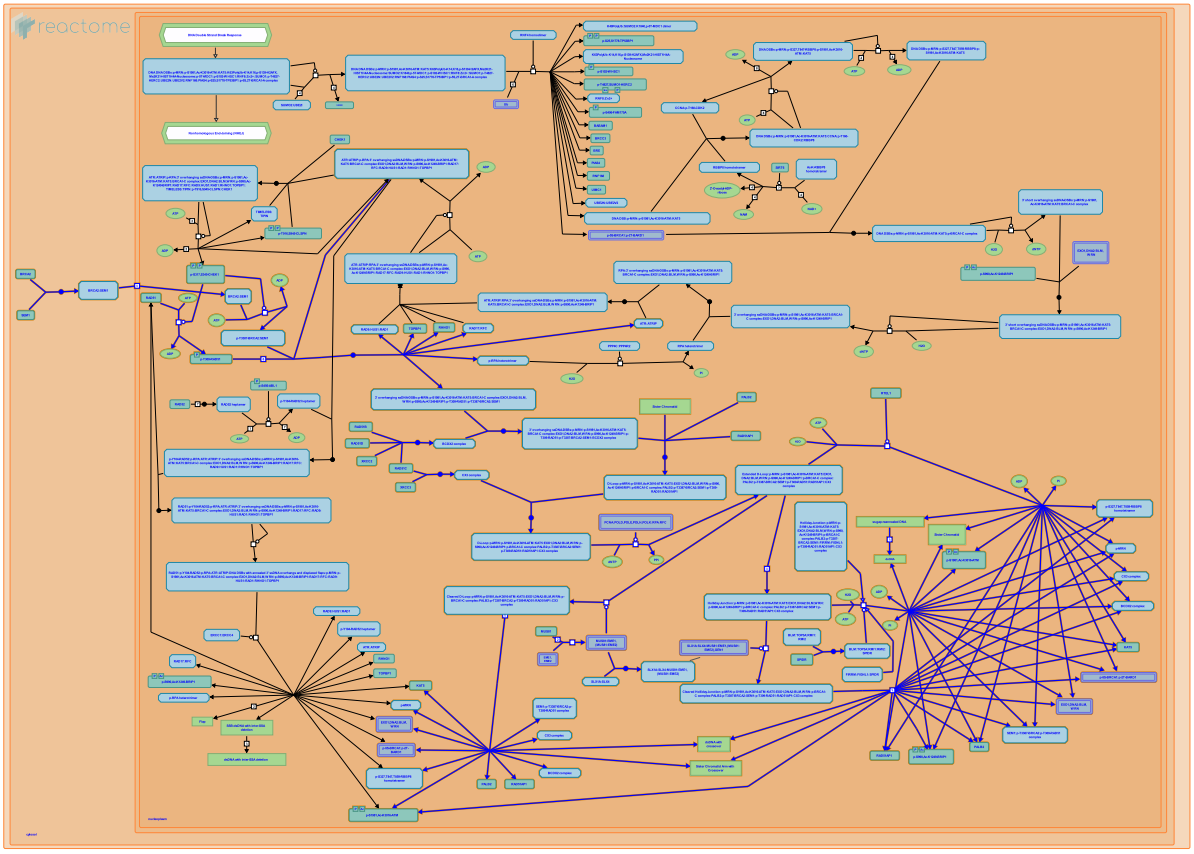
HDR through Homologous Recombination (HRR)



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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.

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. ↗

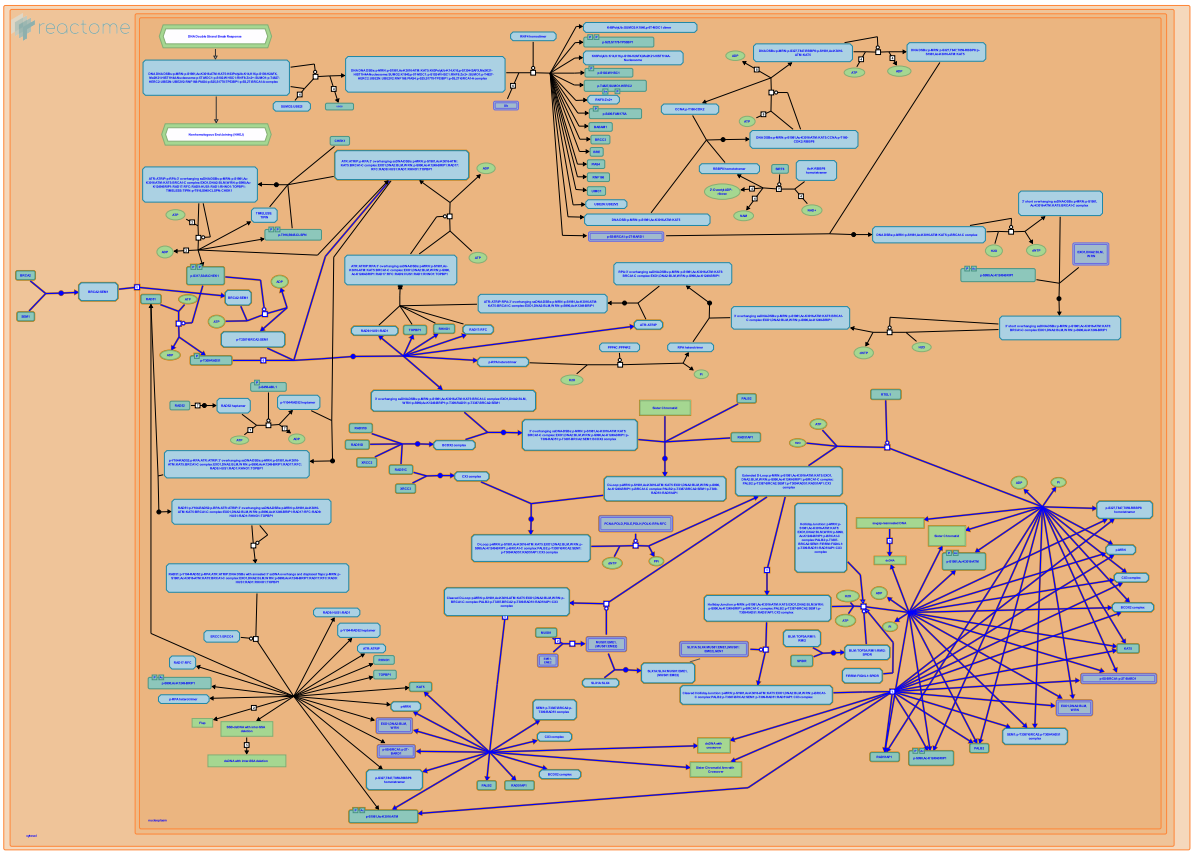
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 3 pathways and 1 reaction (see Table of Contents)

HDR through Homologous Recombination (HRR) ↗

Stable identifier: R-HSA-5685942



Homology directed repair (HDR) through homologous recombination is known as homologous recombination repair (HRR). HRR occurs after extensive resection of DNA double-strand break (DSB) ends, which creates long 3'-ssDNA overhangs. RAD51 coats 3'-ssDNA overhangs in a BRCA2-controlled fashion, creating invasive RAD51 nucleofilaments. The RAD51 nucleofilament invades a sister chromatid DNA duplex, leading to D-loop formation. After the D-loop is extended by DNA repair synthesis, the resulting recombination intermediates in the form of extended D-loops or double Holliday junctions can be resolved through crossover- or non-crossover-generating processes (reviewed by Ciccia and Elledge 2010).

Literature references

Elledge, SJ., Ciccia, A. (2010). The DNA damage response: making it safe to play with knives. *Mol. Cell, 40*, 179-204. ↗

Editions

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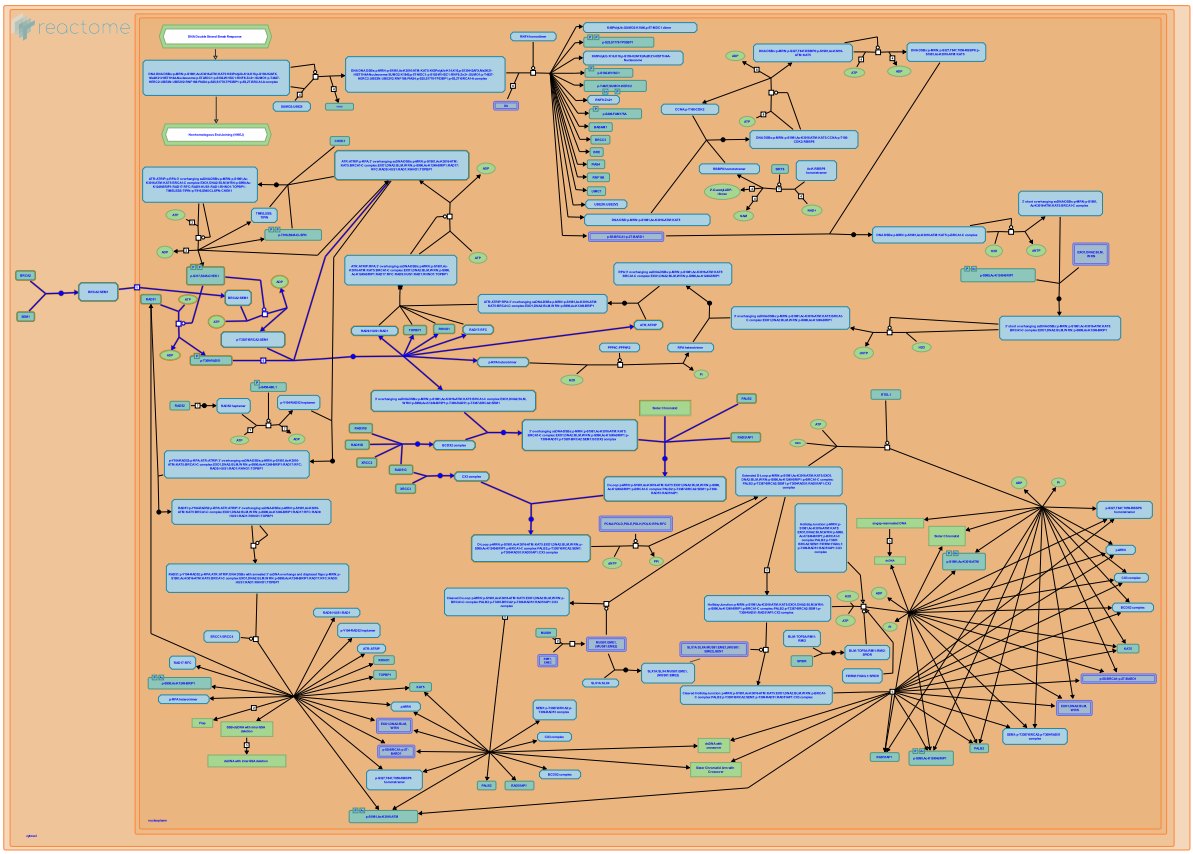
Homologous DNA Pairing and Strand Exchange ↗

Location: HDR through Homologous Recombination (HRR)

Stable identifier: R-HSA-5693579

Compartments: nucleoplasm



The presynaptic phase of homologous DNA pairing and strand exchange begins with the displacement of RPA from 3'-ssDNA overhangs created by extensive resection of DNA double-strand break (DSB) ends. RPA is displaced by the joint action of RAD51 and BRCA2. BRCA2 nucleates RAD51 on 3'-ssDNA overhangs, leading to formation of invasive RAD51 nucleofilaments which are stabilized by the BCDX2 complex (RAD51B:RAD51C:RAD51D:XRCC2). Stable synaptic pairing between recombining DNA molecules involves the invasion of the homologous sister chromatid duplex DNA by the RAD51 nucleofilament and base-pairing between the invading ssDNA and the complementary sister chromatid DNA strand, while the non-complementary strand of the sister chromatid DNA duplex is displaced. This results in the formation of a D-loop structure (Sung et al., 2003). PALB2 and RAD51AP1 synergistically stimulate RAD51 recombinase activity and D-loop formation. PALB2 simultaneously interacts with RAD51, BRCA2 and RAD51AP1 (Modesti et al. 2007, Wiese et al. 2007, Buisson et al. 2010, Dray et al. 2010). PALB2 also interacts with BRCA1, and this interaction fine-tunes the localization of BRCA2 and RAD51 at DNA DSBs (Zhang et al. 2009, Sy et al. 2009). The CX3 complex, composed of RAD51C and XRCC3, binds D-loop structures through interaction with PALB2 and may be involved in the resolution of Holliday junctions (Chun et al. 2013, Park et al. 2014).

While RAD52 promotes formation of invasive RAD51 nucleofilaments in yeast, human BRCA2 performs this function, while human RAD52 regulates single strand annealing (SSA) (reviewed by Ciccia and Elledge 2010).

Literature references

Sy, SM., Yu, X., Egelman, E., Etchin, J., Wiese, C., Tsai, MS. et al. (2010). Enhancement of RAD51 recombinase activity by the tumor suppressor PALB2. *Nat. Struct. Mol. Biol., 17,* 1255-9. ↗

Ye, L., Xia, B., Cai, H., Ma, J., Wu, J., Yu, X. et al. (2009). PALB2 links BRCA1 and BRCA2 in the DNA-damage response. *Curr. Biol., 19,* 524-9. ↗

Sy, SM., Huen, MS., Chen, J. (2009). PALB2 is an integral component of the BRCA complex required for homologous recombination repair. *Proc Natl Acad Sci U S A, 106*, 7155-60. ↗

Buechelmaier, ES., Powell, SN., Chun, J. (2013). Rad51 paralog complexes BCDX2 and CX3 act at different stages in the BRCA1-BRCA2-dependent homologous recombination pathway. *Mol. Cell. Biol., 33*, 387-95. ↗

Folta-Stogniew, E., Radding, CM., Gupta, RC. (1999). Human Rad51 protein can form homologous joints in the absence of net strand exchange. *J Biol Chem, 274*, 1248-56. ↗

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2003-11-23	Authored	Matthews, L.
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2015-06-12	Reviewed	Borowiec, JA.

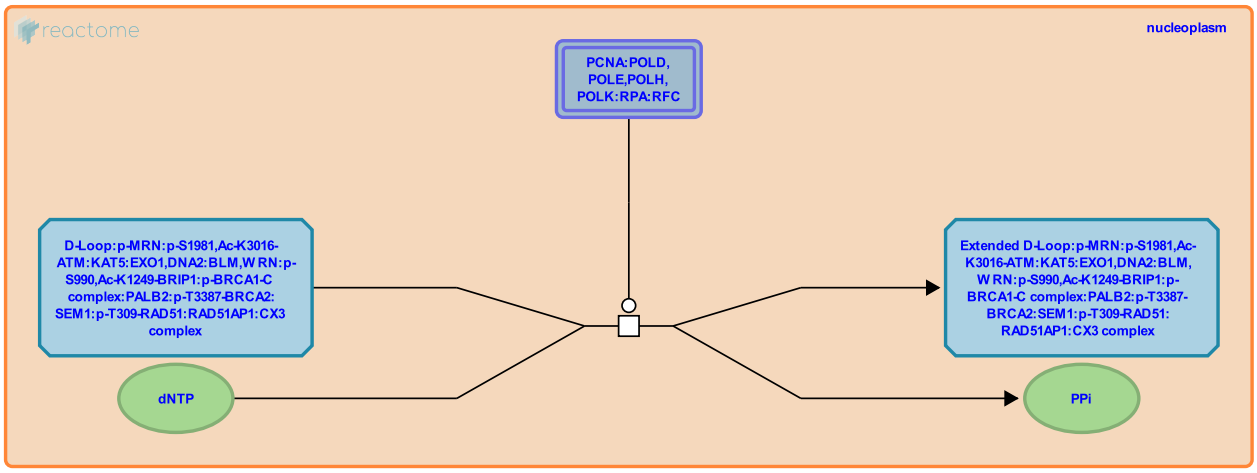
D-loop extension by DNA polymerases ↗

Location: HDR through Homologous Recombination (HRR)

Stable identifier: R-HSA-5693593

Type: transition

Compartments: nucleoplasm



Following branch migration, the invading 3' resected ssDNA end of the double-strand break (DSB) acts as a primer for repair DNA synthesis using the complementary strand of the invaded duplex as a template. The replicative DNA polymerases delta (POLD) and likely epsilon (POLE), as well as translesion synthesis (TLS) DNA polymerases eta (POLH) and kappa (POLK) in complex with PCNA, RFC and RPA are implicated in DNA repair synthesis and D-loop extension. While TLS polymerases increase the efficiency of homologous recombination-related DNA synthesis and can directly interact with D-loop proteins RAD51, PALB2 and BRCA2, it is likely that replicative DNA polymerases POLD and POLE, with their high processivity and fidelity, perform the major role in D-loop extension (McIlwraith et al. 2005, Sebesta et al. 2013, Pomerantz et al. 2013, Buisson et al. 2014). In addition, the presence of RAD51-translocases, homologous to yeast Rad54, that remove RAD51 from the 3' invading strand, may be necessary for the catalytic activity of POLD or POLE (Li et al. 2009, Li and Heyer 2009).

Followed by: Resolution of D-Loop Structures

Literature references

Goodman, MF., O'Donnell, ME., Kurth, I., Pomerantz, RT. (2013). Preferential D-loop extension by a translesion DNA polymerase underlies error-prone recombination. *Nat. Struct. Mol. Biol., 20*, 748-55. ↗

Gerlach, VL., Feaver, WJ., Friedberg, EC., Kunkel, TA., Matsuda, T., Ohashi, E. et al. (2000). Fidelity and processivity of DNA synthesis by DNA polymerase kappa, the product of the human DINB1 gene. *J. Biol. Chem., 275*, 39678-84. ↗

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

Haracska, L., Szabo, JE., Burkovics, P., Zhang, S., Sebesta, M., Krejci, L. et al. (2013). Role of PCNA and TLS polymerases in D-loop extension during homologous recombination in humans. *DNA Repair (Amst.), 12*, 691-8. ↗

West, SC., Vaisman, A., Mcllwraith, MJ., McIlwraith, MJ., Woodgate, R., Fanning, E. et al. (2005). Human DNA polymerase eta promotes DNA synthesis from strand invasion intermediates of homologous recombination. *Mol. Cell, 20*, 783-92. ↗

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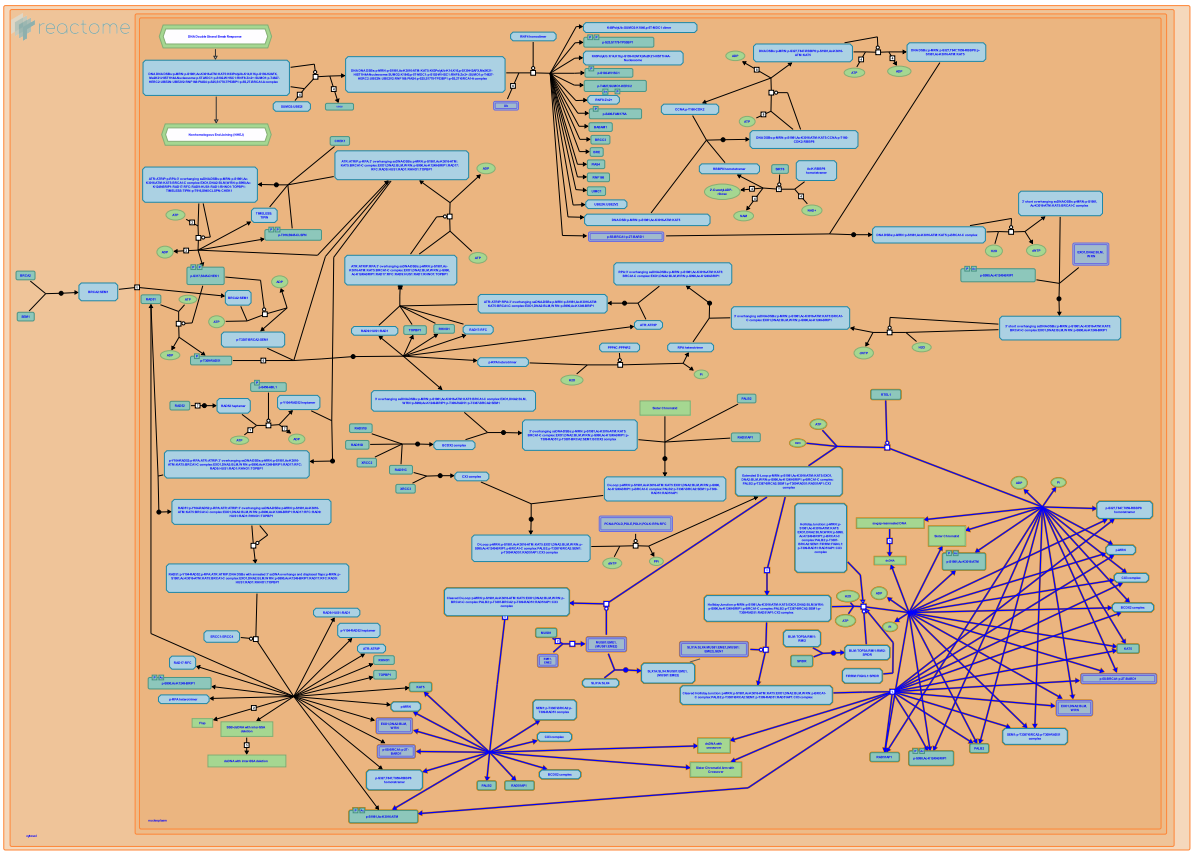
Resolution of D-Loop Structures ↗

Location: HDR through Homologous Recombination (HRR)

Stable identifier: R-HSA-5693537

Compartments: nucleoplasm



Once repair synthesis has occurred, the D-loop structure may be resolved either through Holliday junction intermediates or through synthesis-dependent strand-annealing (SDSA) (Prado and Aguilera 2003, Ciccia and Elledge 2010).

Literature references

Aguilera, A., Prado, F. (2003). Control of cross-over by single-strand DNA resection. *Trends Genet, 19*, 428-31. ↗

Elledge, SJ., Ciccia, A. (2010). The DNA damage response: making it safe to play with knives. *Mol. Cell, 40*, 179-204. ↗

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Table of Contents