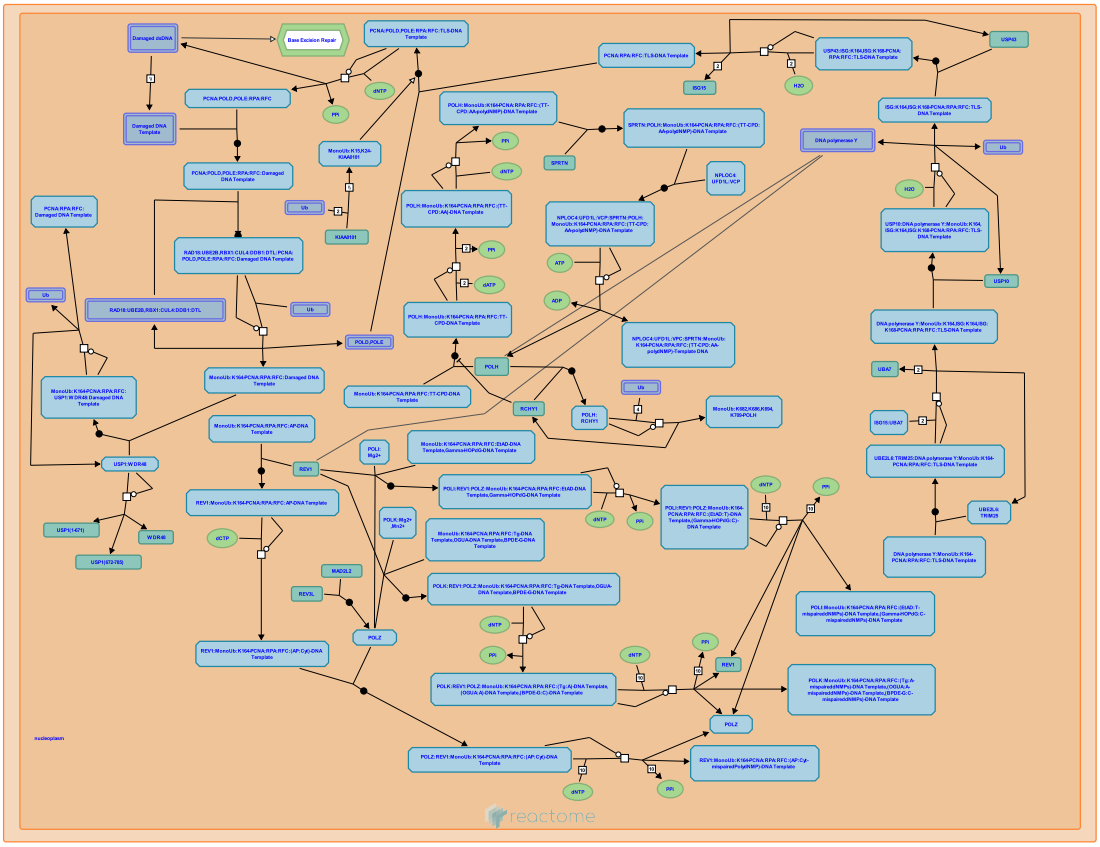
DNA Damage Bypass



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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.

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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. ↗

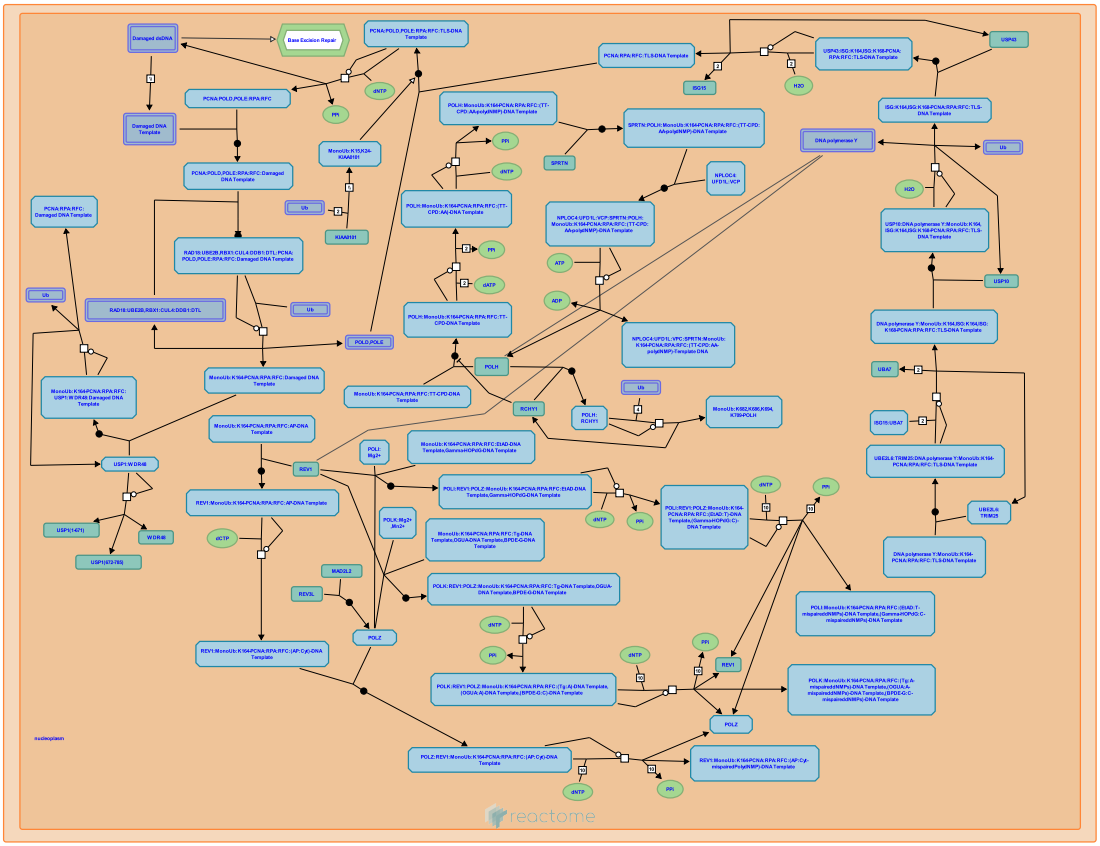
Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

DNA Damage Bypass ↗

Stable identifier: R-HSA-73893

Compartments: nucleoplasm



In addition to various processes for removing lesions from the DNA, cells have developed specific mechanisms for tolerating unrepaired damage during the replication of the genome. These mechanisms are collectively called DNA damage bypass pathways. The Y family of DNA polymerases plays a key role in DNA damage bypass.

Y family DNA polymerases, REV1, POLH (DNA polymerase eta), POLK (DNA polymerase kappa) and POLI (DNA polymerase iota), as well as the DNA polymerase zeta (POLZ) complex composed of REV3L and MAD2L2, are able to carry out translesion DNA synthesis (TLS) or replicative bypass of damaged bases opposite to template lesions that arrest high fidelity, highly processive replicative DNA polymerase complexes delta (POLD) and epsilon (POLE). REV1, POLH, POLK, POLI and POLZ lack 3'->5' exonuclease activity and exhibit low fidelity and weak processivity. The best established TLS mechanisms are annotated here. TLS details that require substantial experimental clarification have been omitted. For recent and past reviews of this topic, please refer to Lehmann 2000, Friedberg et al. 2001, Zhu and Zhang 2003, Takata and Wood 2009, Ulrich 2011, Saugar et al. 2014.

Literature references

Saugar, I., Tercero, JA., Ortiz-Bazán, MA. (2014). Tolerating DNA damage during eukaryotic chromosome replication . *Exp. Cell Res., 329*, 170-177. ↗

Ulrich, HD. (2011). Timing and spacing of ubiquitin-dependent DNA damage bypass. *FEBS Lett., 585*, 2861-7. ↗

Lehmann, AR. (2000). Replication of UV-damaged DNA: new insights into links between DNA polymerases, mutagenesis and human disease. *Gene, 253*, 1-12. ↗

Kisker, C., Friedberg, EC., Fischhaber, PL. (2001). Error-prone DNA polymerases: novel structures and the benefits of infidelity. *Cell, 107*, 9-12. ↗

Wood, RD., Takata, K. (2009). Bypass specialists operate together. *EMBO J., 28*, 313-4. ↗

Editions

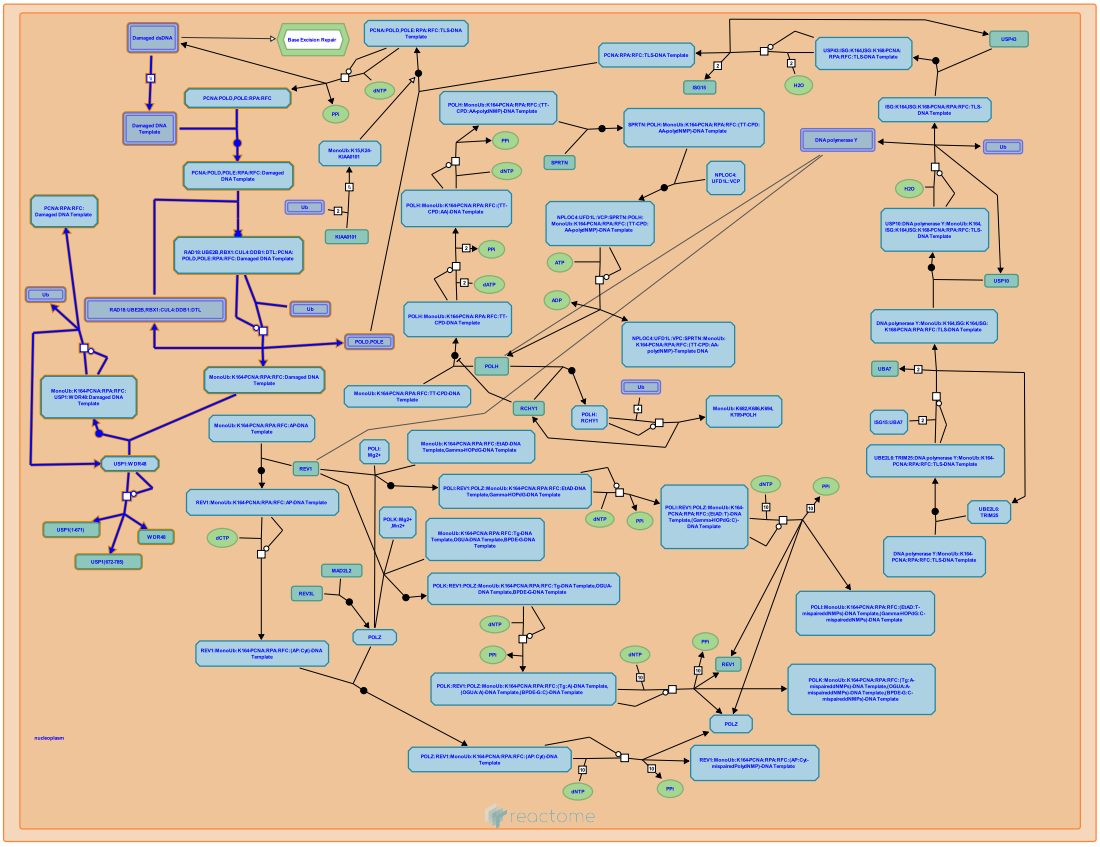
2004-02-02	Authored	Gopinathrao, G.
2014-12-11	Authored, Edited, Revised	Orlic-Milacic, M.
2015-01-07	Reviewed	Borowiec, JA.

Recognition of DNA damage by PCNA-containing replication complex ↗

Location: DNA Damage Bypass

Stable identifier: R-HSA-110314

Compartments: nucleoplasm



Damaged double strand DNA (dsDNA) cannot be successfully used as a template by replicative DNA polymerase delta (POLD) and epsilon (POLE) complexes (Hoege et al. 2002). When the replication complex composed of PCNA, RPA, RFC and POLD or POLE stalls at a DNA damage site, PCNA becomes monoubiquitinated by RAD18 bound to UBE2B (RAD6). POLD or POLE dissociate from monoubiquitinated PCNA, while Y family DNA polymerases - REV1, POLH (DNA polymerase eta), POLK (DNA polymerase kappa) and POLI (DNA polymerase iota) - bind monoubiquitinated PCNA through their ubiquitin binding and PCNA binding motifs, resulting in a polymerase switch and initiation of translesion synthesis (TLS) (Hoege et al. 2002, Friedberg et al. 2005).

Literature references

Friedberg, EC., Lehmann, AR., Fuchs, RP. (2005). Trading places: how do DNA polymerases switch during translesion DNA synthesis?. *Mol. Cell, 18,* 499-505. ↗

Moldovan, GL., Hoege, C., Pfander, B., Pyrowolakis, G., Jentsch, S. (2002). RAD6-dependent DNA repair is linked to modification of PCNA by ubiquitin and SUMO. *Nature, 419,* 135-41. ↗

Editions

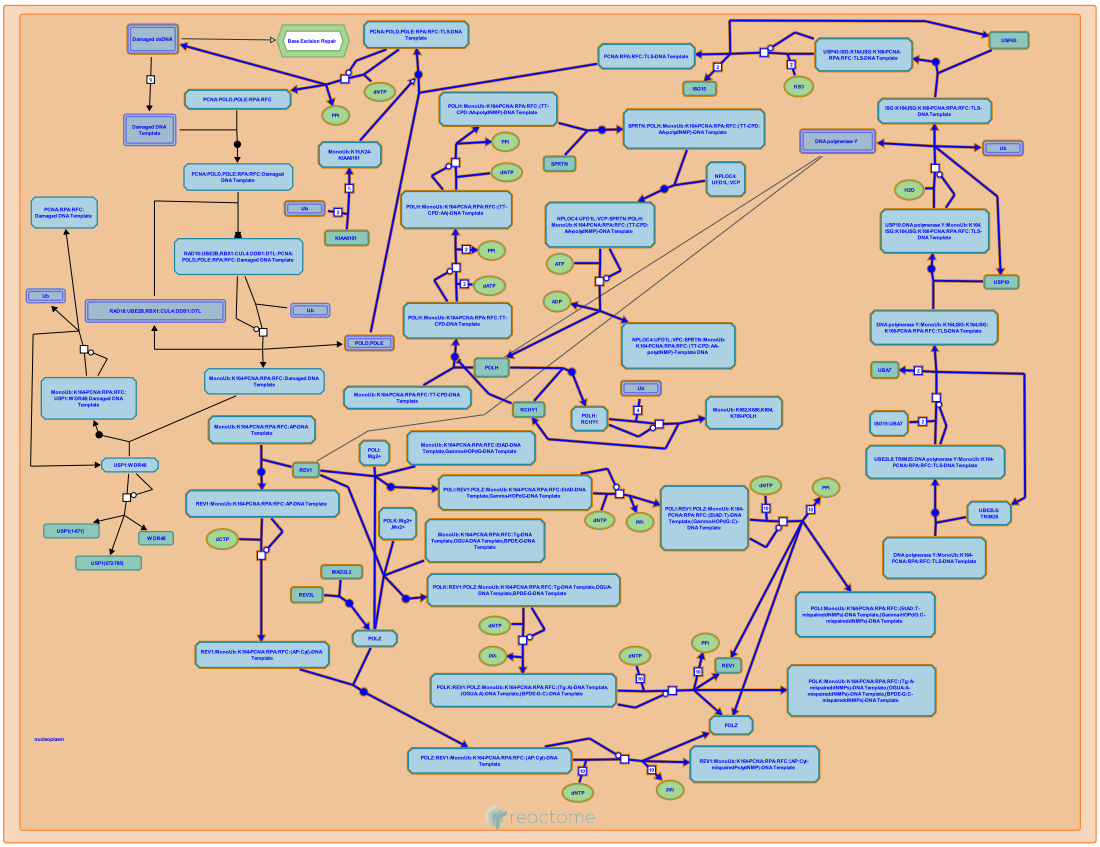
2014-12-11	Authored, Edited	Orlic-Milacic, M.
2015-01-07	Reviewed	Borowiec, JA.

Translesion synthesis by Y family DNA polymerases bypasses lesions on DNA template ↗

Location: DNA Damage Bypass

Stable identifier: R-HSA-110313

Compartments: nucleoplasm



Ubiquitous environmental and endogenous genotoxic agents cause DNA lesions that can interfere with normal DNA metabolism including DNA replication, eventually resulting in mutations that lead to carcinogenesis and/or cell death. Cells possess repair mechanisms like nucleotide excision and base excision repair pathways to maintain the integrity of the genome. However, some types of lesions are repaired very inefficiently and others may not be recognized and repaired before the lesion-containing DNA undergoes DNA replication. To prevent acute cell death through arrested DNA replication at unrepaired lesions, cells have a mechanism, referred to as translesion synthesis (TLS), which allows DNA synthesis to proceed past lesions. TLS depends on the Y family of DNA polymerases (Lindahl and Wood 1999, Masutani et al. 2000, Yang 2014).

Literature references

Lindahl, T., Wood, RD. (1999). Quality control by DNA repair. *Science, 286*, 1897-905. ↗

Yang, W. (2014). An overview of Y-Family DNA polymerases and a case study of human DNA polymerase ?. *Biochemistry, 53*, 2793-803. ↗

Kusumoto, R., Iwai, S., Masutani, C., Hanaoka, F. (2000). Mechanisms of accurate translesion synthesis by human DNA polymerase eta. *EMBO J, 19*, 3100-9. ↗

Editions

2004-01-29	Authored	Gopinathrao, G.
2014-12-11	Edited, Revised	Orlic-Milacic, M.
2015-01-07	Reviewed	Borowiec, JA.

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