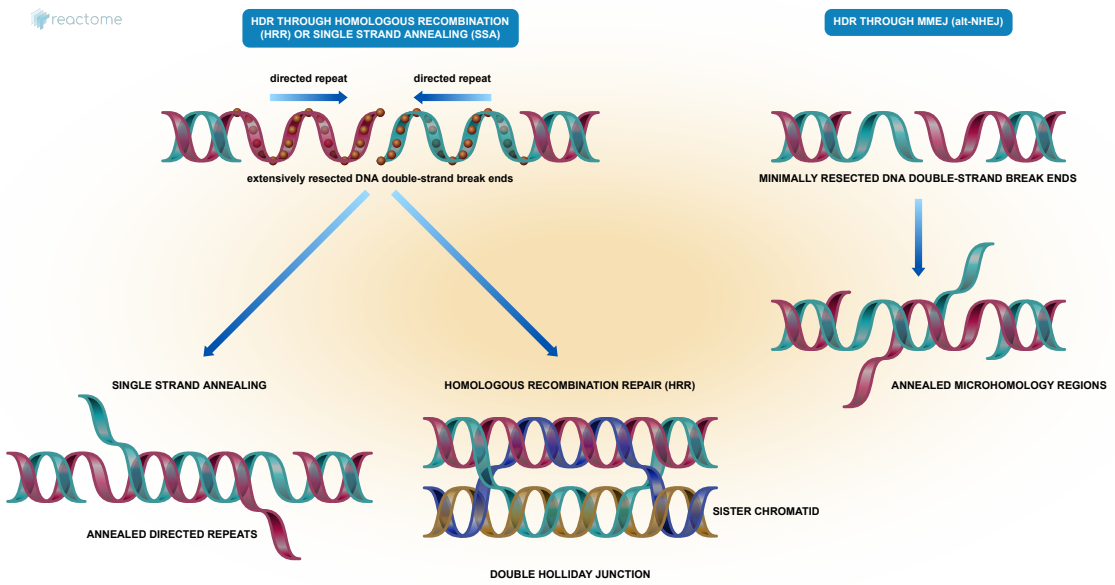
Homology Directed Repair



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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. ↗

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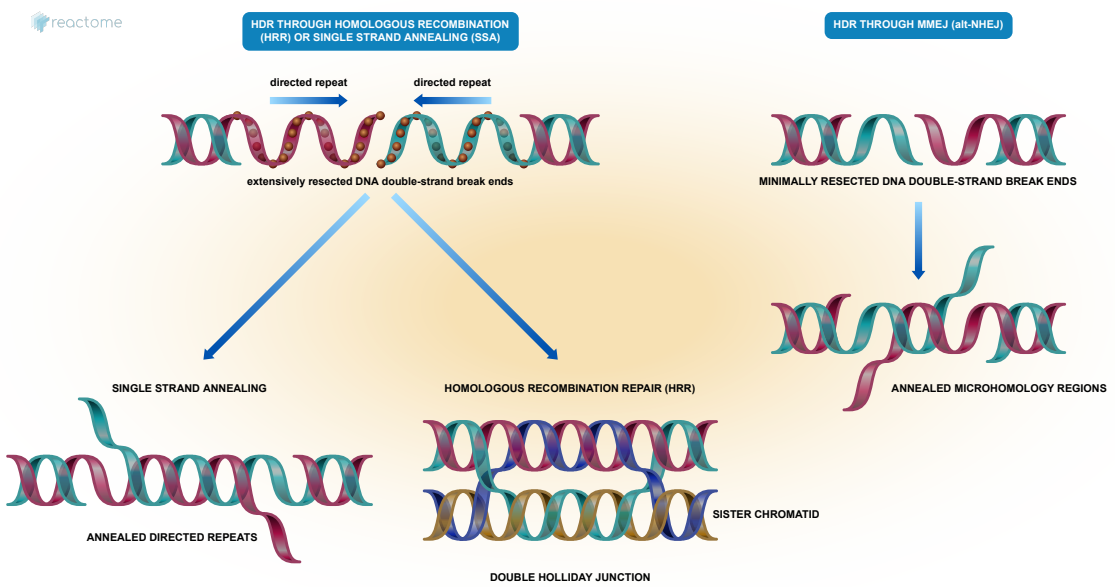
Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Homology Directed Repair ↗

Stable identifier: R-HSA-5693538

Compartments: nucleoplasm



Homology directed repair (HDR) of DNA double strand breaks (DSBs) requires resection of DNA DSB ends. Resection creates 3'-ssDNA overhangs which then anneal with a homologous DNA sequence. This homologous sequence can then be used as a template for DNA repair synthesis that bridges the DSB. HDR preferably occurs through the error-free homologous recombination repair (HRR), but can also occur through the error-prone single strand annealing (SSA), or the least accurate microhomology-mediated end joining (MMEJ).

HRR and SSA share the initial steps that involve ATM signaling, formation of the so-called ionizing radiation-induced foci (IRIF), extensive resection of DNA DSB ends and activation of ATR signaling. In homologous recombination, 3'-ssDNA overhangs anneal with complementary sister chromatid strands. In SSA, 3'-ssDNA overhangs anneal with each other through homologous direct repeats contained in each overhang, resulting in deletions of one of the repeats and the DNA sequence in between the repeats during DNA repair synthesis.

Contrary to HRR and SSA, which both involve annealing of long stretches of highly homologous DNA sequences, MMEJ entails annealing of short regions of two 3'-ssDNA overhangs (up to 20 nucleotides) and is therefore more promiscuous and more likely to join unrelated DNA molecules. The error rate of MMEJ is additionally increased by the low fidelity of the DNA polymerase theta (POLQ), which performs DNA repair synthesis in MMEJ.

For reviews of this topic, please refer to Khanna 2001, Thompson and Schild 2001, Thompson and Schild 2002, Thompson and Limoli 2003, Ciccia and Elledge 2010.

Literature references

Thompson, LH., Schild, D. (2001). Homologous recombinational repair of DNA ensures mammalian chromosome stability. *Mutat Res, 477*, 131-53. ↗

Caldecott, KW. (2004). Origin, Recognition, Signaling and Repair of DNA Double-Strand Breaks in Mammalian Cells, Eukaryotic DNA Damage Surveillance and Repair. *Springer*, 1-40.

Thompson, LH., Schild, D. (2002). Recombinational DNA repair and human disease. *Mutat Res, 509*, 49-78. ↗

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

Khanna, KK. (2001). DNA double-strand breaks: signaling, repair and the cancer connection. *Nat Genet, 27*, 247-54. ↗

Editions

2003-07-14	Authored	Thompson, L.
2003-08-05	Edited	Matthews, L.
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2015-06-12	Reviewed	Borowiec, JA.
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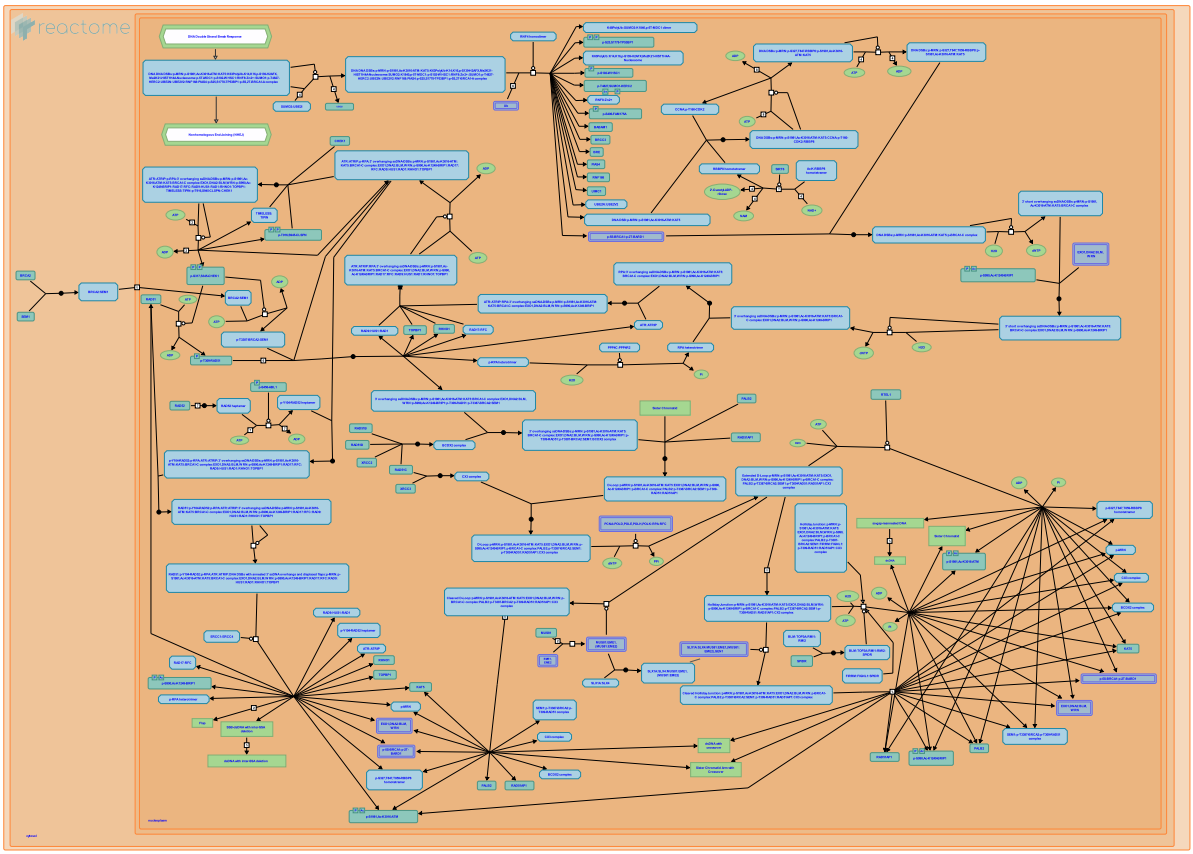
HDR through Homologous Recombination (HRR) or Single Strand Annealing (SSA) ↗

Location: Homology Directed Repair

Stable identifier: R-HSA-5693567

Compartments: nucleoplasm



Homology directed repair (HDR) of replication-independent DNA double-strand breaks (DSBs) via homologous recombination repair (HRR) or single strand annealing (SSA) requires the activation of ATM followed by ATM-mediated phosphorylation of DNA repair proteins. ATM coordinates the recruitment of DNA repair and signaling proteins to DSBs and formation of the so-called ionizing radiation induced foci (IRIF). While IRIFs include chromatin regions kilobases away from the actual DSB, this Reactome pathway represents simplified foci and shows events that happen at the very ends of the broken DNA.

For both HRR and SSA to occur, the ends of the DNA DSB must be processed (resected) to generate lengthy 3' ssDNA tails, and the resulting ssDNA coated with RPA complexes, triggering ATR activation and signaling.

After the resection step, BRCA2 and RAD51 trigger HRR, a very accurate process in which the 3'-ssDNA overhang invades a sister chromatid, base pairs with the complementary strand of the sister chromatid DNA duplex, creating a D-loop, and uses the complementary sister chromatid strand as a template for DNA repair synthesis that bridges the DSB.

The SSA is triggered when 3'-ssDNA overhangs created in the resection step contain highly homologous direct repeats. In a process involving RAD52, the direct repeats in each 3'-ssDNA overhang become annealed, the unannealed 3'-flaps excised, and structures then processed by DNA repair synthesis. SSA results in the loss of one of the annealed repeats and the DNA sequence between the two repeats. Therefore, SSA is error-prone and is probably used as a backup for HRR, with RAD52 loss-of-function mutations being synthetically lethal with mutations in HRR genes, such as BRCA2 (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. ↗

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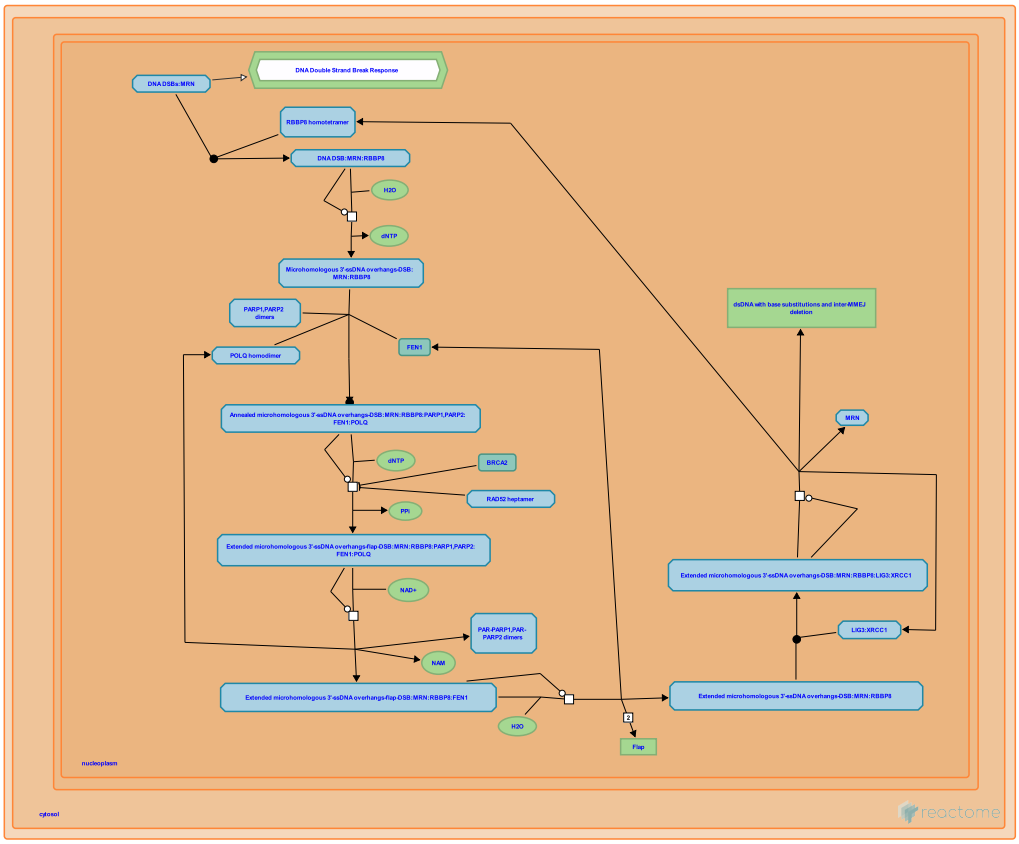
HDR through MMEJ (alt-NHEJ) ↗

Location: Homology Directed Repair

Stable identifier: R-HSA-5685939



Homology directed repair (HDR) through microhomology-mediated end joining (MMEJ) is an error prone process also known as alternative nonhomologous end joining (alt-NHEJ), although it does not involve proteins that participate in the classical NHEJ. Contrary to the classical NHEJ and other HDR pathways, homologous recombination repair (HRR) and single strand annealing (SSA), MMEJ does not require ATM activation. In fact, ATM activation inhibits MMEJ. Therefore, MMEJ may be triggered when the amount of DNA double strand breaks (DSBs) overwhelms DNA repair machinery of higher fidelity or when cells are deficient in components of high fidelity DNA repair.

MMEJ is initiated by a limited resection of DNA DSB ends by the MRN complex (MRE11A:RAD50:NBN) and RBBP8 (CtIP), in the absence of CDK2-mediated RBBP8 phosphorylation and related BRCA1:BARD1 recruitment (Yun and Hiom 2009). Single strand DNA (ssDNA) at resected DNA DSB ends recruits PARP1 or PARP2 homo- or heterodimers, together with DNA polymerase theta (POLQ) and FEN1 5'-flap endonuclease. In a poorly studied sequence of events, POLQ promotes the annealing of two 3'-ssDNA overhangs through microhomologous regions that are optimally 10-19 nucleotides long. Using analogy with POLB-mediated long patch base excision repair (BER), it is plausible that PARP1 (or PARP2) dimers coordinate the extension of annealed 3'-ssDNA overhangs via POLQ-mediated strand displacement synthesis with FEN1-mediated cleavage of the resulting 5'-flaps (Liang et al. 2005, Mansour et al. 2011, Sharma et al. 2015, Kent et al. 2015, Ciccaldi et al. 2015, Mateos-Gomez et al. 2015). The MRN complex subsequently recruits DNA ligase 3 (LIG3) bound to XRCC1 (LIG3:XRCC1) to ligate the remaining single strand nicks (SSBs) at MMEJ sites (Della-Maria et al. 2011).

Similar to single strand annealing (SSA), MMEJ leads to deletion of one of the microhomology regions used for annealing and the DNA sequence in between two annealed microhomology regions. MMEJ, just like classical NHEJ, can result in genomic translocations (Ghezraoui et al. 2014). In addition, since POLQ is an error-prone DNA polymerase, MMEJ introduces frequent base substitutions (Ceccaldi et al. 2015).

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Editions

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