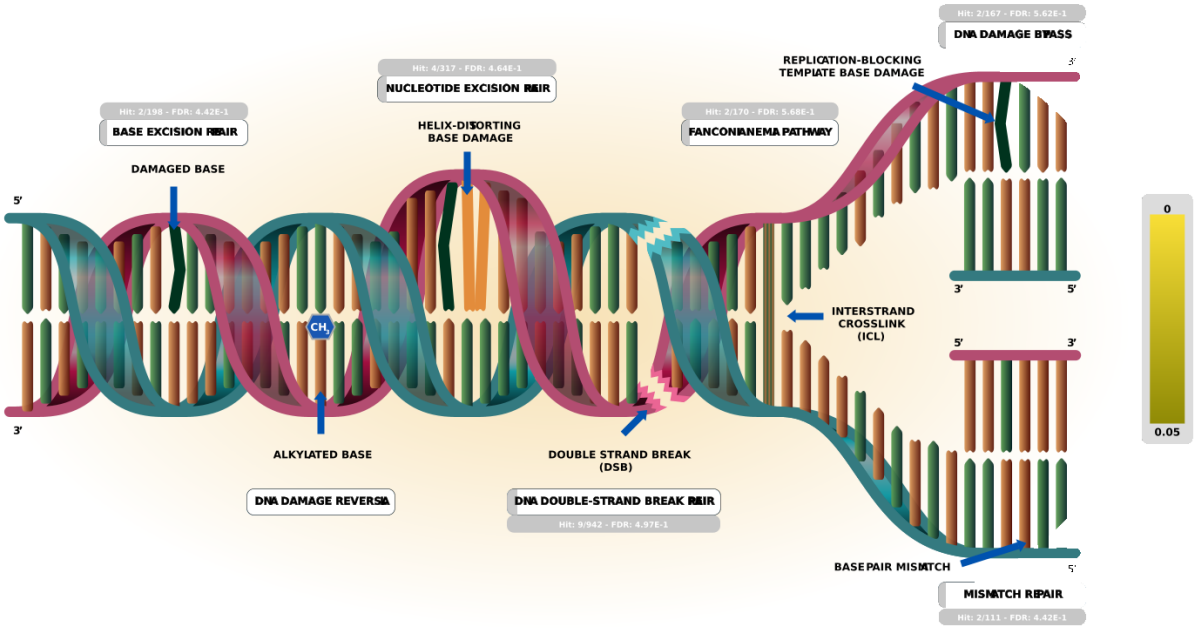
# DNA Repair




Borowiec, JA., Edelbrock, MA., Fousteri, M., Fugger, K., Gillespie, ME., Gopinathrao, G., Hoeijmakers, JH., Huang, TT., Joshi-Tope, G., Khanna, KK., Lees-Miller, S., Lindahl, T., Matthews, L., May, B., Orlic-Milacic, M., Pegg, AE., Schultz, R., Thompson, L., West, SC., Wood, RD.

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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: 81

This document contains 8 pathways (see Table of Contents)

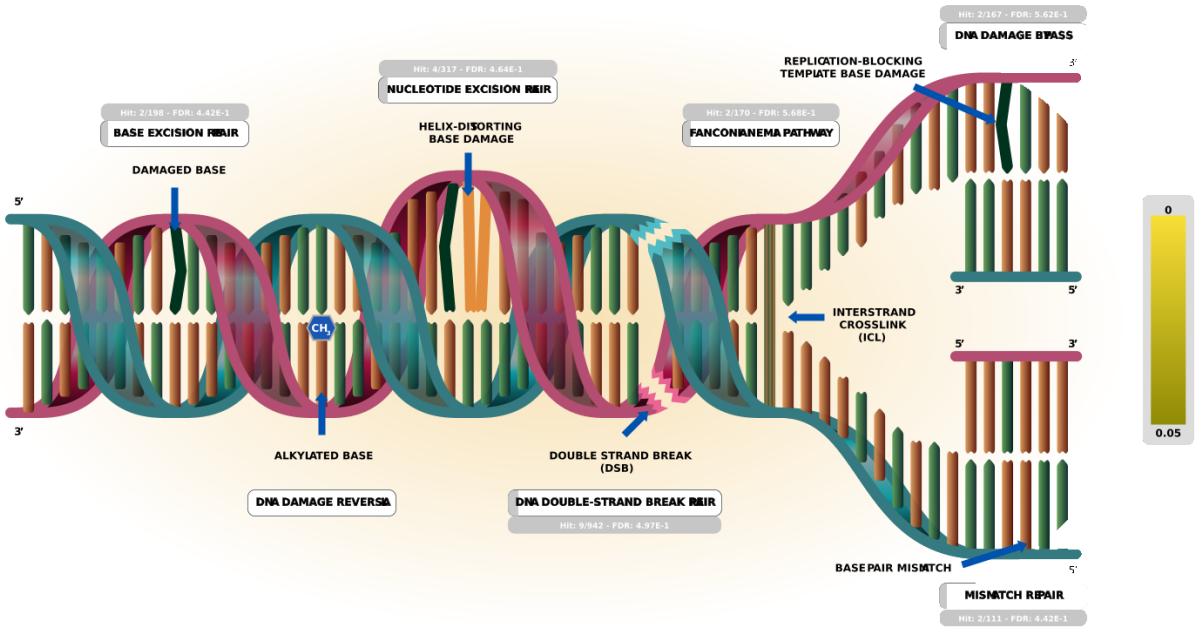
# Analysis properties

- This is an **overrepresentation** analysis: A statistical (hypergeometric distribution) test that determines whether certain Reactome pathways are over-represented (enriched) in the submitted data. It answers the question 'Does my list contain more proteins for pathway X than would be expected by chance?' This test produces a probability score, which is corrected for false discovery rate using the Benjamani-Hochberg method. See more
- 39 out of 39 identifiers in the sample were found in Reactome, where 1141 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent. ↗
- IntAct interactors were included to increase the analysis background. This greatly increases the size of Reactome pathways, which maximises the chances of matching your submitted identifiers to the expanded pathway, but will include interactors that have not undergone manual curation by Reactome and may include interactors that have no biological significance, or unexplained relevance.
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAyMjA5MDEwNDA3MzZfMzEyNTc%3D. This ID is valid for at least 7 days in Reactome's server. Use it to access Reactome services with your data.

## DNA Repair ↗

**Stable identifier:** R-HSA-73894

**Compartments:** nucleoplasm




DNA repair is a phenomenal multi-enzyme, multi-pathway system required to ensure the integrity of the cellular genome. Living organisms are constantly exposed to harmful metabolic by-products, environmental chemicals and radiation that damage their DNA, thus corrupting genetic information. In addition, normal cellular pH and temperature create conditions that are hostile to the integrity of DNA and its nucleotide components. DNA damage can also arise as a consequence of spontaneous errors during DNA replication. The DNA repair machinery continuously scans the genome and maintains genome integrity by removing or mending any detected damage.

Depending on the type of DNA damage and the cell cycle status, the DNA repair machinery utilizes several different pathways to restore the genome to its original state. When the damage and circumstances are such that the DNA cannot be repaired with absolute fidelity, the DNA repair machinery attempts to minimize the harm and patch the insulted genome well enough to ensure cell viability.

Accumulation of DNA alterations that are the result of cumulative DNA damage and utilization of "last resort" low fidelity DNA repair mechanisms is associated with cellular senescence, aging, and cancer. In addition, germline mutations in DNA repair genes are the underlying cause of many familial cancer syndromes, such as Fanconi anemia, xeroderma pigmentosum, Nijmegen breakage syndrome and Lynch syndrome, to name a few.

When the level of DNA damage exceeds the capacity of the DNA repair machinery, apoptotic cell death ensues. Actively dividing cells have a very limited time available for DNA repair and are therefore particularly sensitive to DNA damaging agents. This is the main rationale for using DNA damaging chemotherapeutic drugs to kill rapidly replicating cancer cells.

There are seven main pathways employed in human DNA repair: DNA damage bypass, DNA damage reversal, base excision repair, nucleotide excision repair, mismatch repair, repair of double strand breaks and repair of interstrand crosslinks (Fanconi anemia pathway). DNA repair pathways are intimately associated with other cellular processes such as DNA replication, DNA recombination, cell cycle checkpoint arrest and apoptosis.

The DNA damage bypass pathway does not remove the damage, but instead allows translesion DNA synthesis (TLS) using a damaged template strand. Translesion synthesis allows cells to complete DNA replication, postponing the repair until cell division is finished. DNA polymerases that participate in translesion synthesis are error-prone, frequently introducing base substitutions and/or small insertions and deletions.

The DNA damage reversal pathway acts on a very narrow spectrum of damaging base modifications to remove modifying groups and restore DNA bases to their original state.

The base excision repair (BER) pathway involves a number of DNA glycosylases that cleave a vast array of damaged bases from the DNA sugar-phosphate backbone. DNA glycosylases produce a DNA strand with an abasic site. The abasic site is processed by DNA endonucleases, DNA polymerases and DNA ligases, the choice of which depends on the cell cycle stage, the identity of the participating DNA glycosylase and the presence of any additional damage. Base excision repair yields error-free DNA molecules.

Mismatch repair (MMR) proteins recognize mismatched base pairs or small insertion or deletion loops during DNA replication and correct erroneous base pairing by excising mismatched nucleotides exclusively from the nascent DNA strand, leaving the template strand intact.

Nucleotide excision repair pathway is involved in removal of bulky lesions that cause distortion of the DNA double helix. NER proteins excise the oligonucleotide that contains the lesion from the affected DNA strand, which is followed by gap-filling DNA synthesis and ligation of the repaired DNA molecule.

Double strand breaks (DSBs) in the DNA can be repaired via a highly accurate homologous recombination repair (HRR) pathway, or through error-prone nonhomologous end joining (NHEJ), single strand annealing (SSA) and microhomology-mediated end joining (MMEJ) pathways. DSBs can be directly generated by some DNA damaging agents, such as X-rays and reactive oxygen species (ROS). DSBs can also be intermediates of the Fanconi anemia pathway.

Interstrand crosslinking (ICL) agents damage the DNA by introducing covalent bonds between two DNA strands, which disables progression of the replication fork. The Fanconi anemia proteins repair the ICLs by unhooking them from one DNA strand. TLS enables the replication fork to bypass the unhooked ICL, resulting in two replicated DNA molecules, one of which contains a DSB and triggers double strand break repair, while the sister DNA molecule contains a bulky unhooked ICL, which is removed through NER.

Single strand breaks (SSBs) in the DNA, generated either by DNA damaging agents or as intermediates of DNA repair pathways such as BER, are converted into DSBs if the repair is not complete prior to DNA replication. Simultaneous inhibition of DSB repair and BER through cancer mutations and anti-cancer drugs, respectively, is synthetic lethal in at least some cancer settings, and is a promising new therapeutic strategy.

For reviews of DNA repair pathways, please refer to Lindahl and Wood 1999 and Curtin 2012.

## Literature references

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

Curtin, NJ. (2012). DNA repair dysregulation from cancer driver to therapeutic target. *Nat. Rev. Cancer, 12*, 801-17. ↗

## Editions

| | | |
|---|---|---|
| 2003-07-10 | Authored | Gopinathrao, G., Thompson, L., Hoeijmakers, JH., Lees-Miller, S., Schultz, R., Pegg, AE. et al. |
| 2004-06-01 | Reviewed | West, SC., Khanna, KK., Lindahl, T., Wood, RD. |
| 2013-11-25 | Edited | Gopinathrao, G., Matthews, L. |

## 5 submitted entities found in this pathway, mapping to 5 Reactome entities

| Input | UniProt Id | Input | UniProt Id | Input | UniProt Id |
|---|---|---|---|---|---|
| BRCA1 | P38398 | BRCA2 | P51587 | PARP1 | P09874 |
| PARP2 | Q9UGN5 | p53 | P04637 | | |

## Interactors found in the analysis (7)

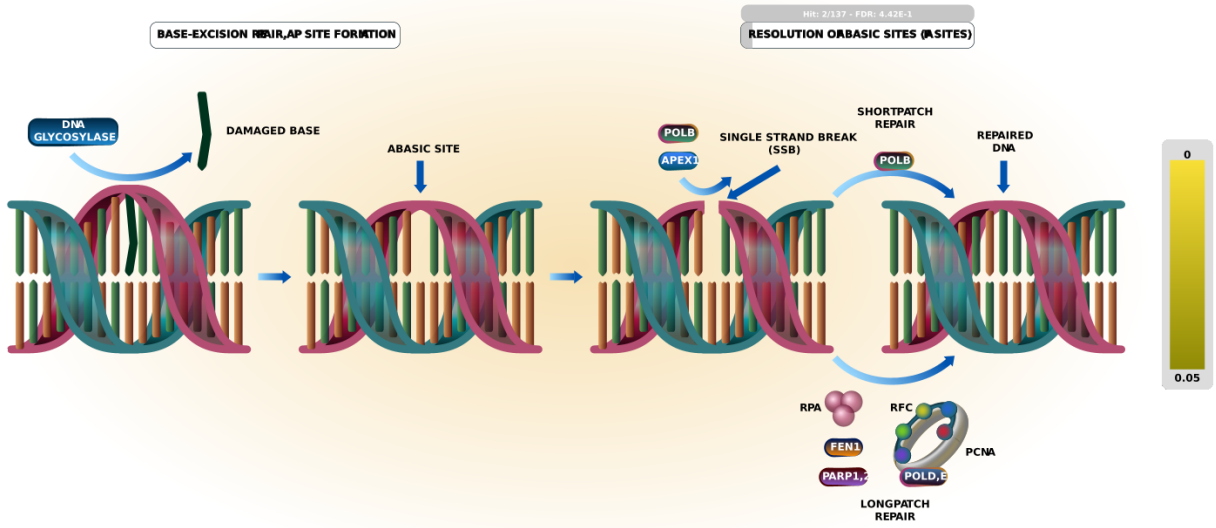
| Input | UniProt Id | Interacts with | Input | UniProt Id | Interacts with |
|---|---|---|---|---|---|
| BRCA1 | P38398, P38398-1 | Q9BX63, O15360, Q12888, P51587, P38398, P46736, P40692, Q92560, P52292, Q99728, Q9BXW9, Q96RL1, Q6UWZ7, Q06609, Q86YC2, O14757 | BRCA2 | P51587 | P38398, O43542, P60896, O43502, Q9Y253, Q9BXW9, P51587, Q06609, Q86YC2 |
| EGFR | P00533 | P00519, P53041, P07992, P45983 | MUC1 | P15941 | P00519 |
| Myc | P01106 | Q8N6T7, Q12888, P52292, P52701 | PARP1 | P09874 | Q8N2W9, P78527 |
| p53 | P04637 | O96017, P38398, Q09472, P63279, Q12888, Q92993, Q8N2W9, P51587, Q96PM5 | | | |

## Base Excision Repair ↗

**Location:** DNA Repair

**Stable identifier:** R-HSA-73884

**Compartments:** nucleoplasm




Of the three major pathways involved in the repair of nucleotide damage in DNA, base excision repair (BER) involves the greatest number of individual enzymatic activities. This is the consequence of the numerous individual glycosylases, each of which recognizes and removes a specific modified base(s) from DNA. BER is responsible for the repair of the most prevalent types of DNA lesions, oxidatively damaged DNA bases, which arise as a consequence of reactive oxygen species generated by normal mitochondrial metabolism or by oxidative free radicals resulting from ionizing radiation, lipid peroxidation or activated phagocytic cells. BER is a two-step process initiated by one of the DNA glycosylases that recognizes a specific modified base(s) and removes that base through the catalytic cleavage of the glycosydic bond, leaving an abasic site without disruption of the phosphate-sugar DNA backbone. Subsequently, abasic sites are resolved by a series of enzymes that cleave the backbone, insert the replacement residue(s), and ligate the DNA strand. BER may occur by either a single-nucleotide replacement pathway or a multiple-nucleotide patch replacement pathway, depending on the structure of the terminal sugar phosphate residue. The glycosylases found in human cells recognize "foreign adducts" and not standard functional modifications such as DNA methylation (Lindahl and Wood 1999, Sokhansanj et al. 2002).

## Literature references


Fitch, JP., Sokhansanj, BA., Rodrigue, GR., Wilson DM, 3rd. (2002). A quantitative model of human DNA base excision repair. I. Mechanistic insights. *Nucleic Acids Res, 30*, 1817-25. ↗

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


## Editions

| | | |
|---|---|---|
| 2003-07-14 | Authored, Edited | Joshi-Tope, G. |
| 2004-02-03 | Authored, Edited | Matthews, L. |
| 2014-12-04 | Authored, Edited, Revised | Orlic-Milacic, M. |
| 2014-12-22 | Reviewed | Borowiec, JA. |

## 2 submitted entities found in this pathway, mapping to 2 Reactome entities

| Input | UniProt Id |
|---|---|
| PARP1 | P09874 |

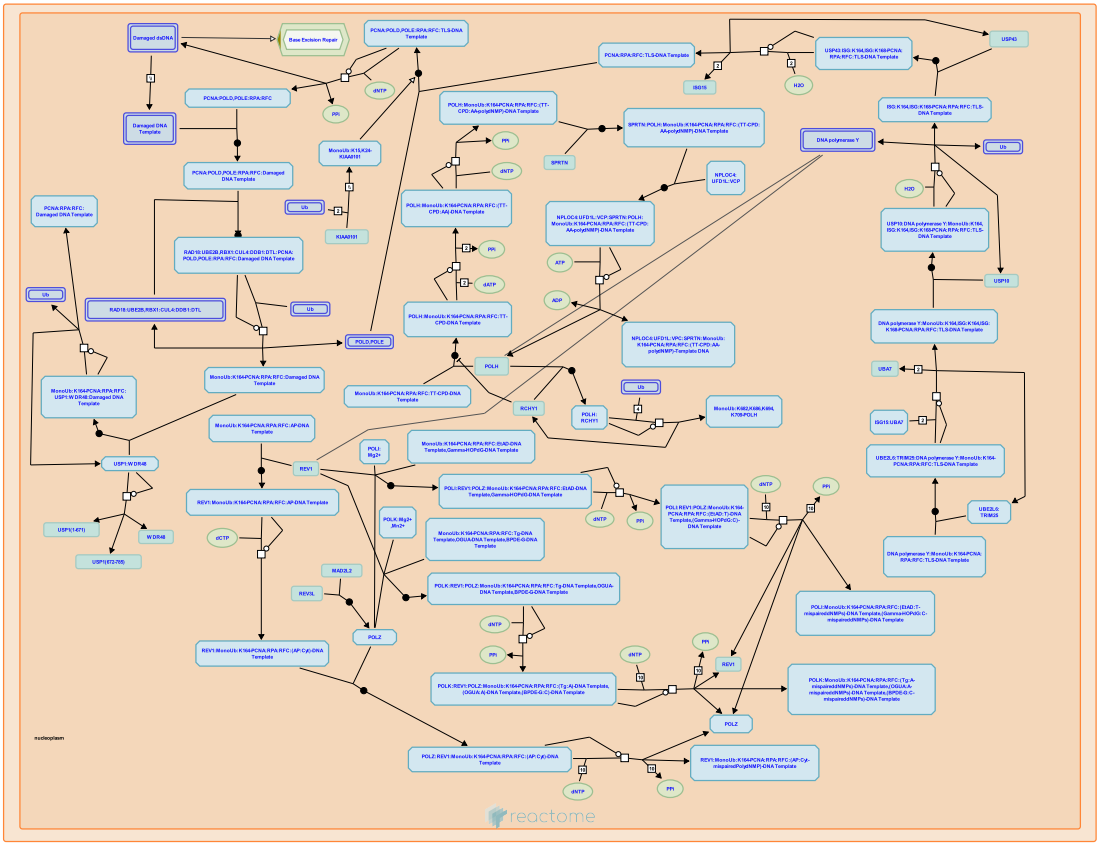
| Input | UniProt Id |
|---|---|
| PARP2 | Q9UGN5 |

## DNA Damage Bypass ↗

**Location:** DNA Repair

**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. |

## Interactors found in the analysis (2)

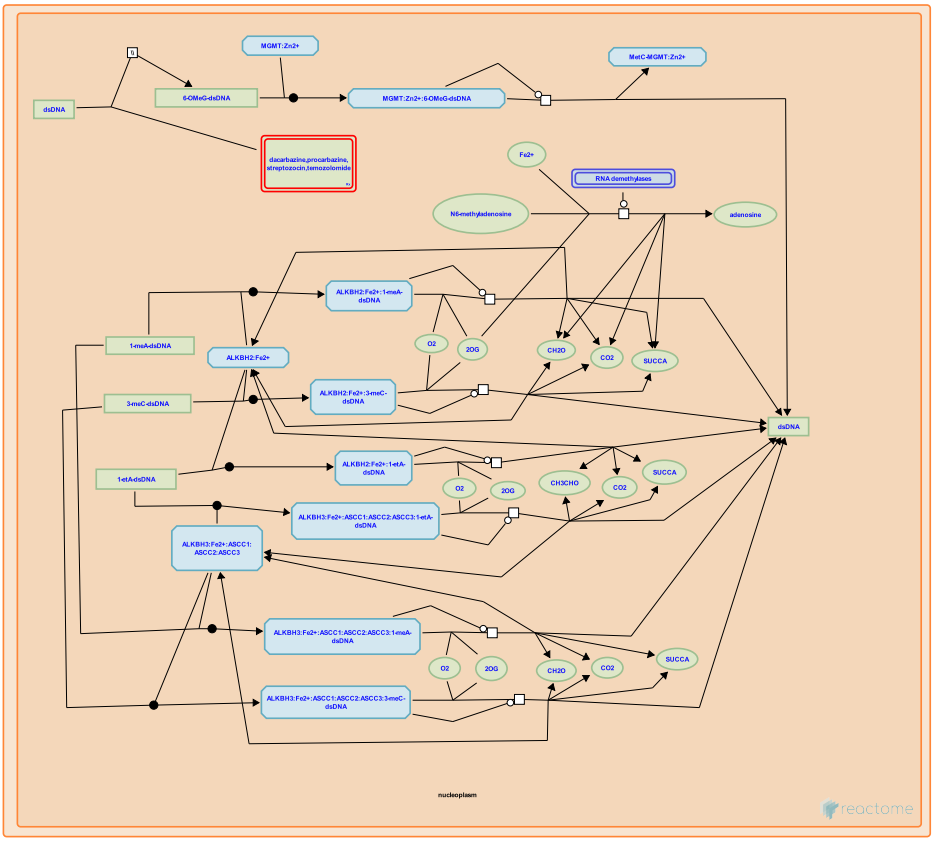
| Input | UniProt Id | Interacts with | Input | UniProt Id | Interacts with |
|---|---|---|---|---|---|
| BRCA2 | P51587 | Q9Y253 | p53 | P04637 | Q96PM5 |

## DNA Damage Reversal ↗

**Location:** DNA Repair

**Stable identifier:** R-HSA-73942

**Compartments:** nucleoplasm




DNA damage can be directly reversed by dealkylation (Mitra and Kaina 1993). Three enzymes play a major role in reparative DNA dealkylation: MGMT, ALKBH2 and ALKBH3. MGMT dealkylates O-6-methylguanine in a suicidal reaction that inactivates the enzyme (Daniels et al. 2000, Rasimas et al. 2004, Duguid et al. 2005, Tubbs et al. 2007), while ALKBH2 and ALKBH3 dealkylate 1-methyladenine, 3-methyladenine, 3-methylcytosine and 1-ethyladenine (Duncan et al. 2002, Dango et al. 2011).

## Literature references


Pegg, AE., Tainer, JA., Tubbs, JL. (2007). DNA binding, nucleotide flipping, and the helix-turn-helix motif in base repair by O6-alkylguanine-DNA alkyltransferase and its implications for cancer chemotherapy. *DNA Repair (Amst.), 6*, 1100-15. ↗

Daniels, DS., Kanugula, S., Tainer, JA., Mol, CD., Arvai, AS., Pegg, AE. (2000). Active and alkylated human AGT structures: a novel zinc site, inhibitor and extrahelical base binding. *EMBO J., 19*, 1719-30. ↗

Rasimas, JJ., Pegg, AE., Ropson, IJ., Dalessio, PA., Fried, MG. (2004). Active-site alkylation destabilizes human O6-alkylguanine DNA alkyltransferase. *Protein Sci., 13*, 301-5. ↗

Rice, PA., He, C., Duguid, EM. (2005). The structure of the human AGT protein bound to DNA and its implications for damage detection. *J. Mol. Biol., 350*, 657-66. ↗

Xiong, LJ., Park, K., Mosammaparast, N., Dango, S., Shi, Y., Gygi, S. et al. (2011). DNA unwinding by ASCC3 helicase is coupled to ALKBH3-dependent DNA alkylation repair and cancer cell proliferation. *Mol. Cell, 44*, 373-84. ↗

## Editions

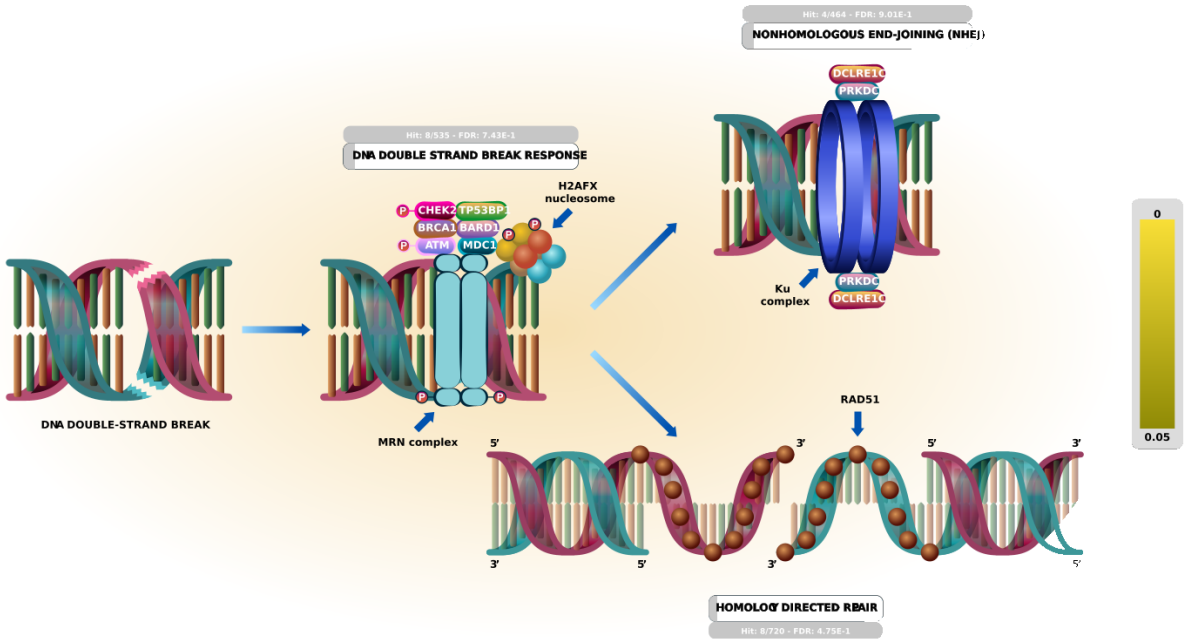
| | | |
|---|---|---|
| 2004-02-04 | Edited, Reviewed | Joshi-Tope, G. |
| 2004-02-04 | Authored | Pegg, AE. |
| 2014-12-16 | Edited, Revised | Orlic-Milacic, M. |
| 2015-02-06 | Reviewed | Gillespie, ME. |

## DNA Double-Strand Break Repair ↗

**Location:** DNA Repair

**Stable identifier:** R-HSA-5693532

**Compartments:** nucleoplasm




Double-strand breaks (DSBs), one of the most deleterious types of DNA damage along with interstrand crosslinks, are caused by ionizing radiation or certain chemicals such as bleomycin. DSBs also occur physiologically, during the processes of DNA replication, meiotic exchange, and V(D)J recombination.

DSBs are sensed (detected) by the MRN complex. Binding of the MRN complex to the DSBs usually triggers ATM kinase activation, thus initiating the DNA double strand break response. ATM phosphorylates a number of proteins involved in DNA damage checkpoint signaling, as well as proteins directly involved in the repair of DNA DSBs. DSBs are repaired via homology directed repair (HDR) or via nonhomologous end-joining (NHEJ).

HDR 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). MMEJ takes place when DSB response cannot be initiated.

While HRR is limited to actively dividing cells with replicated DNA, error-prone NHEJ pathway functions at all stages of the cell cycle, playing the predominant role in both the G1 phase and in S-phase regions of DNA that have not yet replicated. During NHEJ, the Ku70:Ku80 heterodimer (also known as the Ku complex or XRCC5:XRCC6) binds DNA DSB ends, competing away the MRN complex and preventing MRN-mediated resection of DNA DSB ends. The catalytic subunit of the DNA-dependent protein kinase (DNA-PKcs, PRKDC) is then recruited to DNA-bound Ku to form the DNA-PK holoenzyme. Two DNA-PK complexes, one at each side of the break, bring DNA DSB ends together, joining them in a synaptic complex. DNA-PK complex recruits DCLRE1C (ARTEMIS) to DNA DSB ends, leading to trimming of 3'- and 5'-overhangs at the break site, followed by ligation.

For review of this topic, please refer to Ciccia and Elledge 2010.

## Literature references


Lobrich, M., Rothkamm, K., Kruger, I., Thompson, LH. (2003). Pathways of DNA double-strand break repair during the mammalian cell cycle. *Mol Cell Biol, 23*, 5706-15. ↗

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


## Editions

| | | |
|---|---|---|
| 2003-07-14 | Authored | Thompson, L., Lees-Miller, S. |
| 2003-08-05 | Edited | Matthews, L. |
| 2015-05-12 | Authored, Edited, Revised | Orlic-Milacic, M. |
| 2015-06-12 | Reviewed | Borowiec, JA. |

## 5 submitted entities found in this pathway, mapping to 5 Reactome entities

| Input | UniProt Id | Input | UniProt Id | Input | UniProt Id |
|---|---|---|---|---|---|
| BRCA1 | P38398 | BRCA2 | P51587 | PARP1 | P09874 |
| PARP2 | Q9UGN5 | p53 | P04637 | | |

## Interactors found in the analysis (7)

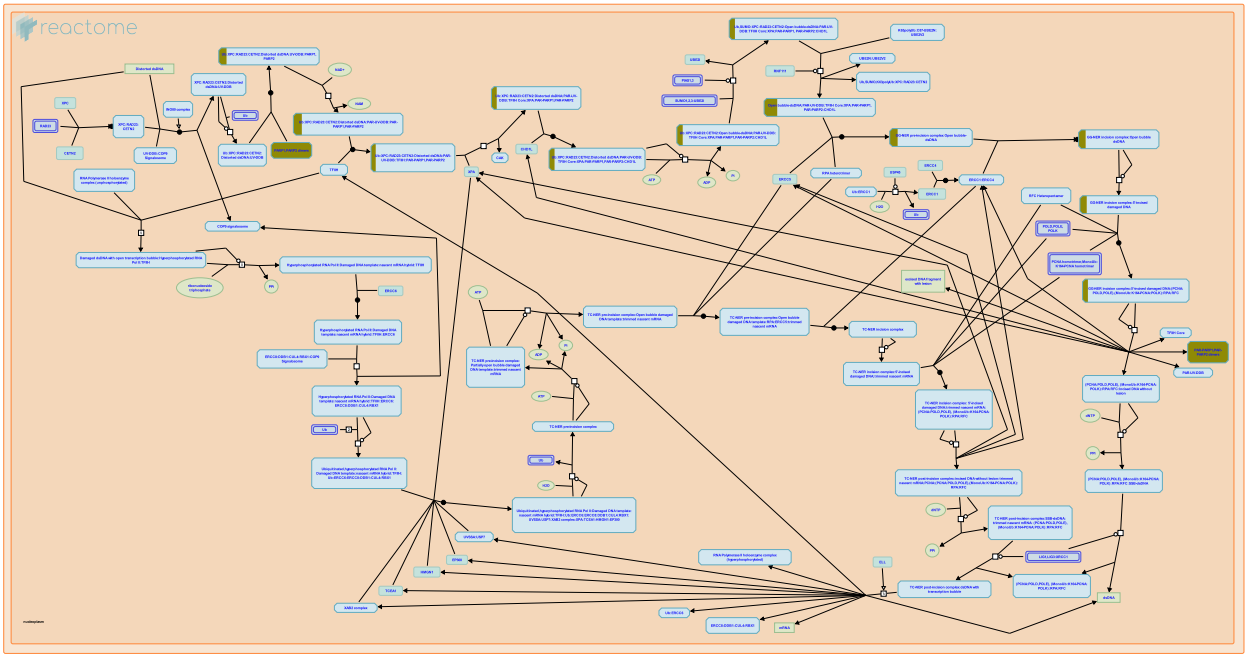
| Input | UniProt Id | Interacts with | Input | UniProt Id | Interacts with |
|---|---|---|---|---|---|
| BRCA1 | P38398, P38398-1 | Q9BX63, Q12888, P51587, P38398, P46736, Q92560, P52292, Q99728, Q96RL1, Q6UWZ7, Q06609, Q86YC2, O14757 | BRCA2 | P51587 | P38398, O43542, P60896, O43502, P51587, Q06609, Q86YC2 |
| EGFR | P00533 | P00519, P53041, P45983 | MUC1 | P15941 | P00519 |
| Myc | P01106 | Q8N6T7, Q12888, P52292 | PARP1 | P09874 | Q8N2W9, P78527 |
| p53 | P04637 | O96017, P38398, P63279, Q12888, Q92993, Q8N2W9, P51587 | | | |

## Nucleotide Excision Repair ↗

**Location:** DNA Repair

**Stable identifier:** R-HSA-5696398

**Compartments:** nucleoplasm



Nucleotide excision repair (NER) was first described in the model organism E. coli in the early 1960s as a process whereby bulky base damage is enzymatically removed from DNA, facilitating the recovery of DNA synthesis and cell survival. Deficient NER processes have been identified from the cells of cancer-prone patients with different variants of xeroderma pigmentosum (XP), trichothiodystrophy (TTD), and Cockayne's syndrome. The XP cells exhibit an ultraviolet radiation hypersensitivity that leads to a hyper-mutability response to UV, offering a direct connection between deficient NER, increased mutation rate, and cancer. While the NER pathway in prokaryotes is unique, the pathway utilized in yeast and higher eukaryotes is highly conserved.

NER is involved in the repair of bulky adducts in DNA, such as UV-induced photo lesions (both 6-4 photo-products (6-4 PPDs) and cyclobutane pyrimidine dimers (CPDs)), as well as chemical adducts formed from exposure to aflatoxin, benzopyrene and other genotoxic agents. Specific proteins have been identified that participate in base damage recognition, cleavage of the damaged strand on both sides of the lesion, and excision of the oligonucleotide bearing the lesion. Reparative DNA synthesis and ligation restore the strand to its original state.

NER consists of two related pathways called global genome nucleotide excision repair (GG-NER) and transcription-coupled nucleotide excision repair (TC-NER). The pathways differ in the way in which DNA damage is initially recognized, but the majority of the participating molecules are shared between these two branches of NER. GG-NER is transcription-independent, removing lesions from non-coding DNA strands, as well as coding DNA strands that are not being actively transcribed. TC-NER repairs damage in transcribed strands of active genes.

Several of the proteins involved in NER are key components of the basal transcription complex TFIIH. An ubiquitin ligase complex composed of DDB1, CUL4A or CUL4B and RBX1 participates in both GG-NER and TC-NER, implying an important role of ubiquitination in NER regulation. The establishment of mutant mouse models for NER genes and other DNA repair-related genes has been useful in demonstrat-

ing the associations between NER defects and cancer.

For past and recent reviews of nucleotide excision repair, please refer to Lindahl and Wood 1998, Friedberg et al. 2002, Christmann et al. 2003, Hanawalt and Spivak 2008, Marteijn et al. 2014).

## Literature references


Fousteri, M., Vermeulen, W. (2013). Mammalian transcription-coupled excision repair. *Cold Spring Harb Perspect Biol , 5*, a012625.

Tomicic, MT., Roos, WP., Christmann, M., Kaina, B. (2003). Mechanisms of human DNA repair: an update. *Toxicology, 193*, 3-34.

Lans, H., Marteijn, JA., Hoeijmakers, JH., Vermeulen, W. (2014). Understanding nucleotide excision repair and its roles in cancer and ageing. *Nat. Rev. Mol. Cell Biol., 15*, 465-81.

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

Friedberg, EC. (2002). How nucleotide excision repair protects against cancer. *Nat Rev Cancer, 1*, 22-33.


## Editions

| | | |
|---|---|---|
| 2003-07-24 | Authored | Hoeijmakers, JH. |
| 2015-05-28 | Authored, Edited, Revised | Orlic-Milacic, M. |
| 2015-08-03 | Reviewed | Fousteri, M. |
| 2022-05-18 | Edited | Gopinathrao, G. |

## 2 submitted entities found in this pathway, mapping to 2 Reactome entities

| Input | UniProt Id | Input | UniProt Id |
|---|---|---|---|
| PARP1 | P09874 | PARP2 | Q9UGN5 |

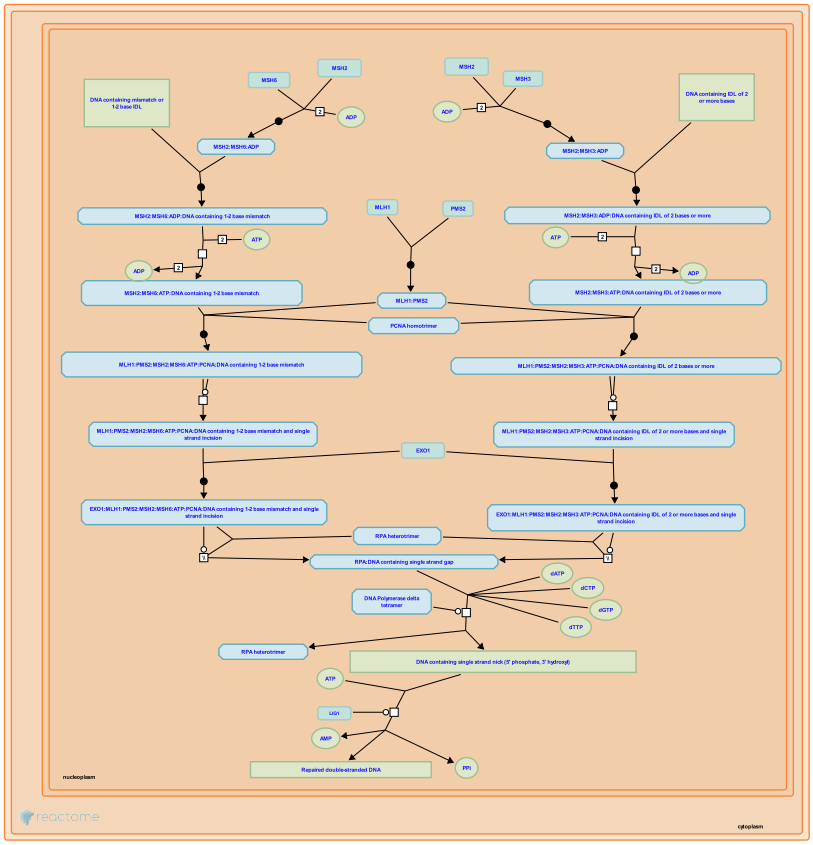
## Interactors found in the analysis (2)

| Input | UniProt Id | Interacts with | Input | UniProt Id | Interacts with |
|---|---|---|---|---|---|
| EGFR | P00533 | P07992 | p53 | P04637 | Q09472, P63279 |

## Mismatch Repair ↗

**Location:** DNA Repair

**Stable identifier:** R-HSA-5358508




The mismatch repair (MMR) system corrects single base mismatches and small insertion and deletion loops (IDLs) of unpaired bases. MMR is primarily associated with DNA replication and is highly conserved across prokaryotes and eukaryotes. MMR consists of the following basic steps: a sensor (MutS homologue) detects a mismatch or IDL, the sensor activates a set of proteins (a MutL homologue and an exonuclease) that select the nascent DNA strand to be repaired, nick the strand, exonucleolytically remove a region of nucleotides containing the mismatch, and finally a DNA polymerase resynthesizes the strand and a ligase seals the remaining nick (reviewed in Kolodner and Marsischkny 1999, Iyer et al. 2006, Li 2008, Fukui 2010, Jiricny 2013).

Humans have 2 different MutS complexes. The MSH2:MSH6 heterodimer (MutSalpha) recognizes single base mismatches and small loops of one or two unpaired bases. The MSH2:MSH3 heterodimer (MutSbeta) recognizes loops of two or more unpaired bases. Upon binding a mismatch, the MutS complex becomes activated in an ATP-dependent manner allowing for subsequent downstream interactions and movement on the DNA substrate. (There are two mechanisms proposed: a sliding clamp and a switch diffusion model.) Though the order of steps and structural details are not fully known, the activated MutS complex interacts with MLH1:PMS2 (MutLalpha) and PCNA, the sliding clamp present at replication foci. The role of PCNA is multifaceted as it may act as a processivity factor in recruiting MMR proteins to replicating DNA, interact with MLH1:PMS2 and Exonuclease 1 (EXO1) to initiate excision of the recently replicated strand and direct DNA polymerase delta to initiate replacement of bases. MLH1:PMS2 makes an incision in the strand to be repaired and EXO1 extends the incision to make a single-stranded gap of up to 1 kb that removes the mismatched base(s). (Based on assays of purified human proteins, there is also a variant of the mismatch repair pathway that does not require EXO1, however the mechanism is not clear. EXO1 is almost always required, it is possible that the exonuclease activity of DNA polymerase delta may

compensate in some situations and it has been proposed that other endonucleases may perform redundant functions in the absence of EXO1.) RPA binds the single-stranded region and a new strand is synthesized across the gap by DNA polymerase delta. The remaining nick is sealed by DNA ligase I (LIG1).

Concentrations of MMR proteins MSH2:MSH6 and MLH1:PMS2 increase in human cells during S phase and are at their highest level and activity during this phase of the cell cycle (Edelbrock et al. 2009). Defects in MSH2, MSH6, MLH1, and PMS2 cause hereditary nonpolyposis colorectal cancer (HNPCC, also known as Lynch syndrome) (reviewed in Martin-Lopez and Fishel 2013).

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## Editions

| | | |
|---|---|---|
| 2014-03-28 | Authored, Edited | May, B. |
| 2014-05-23 | Reviewed | Edelbrock, MA. |

## Interactors found in the analysis (2)

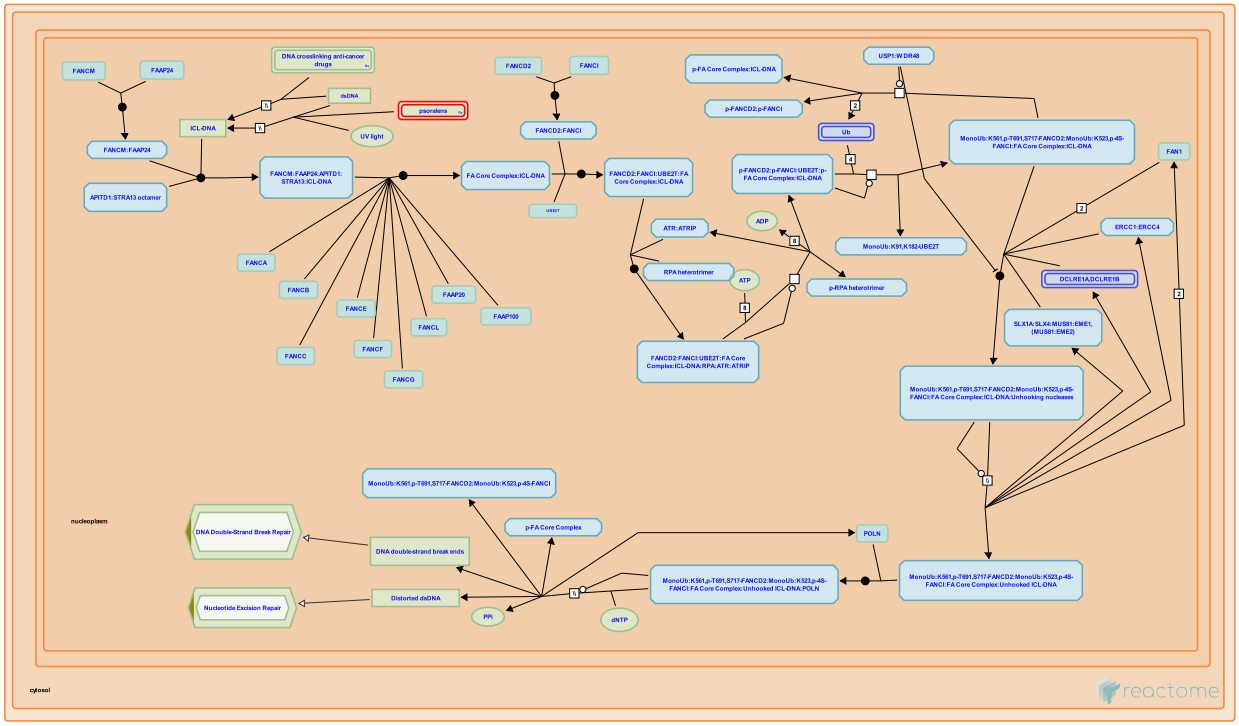
| Input | UniProt Id | Interacts with | Input | UniProt Id | Interacts with |
|---|---|---|---|---|---|
| BRCA1 | P38398 | P40692 | Myc | P01106 | P52701 |

## Fanconi Anemia Pathway ↗

**Location:** DNA Repair

**Stable identifier:** R-HSA-6783310

**Compartments:** nucleoplasm




Fanconi anemia (FA) is a genetic disease of genome instability characterized by congenital skeletal defects, aplastic anemia, susceptibility to leukemias, and cellular sensitivity to DNA damaging agents. Patients with FA have been categorized into at least 15 complementation groups (FA-A, -B, -C, -D1, -D2, -E, -F, -G, -I, -J, -L, -M, -N, -O and -P). These complementation groups correspond to the genes FANCA, FANCB, FANCC, FANCD1/BRCA2, FANCD2, FANCE, FANCF, FANCG, FANCJ/BRIP1, FANCL, FANCM, FANCN/PALB2, FANCO/RAD51C and FANCP/SLX4. Eight of these proteins, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM, together with FAAP24, FAAP100, FAAP20, APITD1 and STRA13, form a nuclear complex termed the FA core complex. The FA core complex is an E3 ubiquitin ligase that recognizes and is activated by DNA damage in the form of interstrand crosslinks (ICLs), triggering monoubiquitination of FANCD2 and FANCI, which initiates repair of ICL-DNA.

FANCD2 and FANCI form a complex and are mutually dependent on one another for their respective monoubiquitination. After DNA damage and during S phase, FANCD2 localizes to discrete nuclear foci that colocalize with proteins involved in homologous recombination repair, such as BRCA1 and RAD51. The FA pathway is regulated by ubiquitination and phosphorylation of FANCD2 and FANCI. ATR-dependent phosphorylation of FANCI and FANCD2 promotes monoubiquitination of FANCD2, stimulating the FA pathway (Cohn and D'Andrea 2008, Wang 2007). The complex of USP1 and WDR48 (UAF1) is responsible for deubiquitination of FANCD2 and negatively regulates the FA pathway (Cohn et al. 2007).

Monoubiquitinated FANCD2 recruits DNA nucleases, including SLX4 (FANCP) and FAN1, which unhook the ICL from one of the two covalently linked DNA strands. The DNA polymerase nu (POLN) performs translesion DNA synthesis using the DNA strand with unhooked ICL as a template, thereby bypassing the unhooked ICL. The unhooked ICL is subsequently removed from the DNA via nucleotide excision repair (NER). Incision of the stalled replication fork during the unhooking step generates a double strand break

(DSB). The DSB is repaired via homologous recombination repair (HRR) and involves the FA genes BRCA2 (FANCD1), PALB2 (FANCN) and BRIP1 (FANCJ) (reviewed by Deans and West 2011, Kottemann and Smogorzewska 2013). Homozygous mutations in BRCA2, PALB2 or BRIP1 result in Fanconi anemia, while heterozygous mutations in these genes predispose carriers to primarily breast and ovarian cancer. Well established functions of BRCA2, PALB2 and BRIP1 in DNA repair are BRCA1 dependent, but it is not yet clear whether there are additional roles for these proteins in the Fanconi anemia pathway that do not rely on BRCA1 (Evans and Longo 2014, Jiang and Greenberg 2015). Heterozygous BRCA1 mutations predispose carriers to breast and ovarian cancer with high penetrance. Complete loss of BRCA1 function is embryonic lethal. It has only recently been reported that a partial germline loss of BRCA1 function via mutations that diminish protein binding ability of the BRCT domain of BRCA1 result in a FA-like syndrome. BRCA1 has therefore been designated as the FANCS gene (Jiang and Greenberg 2015).

The FA pathway is involved in repairing DNA ICLs that arise by exposure to endogenous mutagens produced as by-products of normal cellular metabolism, such as aldehyde containing compounds. Disruption of the aldehyde dehydrogenase gene ALDH2 in FANCD2 deficient mice leads to severe developmental defects, early lethality and predisposition to leukemia. In addition to this, the double knockout mice are exceptionally sensitive to ethanol consumption, as ethanol metabolism results in accumulated levels of aldehydes (Langevin et al. 2011).

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## Editions

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## Interactors found in the analysis (2)

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|---|---|---|---|---|---|
| BRCA1 | P38398 | O15360, Q9BXW9 | BRCA2 | P51587 | Q9BXW9 |

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