Defective homologous recombination repair (HRR) due to BRCA2 loss of function

Impaired BRCA2 binding to SEM1 (DSS1)

Impaired BRCA2 translocation to the nucleus

Impaired BRCA2 binding to RAD51

Impaired BRCA2 binding to PALB2

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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.

13/11/2022
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


Reactome database release: 82

This document contains 5 pathways (see Table of Contents)

https://reactome.org
Defective homologous recombination repair (HRR) due to BRCA2 loss of function

Stable identifier: R-HSA-9701190

Compartments: nucleoplasm

Diseases: cancer

BRCA2 (FANCD1) is a tumor suppressor gene located on chromosomal arm 13q. BRCA2 protein is a mediator of the core mechanism of homologous recombination repair (HRR), essential for the recruitment of RAD51 recombinase to resected DNA double-strand breaks (DSBs). Monoallelic pathogenic germline mutations in BRCA2 are one of the underlying causes of the hereditary breast and ovarian cancer (HBOC) syndrome, with carriers having close to 50% lifetime risk for development of breast cancer and about 15% lifetime risk for development of ovarian cancer. In addition, BRCA2 germline mutation carriers are predisposed to cancers of the fallopian tube, pancreas, stomach, larynx and prostate. Biallelic germline mutations in BRCA2 cause Fanconi anemia subtype characterized by brain and soft tissue tumors, including medulloblastoma and Wilms tumor. BRCA2-deficient cells are defective in the formation of RAD51 foci upon treatment with DSB-inducing DNA damaging agents and accumulate chromatid breaks and radial chromosomes.

Besides its crucial role in HRR, BRCA2 is also implicated in protection of replication forks, centrosome duplication, spindle assembly checkpoint and cytokinesis. Recently published studies show the involvement of BRCA2 in the turnover of R-loops (hybrids between RNA and single strand DNA that are generated as intermediates of gene transcription). Unscheduled accumulated R-loops may be processed into DSBs, leading to genomic instability. Finally, BRCA2 is involved in pathway choice of DSB repair by inhibiting DNA polymerase theta-mediated end-joining (TMEJ) until M-phase (reviewed in Petropoulos and Halazonetis 2021, and Llorens-Agost et al. 2021). TMEJ is the predominant pathway for microhomology-mediated end joining MMEJ/alternative-nonhomologous end joining (alt-NHEJ, a-EJ) in mammals (reviewed in Ramsden et al. 2022).
BRCA2 haploinsufficiency is frequently observed in cancers, with close to 50% of BRCA2-mutant breast cancers retaining one wild type allele, suggesting that in some tissues at least heterozygous loss of BRCA2 function is sufficient for carcinogenesis. Promoter hypermethylation is not an obvious contributor to BRCA2 gene inactivation and no pathogenic mutations in the promoter region have been identified so far.


**Literature references**


**Editions**

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[https://reactome.org](https://reactome.org)
Impaired BRCA2 binding to SEM1 (DSS1)

Location: Defective homologous recombination repair (HRR) due to BRCA2 loss of function

Stable identifier: R-HSA-9763198

Compartments: cytosol

Diseases: cancer

This pathway describes BRCA2 cancer mutations that affect the ability of BRCA2 to bind to SEM1 (DSS1), a small protein of 70 amino acids that regulates BRCA2 stability and its nuclear localization (reviewed in Le et al. 2021).

Literature references


Editions

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Impaired BRCA2 translocation to the nucleus

**Location:** Defective homologous recombination repair (HRR) due to BRCA2 loss of function

**Stable identifier:** R-HSA-9709275

**Compartments:** cytosol

**Diseases:** cancer

This pathway describes truncating mutations in BRCA2 that result in mutant proteins lacking nuclear localization signals (NLSs) in the C-terminal domain. These truncated BRCA2 proteins mainly localize to the cytosol, impairing the ability of BRCA2 mutants to participate in homologous recombination repair (HRR) in the nucleus. Truncating mutations are the most frequent BRCA2 mutations detected in cancer (Spain et al. 1999, Yano et al. 2000, Ma et al. 2017).

**Literature references**


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A critical function of BRCA2 is to bind RAD51 and nucleate RAD51 filament formation on single-stranded DNA. BRCA2 has two regions that interact with RAD51: 8 BRC repeats encoded by exon 11 (Bork et al. 1996, Wong et al. 1997) and a C-terminal RAD51 binding domain called TR2 (Sharan et al. 1997).

**Literature references**


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Impaired BRCA2 binding to PALB2

Location: Defective homologous recombination repair (HRR) due to BRCA2 loss of function

Stable identifier: R-HSA-9709603

Compartments: nucleoplasm

Diseases: cancer

This pathway describes BRCA2 missense mutations that affect the N-terminus of BRCA2 and impair the ability of BRCA2 to bind PALB2, which is a crucial step in homologous recombination repair (HRR) of DNA double-strand breaks (DSBs) (Xia et al. 2006).

Literature references


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