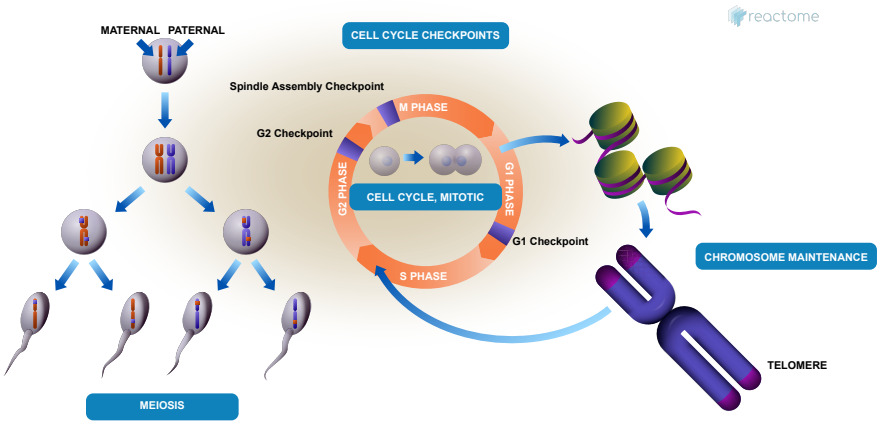
Cell Cycle



Bolcun-Filas, E., Bosco, G., Cohen, PE., Gillespie, ME., Gopinathrao, G., Grana, X., Hardwick, KG., Hoffmann, I., Holloway, JK., Joshi-Tope, G., Khanna, KK., Knudsen, E., Lyndaker, A., MacPherson, D., Manfredi, JJ., Matthews, L., May, B., O'Donnell, M., Orlic-Milacic, M., Sanchez, Y., Schimenti, JC., Strong, E., Walworth, N., Yen, TJ.

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01/05/2025

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., Fabregat, A., Fabregat, A., Fabregat, A., Fabregat, A., Fabregat, A. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Sidiropoulos, K., Sidiropoulos, K., Sidiropoulos, K., Sidiropoulos, K., Sidiropoulos, K. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Fabregat, A., Fabregat, A., Fabregat, A., Fabregat, A., Fabregat, A. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

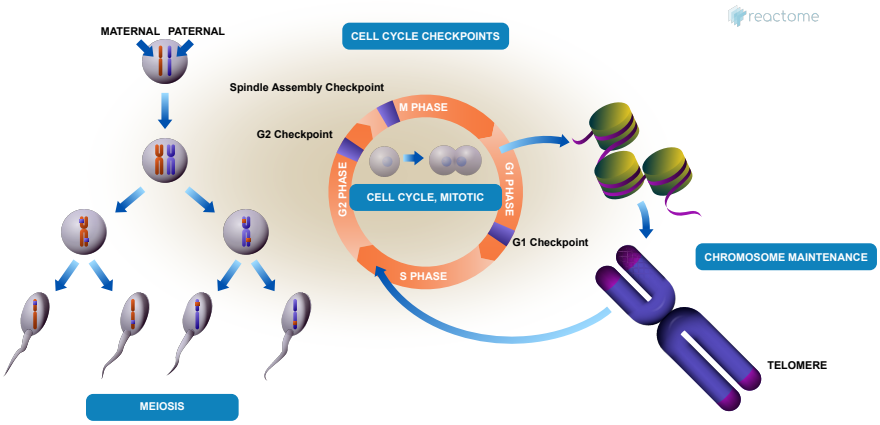
Fabregat, A., Fabregat, A., Fabregat, A., Fabregat, A., Fabregat, A., Fabregat, A. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 92

This document contains 5 pathways (see Table of Contents)

Cell Cycle ↗

Stable identifier: R-HSA-1640170



The replication of the genome and the subsequent segregation of chromosomes into daughter cells are controlled by a series of events collectively known as the **cell cycle**. DNA replication is carried out during a discrete temporal period known as the S (synthesis)-phase, and chromosome segregation occurs during a massive reorganization to cellular architecture at mitosis. Two gap-phases separate these major cell cycle events: G1 between mitosis and S-phase, and G2 between S-phase and mitosis. In the development of the human body, cells can exit the cell cycle for a period and enter a quiescent state known as G0, or terminally differentiate into cells that will not divide again, but undergo morphological development to carry out the wide variety of specialized functions of individual tissues.

A family of protein serine/threonine kinases known as the cyclin-dependent kinases (CDKs) controls progression through the cell cycle. As the name suggests, the activity of the catalytic subunit is dependent on binding to a cyclin partner. The human genome encodes several cyclins and several CDKs, with their names largely derived from the order in which they were identified. The oscillation of cyclin abundance is one important mechanism by which these enzymes phosphorylate key substrates to promote events at the relevant time and place. Additional post-translational modifications and interactions with regulatory proteins ensure that CDK activity is precisely regulated, frequently confined to a narrow window of activity.

In addition, genome integrity in the cell cycle is maintained by the action of a number of signal transduction pathways, known as **cell cycle checkpoints**, which monitor the accuracy and completeness of DNA replication during S phase and the orderly chromosomal condensation, pairing and partition into daughter cells during mitosis.

Replication of telomeric DNA at the ends of human chromosomes and packaging of their centromeres into chromatin are two aspects of **chromosome maintenance** that are integral parts of the cell cycle.

Meiosis is the specialized form of cell division that generates haploid gametes from diploid germ cells, associated with recombination (exchange of genetic material between chromosomal homologs).

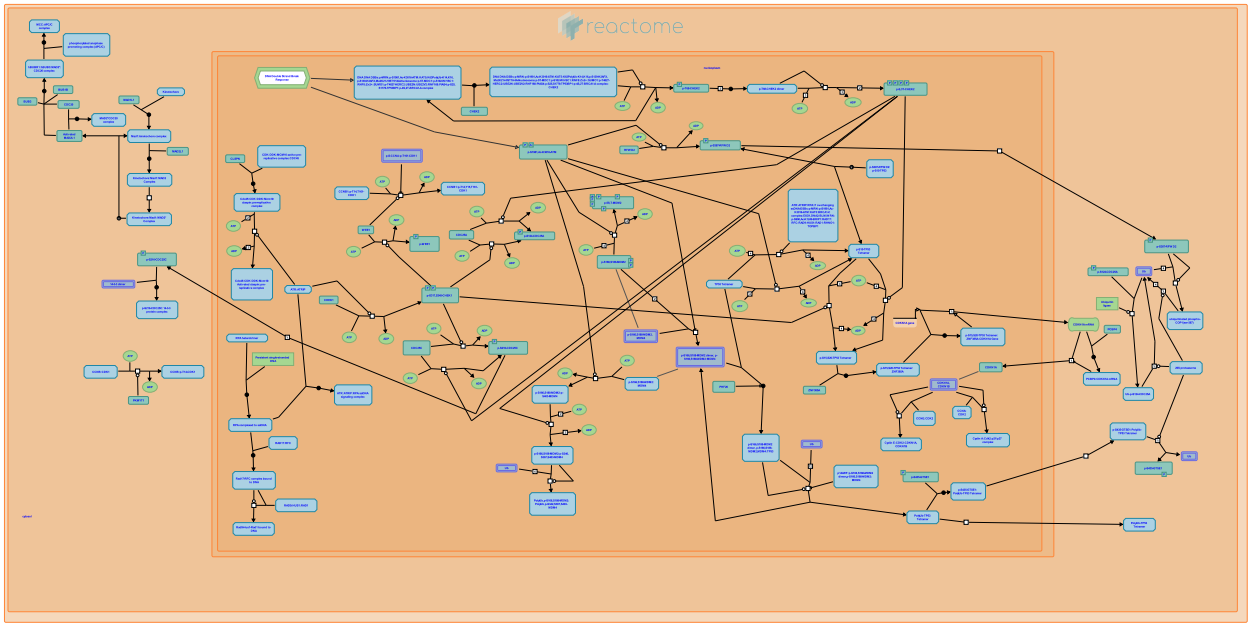
Editions

2011-10-10	Edited	Matthews, L.

Cell Cycle Checkpoints ↗

Location: Cell Cycle

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.

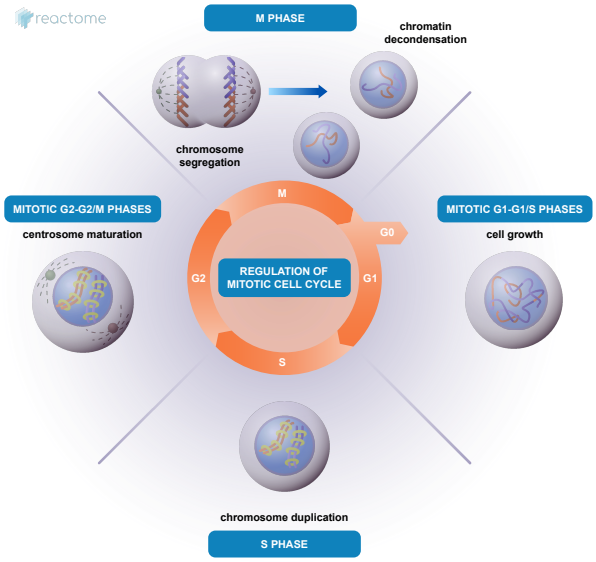
Editions

2005-01-01	Authored	O'Donnell, M., Walworth, N., Hoffmann, I., Khanna, KK., Yen, TJ.
2013-11-25	Edited	Matthews, L.
2025-03-04	Reviewed	Sanchez, Y., Knudsen, E., Hardwick, KG.

Cell Cycle, Mitotic ↗

Location: Cell Cycle

Stable identifier: R-HSA-69278



The events of replication of the genome and the subsequent segregation of chromosomes into daughter cells make up the cell cycle. DNA replication is carried out during a discrete temporal period known as the S (synthesis)-phase, and chromosome segregation occurs during a massive reorganization of cellular architecture at mitosis. Two gap-phases separate these cell cycle events: G1 between mitosis and S-phase, and G2 between S-phase and mitosis. Cells can exit the cell cycle for a period and enter a quiescent state known as G0, or terminally differentiate into cells that will not divide again, but undergo morphological development to carry out the wide variety of specialized functions of individual tissues.

A family of protein serine/threonine kinases known as the cyclin-dependent kinases (CDKs) controls progression through the cell cycle. As the name suggests, the kinase activity of the catalytic subunits is dependent on binding to cyclin partners, and control of cyclin abundance is one of several mechanisms by which CDK activity is regulated throughout the cell cycle.

A complex network of regulatory processes determines whether a quiescent cell (in G0 or early G1) will leave this state and initiate the processes to replicate its chromosomal DNA and divide. This regulation, during the **Mitotic G1-G1/S phases** of the cell cycle, centers on transcriptional regulation by the DREAM complex, with major roles for D and E type cyclin proteins.

Chromosomal DNA synthesis occurs in the **S phase**, or the synthesis phase, of the cell cycle. The cell duplicates its hereditary material, and two copies of each chromosome are formed. A key aspect of the **regulation of DNA** replication is the assembly and modification of a pre-replication complex assembled on ORC proteins.

Mitotic G2-G2/M phases encompass the interval between the completion of DNA synthesis and the beginning of mitosis. During G2, the cytoplasmic content of the cell increases. At G2/M transition, duplicated centrosomes mature and separate and CDK1:cyclin B complexes become active, setting the stage for spindle assembly and chromosome condensation at the start of mitotic **M phase**. Mitosis, or M phase, results in the generation of two daughter cells each with a complete diploid set of chromosomes. Events of the **M/G1 transition**, progression out of mitosis and division of the cell into two daughters (cytokinesis) are regulated by the Anaphase Promoting Complex.

The Anaphase Promoting Complex or Cyclosome (APC/C) plays additional roles in **regulation of the mitotic cell cycle**, insuring the appropriate length of the G1 phase. The APC/C itself is regulated by phosphorylation and interactions with checkpoint proteins.

Editions

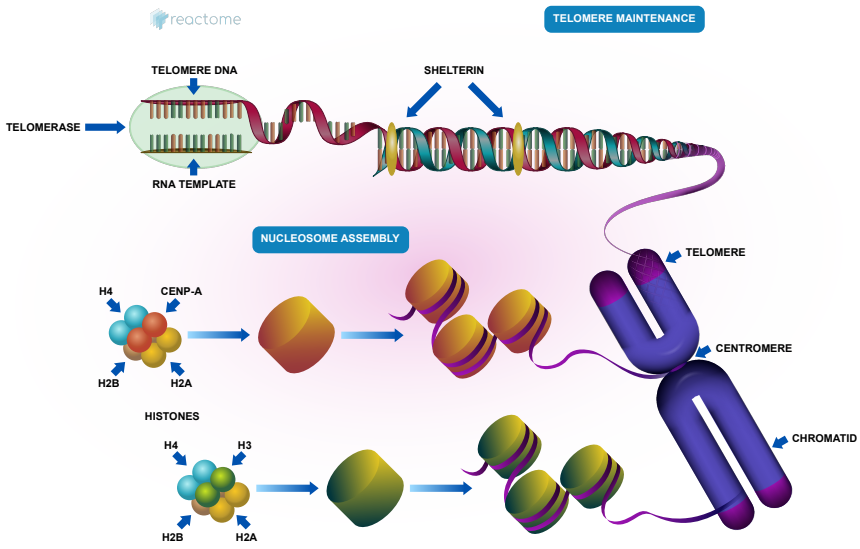
2005-01-01	Authored	O'Donnell, M., Walworth, N., Bosco, G.
2010-01-19	Revised	Matthews, L.
2011-06-15	Reviewed	Grana, X.
2011-08-25	Reviewed	MacPherson, D.
2011-08-27	Revised	Orlic-Milacic, M.
2013-11-25	Edited	Gopinathrao, G., Matthews, L.
2018-07-10	Reviewed	Manfredi, JJ.

Chromosome Maintenance ↗

Location: Cell Cycle

Stable identifier: R-HSA-73886

Compartments: nuclear envelope, nucleoplasm



Maintenance of chromosomal organization is critical for stable chromosome function. Two aspects of maintenance annotated in Reactome are centromeric chromatin assembly outside the context of DNA replication, involving **nucleosome assembly** with the histone H3 variant CenH3 (also called CENP-A), and the **maintenance of telomeres**, protein-DNA complexes at the ends of linear chromosomes that are important for genome stability.

Editions

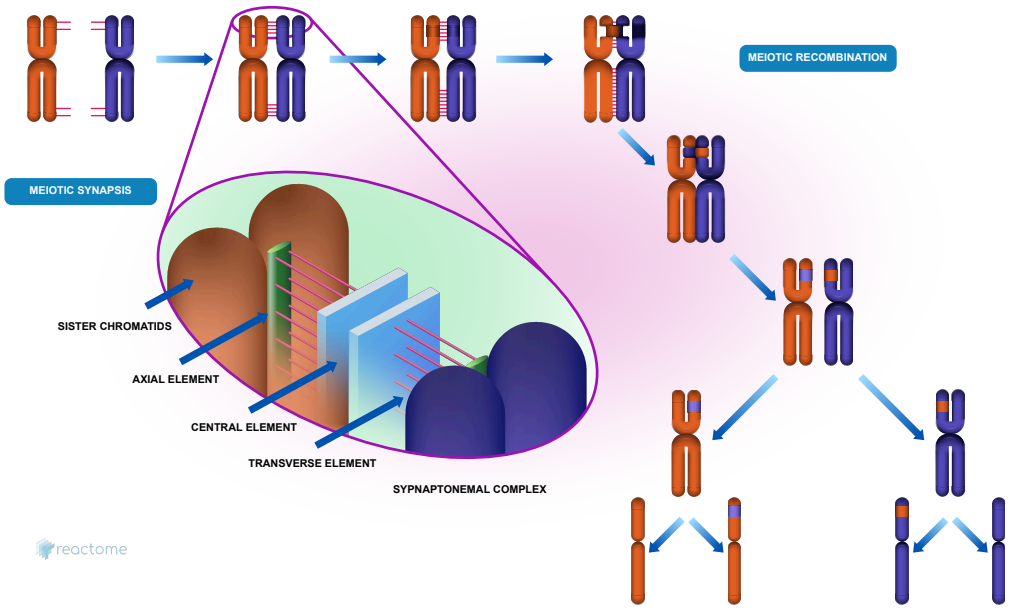
2025-03-04	Authored	Gillespie, ME.
2025-03-04	Edited	Joshi-Tope, G.

Meiosis

Location: Cell Cycle

Stable identifier: R-HSA-1500620

Compartments: nuclear envelope, nucleoplasm



During meiosis the replicated chromosomes of a single diploid cell are segregated into 4 haploid daughter cells by two successive divisions, meiosis I and meiosis II. In meiosis I, the distinguishing event of meiosis, pairs (bivalents) of homologous chromosomes in the form of sister chromatids are paired by **synapsis** along their regions of homologous DNA (Yang and Wang 2009), and then segregated, resulting in haploid daughters containing sister chromatids paired at their centromeres (Cohen et al. 2006, Handel and Schimenti 2010). The sister chromatids are then separated and segregated during meiosis II.

Recombination between chromosomal homologues but not between sister chromatids occurs during prophase of meiosis I (Inagaki et al. 2010). Though hundreds of recombination events are initiated, most are resolved without crossovers and only tens proceed to become crossovers. In mammals recombination events are required between homologues for normal pairing, synapsis, and segregation.

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Editions

2011-02-05	Reviewed	Schimenti, JC., Cohen, PE., Holloway, JK.
2011-02-25	Reviewed	Bolcun-Filas, E., Lyndaker, A., Strong, E.
2011-08-19	Authored, Edited	May, B.

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