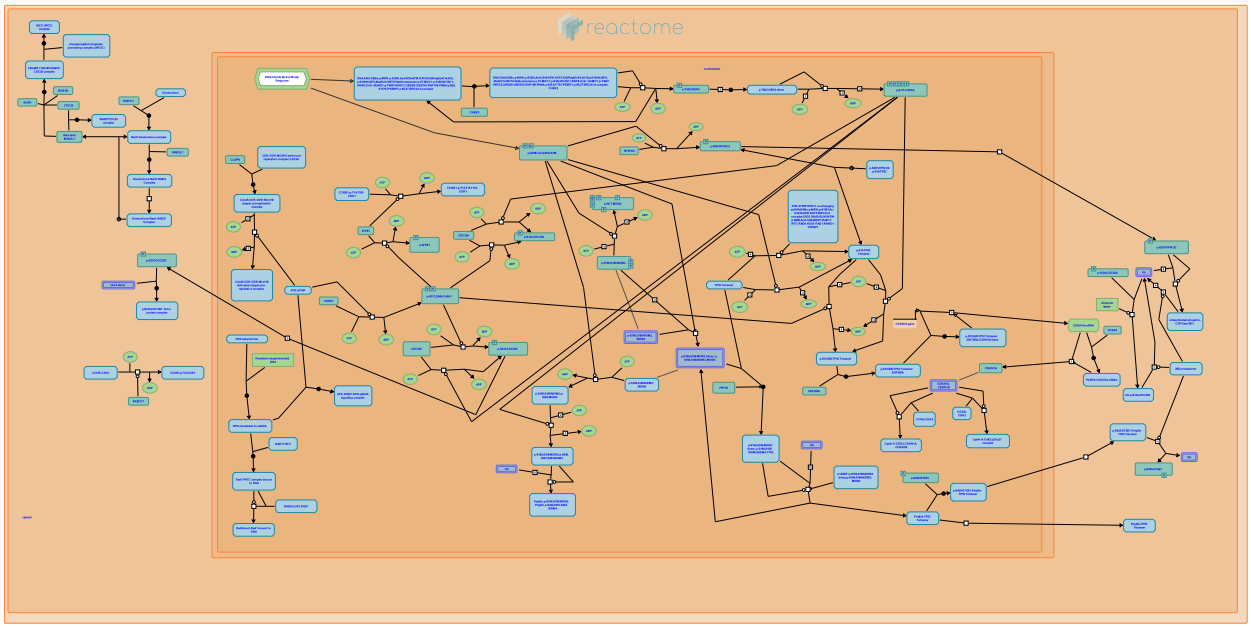
Cell Cycle Checkpoints



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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.

17/05/2024

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

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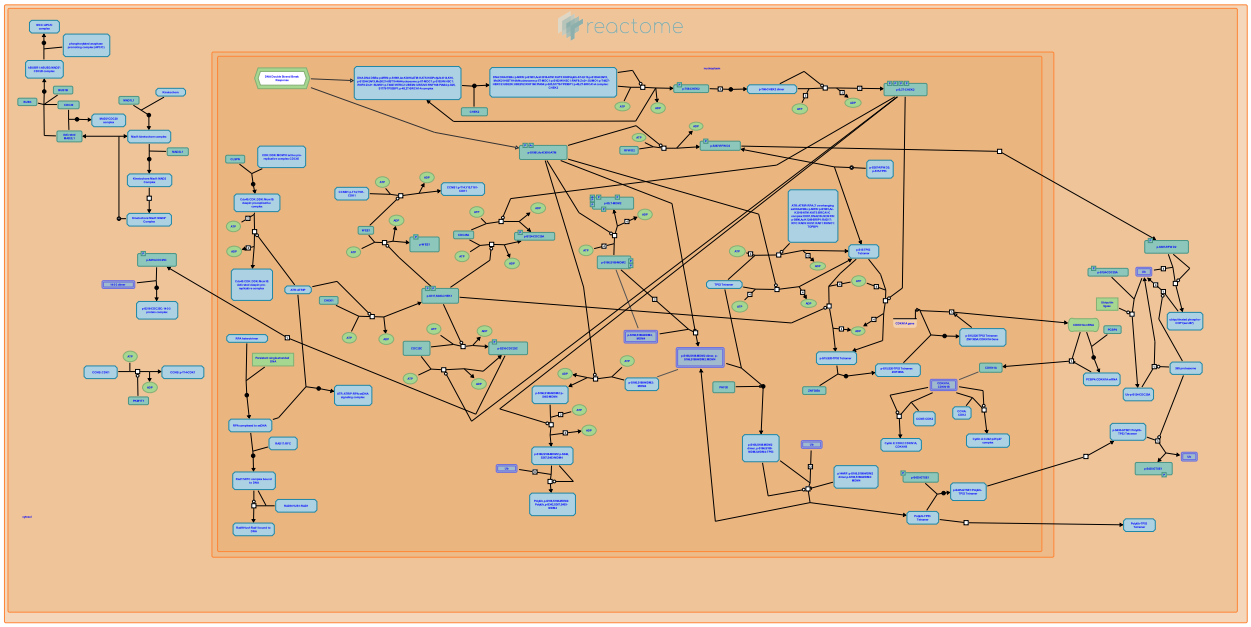
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Cell Cycle Checkpoints ↗

Stable identifier: R-HSA-69620



A hallmark of the human cell cycle in normal somatic cells is its precision. This remarkable fidelity is achieved by a number of signal transduction pathways, known as checkpoints, which monitor cell cycle progression ensuring an interdependency of S-phase and mitosis, the integrity of the genome and the fidelity of chromosome segregation.

Checkpoints are layers of control that act to delay CDK activation when defects in the division program occur. As the CDKs functioning at different points in the cell cycle are regulated by different means, the various checkpoints differ in the biochemical mechanisms by which they elicit their effect. However, all checkpoints share a common hierarchy of a sensor, signal transducers, and effectors that interact with the CDKs.

The stability of the genome in somatic cells contrasts to the almost universal genomic instability of tumor cells. There are a number of documented genetic lesions in checkpoint genes, or in cell cycle genes themselves, which result either directly in cancer or in a predisposition to certain cancer types. Indeed, restraint over cell cycle progression and failure to monitor genome integrity are likely prerequisites for the molecular evolution required for the development of a tumor. Perhaps most notable amongst these is the p53 tumor suppressor gene, which is mutated in >50% of human tumors. Thus, the importance of the checkpoint pathways to human biology is clear.

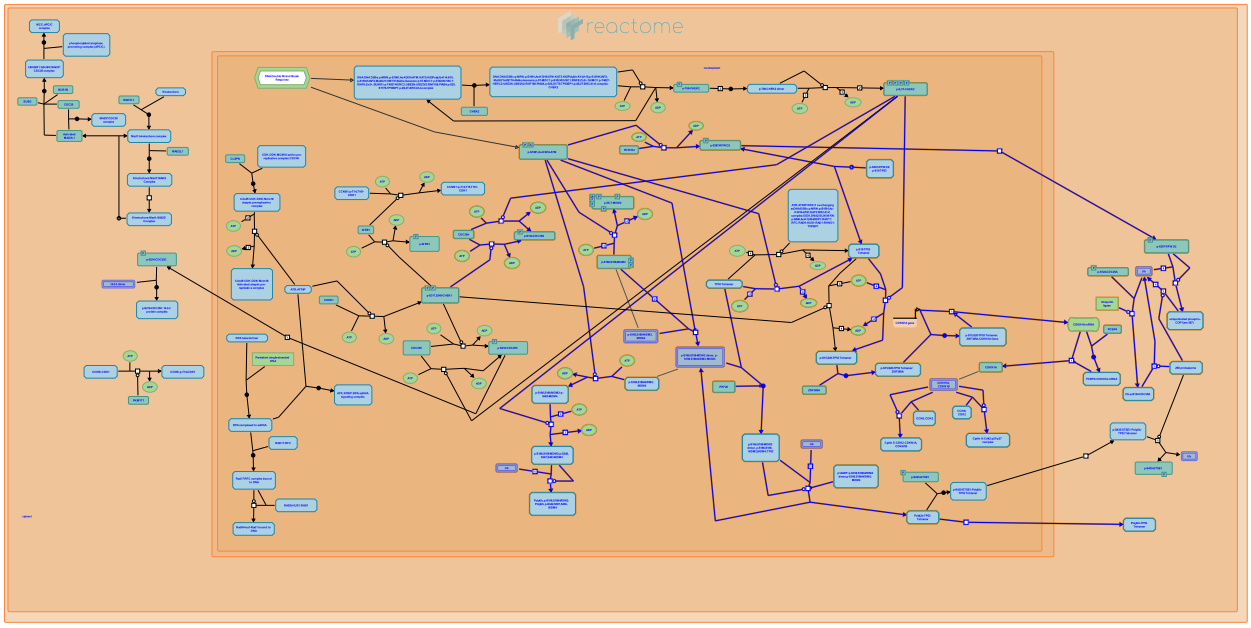
Editions

2005-01-01	Authored	O'Donnell, M., Walworth, N., Hoffmann, I., Khanna, KK., Yen, TJ.
2013-11-25	Edited	Matthews, L.
2024-03-06	Reviewed	Sanchez, Y., Knudsen, E., Hardwick, KG.

G1/S DNA Damage Checkpoints ↗

Location: Cell Cycle Checkpoints

Stable identifier: R-HSA-69615



In the G1 phase there are two types of DNA damage responses, the p53-dependent and the p53-independent pathways. The p53-dependent responses inhibit CDKs through the up-regulation of genes encoding CKIs mediated by the p53 protein, whereas the p53-independent mechanisms inhibit CDKs through the inhibitory T14Y15 phosphorylation of Cdk2. Failure of DNA damage checkpoints in G1 leads to mutagenic replication of damaged templates and other replication defects.

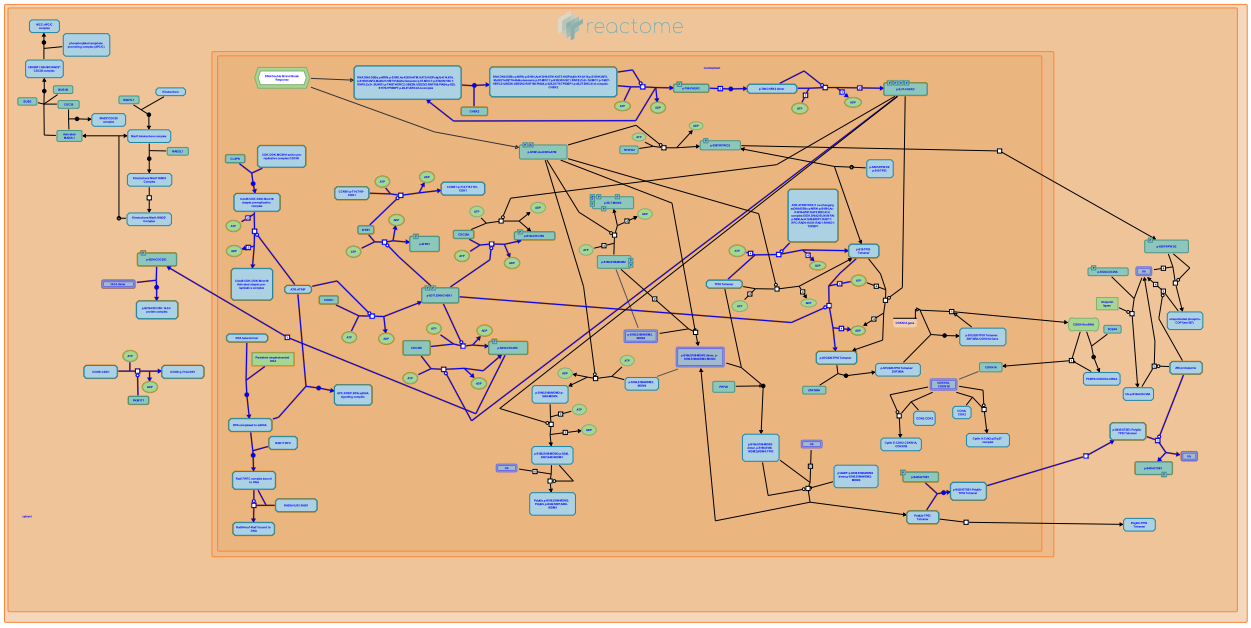
Editions

2003-06-05	Authored	Hoffmann, I., Khanna, KK.

G2/M Checkpoints ↗

Location: Cell Cycle Checkpoints

Stable identifier: R-HSA-69481



G2/M checkpoints include the checks for damaged DNA, unreplicated DNA, and checks that ensure that the genome is replicated once and only once per cell cycle. If cells pass these checkpoints, they follow normal transition to the M phase. However, if any of these checkpoints fail, mitotic entry is prevented by specific G2/M checkpoint events.

The G2/M checkpoints can fail due to the presence of unreplicated DNA or damaged DNA. In such instances, the cyclin-dependent kinase, Cdc2(Cdk1), is maintained in its inactive, phosphorylated state, and mitotic entry is prevented. Events that ensure that origins of DNA replication fire once and only once per cell cycle are also an example of a G2/M checkpoint.

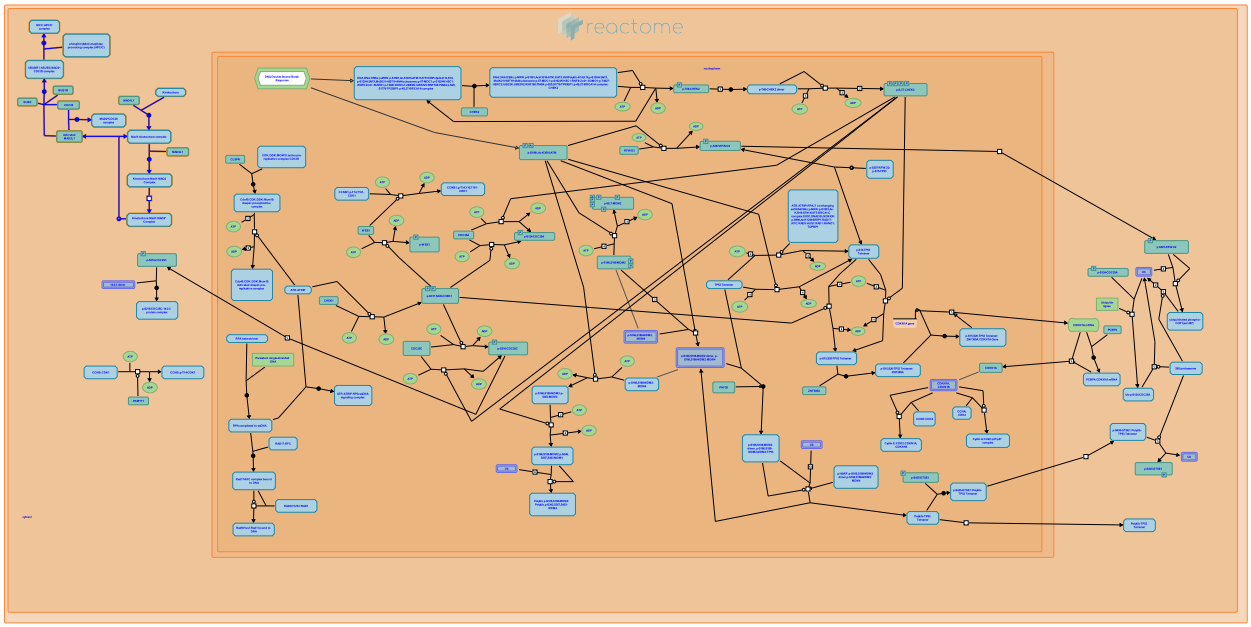
In the event of high levels of DNA damage, the cells may also be directed to undergo apopotosis (not covered).

Mitotic Spindle Checkpoint ↗

Location: Cell Cycle Checkpoints

Stable identifier: R-HSA-69618

Compartments: cytosol



The mitotic checkpoint or spindle assembly checkpoint is an evolutionarily conserved mechanism that ensures that cells with misaligned chromosomes do not exit mitosis and divide to form aneuploid cells. As chromosome attachment to the spindle microtubules is a stochastic process, not all chromosomes achieve alignment at the spindle equator at the same time. It is therefore essential that even a single unaligned chromosome can prevent the onset of anaphase. The ability of the checkpoint to monitor the status of chromosome alignment is achieved by assigning checkpoint proteins to the kinetochore, a macromolecular complex that resides at centromeres of chromosomes that establishes connections with spindle microtubules.

The checkpoint proteins monitor, in an unknown way, the mechanical activities between kinetochore-associated proteins and microtubules. Defects in mechanical activities at kinetochores activate the resident checkpoint proteins to initiate a signal that is amplified throughout the cell that ultimately prevents the activation of the proteolytic process that is required for sister chromatid separation and the onset of anaphase. Kinetochores of unaligned chromosomes differ from those of aligned chromosomes in two ways. Kinetochores of aligned chromosomes are saturated with between 20 to 30 microtubules. In addition, poleward directed forces exerted at each sister kinetochore generates tension between them. Unaligned kinetochores on the other hand, are not saturated with microtubules and are not under tension. The mitotic checkpoint detects the presence of unattached kinetochores rather than monitoring for the presence of attached kinetochores. Consequently, unattached kinetochores emit an inhibitory signal that inhibits the biochemical events that are required to initiate the onset of anaphase. The mechanism by which this inhibitory signal is generated at unattached kinetochores has not precisely been determined but the signal is generated as a result of the lack of microtubule occupancy and kinetochore tension. A single unattached kinetochore is capable of preventing cells from exiting mitosis. The mitotic checkpoint provides a way for a localized defect to affect the global biochemical status of the cell. In principle, the signal that is generated at an unattached kinetochore diffuses throughout the cell to affect its target. There are currently two models for how this is achieved. One model is based on the observation that the Mad2 checkpoint protein binds and is rapidly released from unattached kinetochores. The kinetochore is believed to act as a catalyst that converts Mad2 into an inhibitory state that diffuses throughout the cell upon its release from the kinetochore. A second model proposes that the signal is amplified by a kinase cascade much like a conventional signal transduction pathway. This kinase cascade is believed to be comprised of the checkpoint kinases, hBUBR1, hBUB1, hMPS1.

Literature references

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Editions

2004-05-05	Authored	Yen, TJ.

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