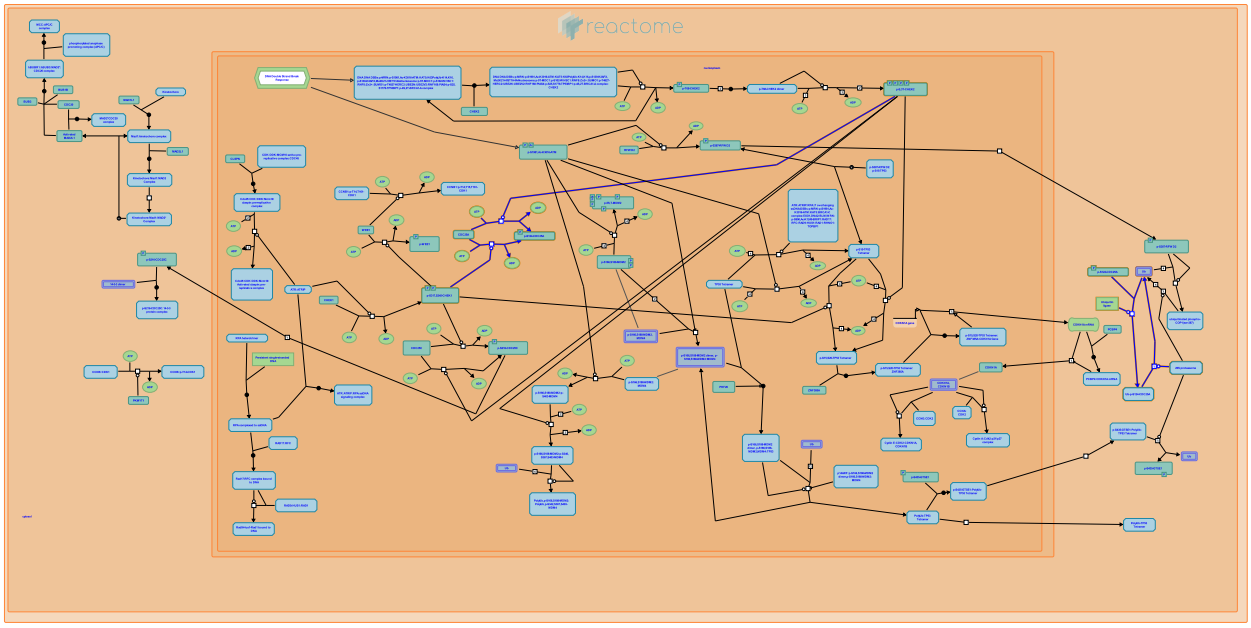
p53-Independent G1/S DNA damage check-point



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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. ↗

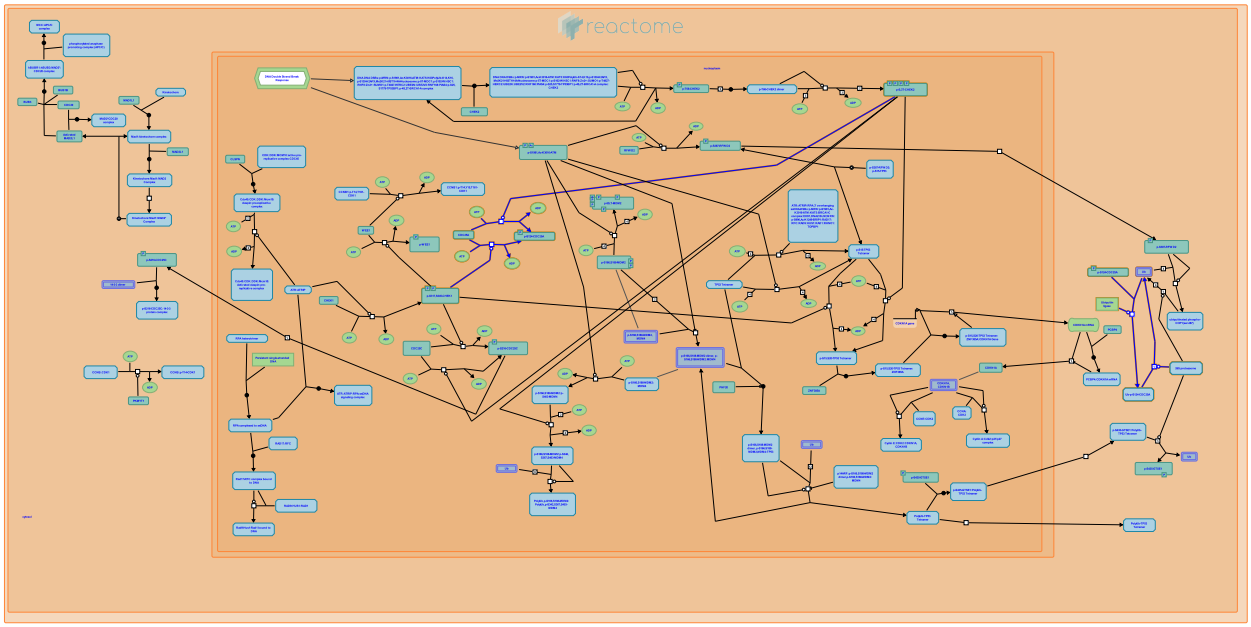
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 2 pathways (see Table of Contents)

p53-Independent G1/S DNA damage checkpoint ↗

Stable identifier: R-HSA-69613



The G1 arrest induced by DNA damage has been ascribed to the transcription factor and tumor suppressor protein p53. To be effective within minutes after DNA damage, induction of the G1 block should exploit transcription and protein synthesis independent mechanisms.

Upon exposure to ultraviolet light (UV) or ionizing radiation (IR), the abundance and activity of a protein, Cdc25A, rapidly decreases; this DNA damage response is not dependent on p53. The rapid destruction of Cdc25A phosphatase prevents entry of a cell into S-phase, by maintaining the CyclinE:Cdk2 complexes in their T14Y15 phosphorylated form.

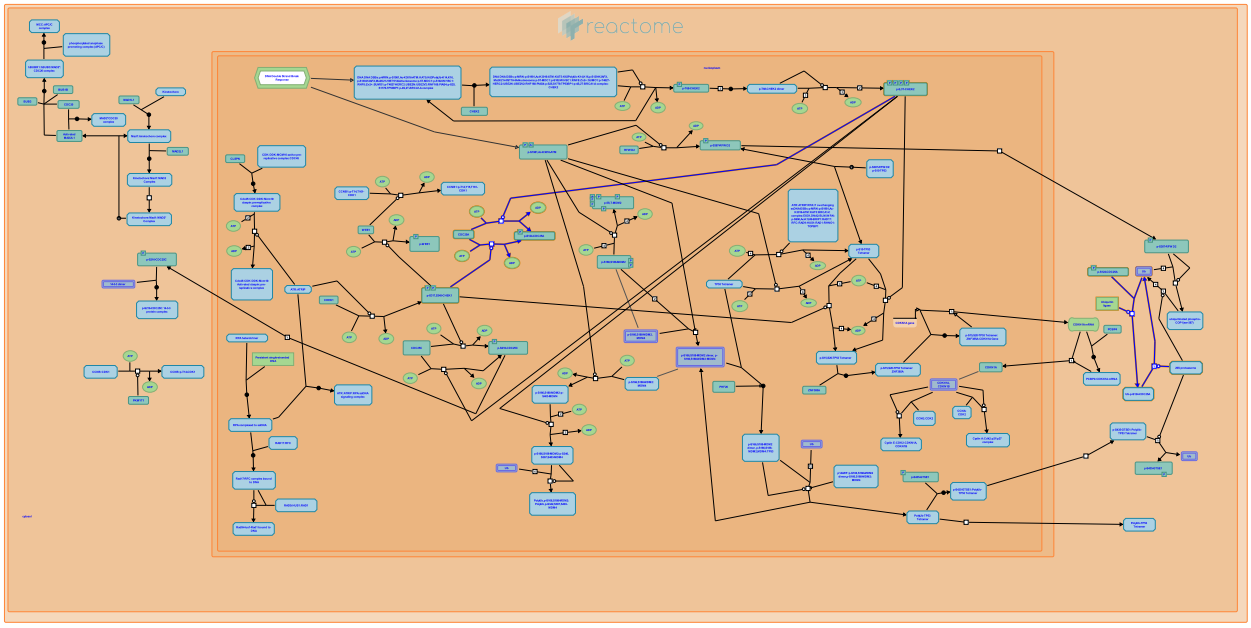
Literature references

Syljuâsen, RG., Lukas, J., Welcker, M., Lukas, C., Mailand, N. (2000). Rapid destruction of human Cdc25A in response to DNA damage. *Science, 288*, 1425-9. ↗

p53-Independent DNA Damage Response ↗

Location: p53-Independent G1/S DNA damage checkpoint

Stable identifier: R-HSA-69610



In response to DNA damage due to exposure to ultraviolet light or to ionizing radiation, Cdc25A is phosphorylated by Chk1 or Chk2. The phosphorylation of Cdc25A at ser-123, in response to DNA damage from ionizing radiation is a signal for ubiquitination and subsequent degradation of Cdc25A. The destruction of Cdc25A prevents the normal G1/S transition. Cdc25A is required for the activation of the Cyclin E:Cdk2 complexes via dephosphorylation.

Chk1 is activated in response to DNA damage due to uv light. However, the phosphorylation occurs at a different site.

Literature references

Lukas, J., Syljuåsen, RG., Mailand, N. (2001). The ATM-Chk2-Cdc25A checkpoint pathway guards against radioresistant DNA synthesis. *Nature, 410*, 842-7. ↗

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