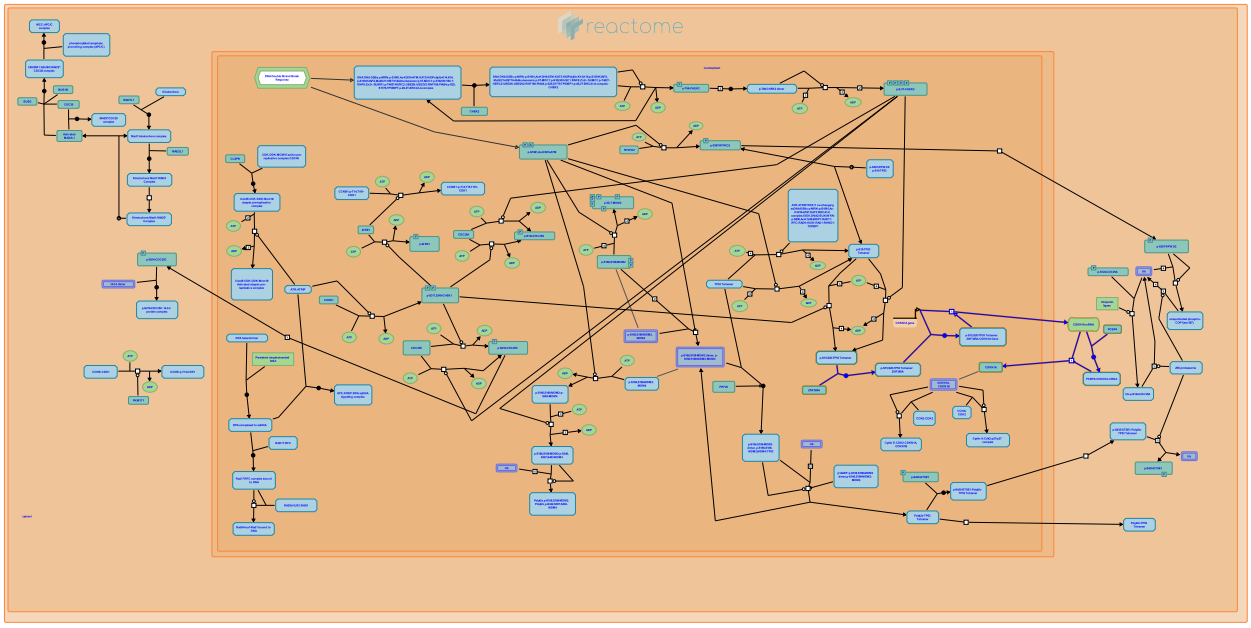
Editions

2008-05-08	Revised	Matthews, L.
2008-05-08	Reviewed	Sanchez, Y.
2008-05-12	Edited	Matthews, L.

Transcriptional activation of p53 responsive genes

Location: p53-Dependent G1 DNA Damage Response

Stable identifier: R-HSA-69560



p53 causes G1 arrest by inducing the expression of a cell cycle inhibitor, p21 (El-Deiry et al, 1993; Harper et al, 1993; Xiong et al, 1993). P21 binds and inactivates Cyclin-Cdk complexes that mediate G1/S progression, resulting in lack of phosphorylation of Rb, E2F sequestration and cell cycle arrest at the G1/S transition. Mice with a homozygous deletion of p21 gene are deficient in their ability to undergo a G1/S arrest in response to DNA damage (Deng et al, 1995).

Literature references

Xiong, Y., Hannon, GJ., Kobayashi, R., Casso, D., Beach, D., Zhang, H. (1994). p21 is a universal inhibitor of cyclin kinases. *Nature, 366*, 701-4.

Tokino, T., el-Deiry, WS., Kinzler, KW., Vogelstein, B., Lin, D., Mercer, WE. et al. (1993). WAF1, a potential mediator of p53 tumor suppression. *Cell, 75*, 817-25.

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

Zhang, P., Elledge, SJ., Deng, C., Leder, P., Harper, JW. (1995). Mice lacking p21CIP1/WAF1 undergo normal development, but are defective in G1 checkpoint control. *Cell, 82*, 675-84.

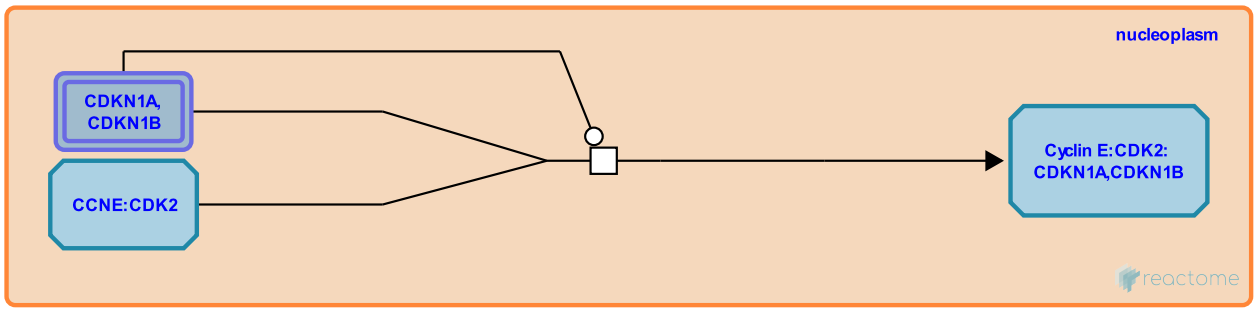
Inactivation of Cyclin E:Cdk2 complexes by p27/p21 ↗

Location: p53-Dependent G1 DNA Damage Response

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.

Literature references

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

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

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

Editions

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

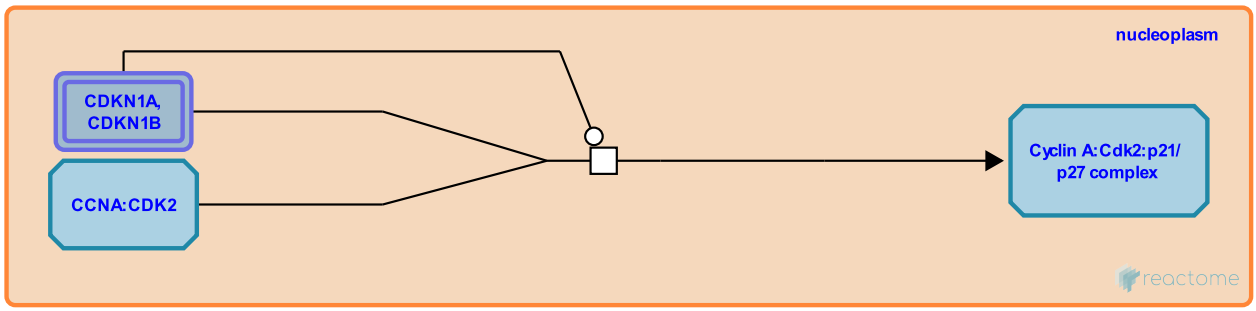
Inactivation of Cyclin A:Cdk2 complexes by p27/p21 ↗

Location: p53-Dependent G1 DNA Damage Response

Stable identifier: R-HSA-187934

Type: transition

Compartments: nucleoplasm



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

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

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