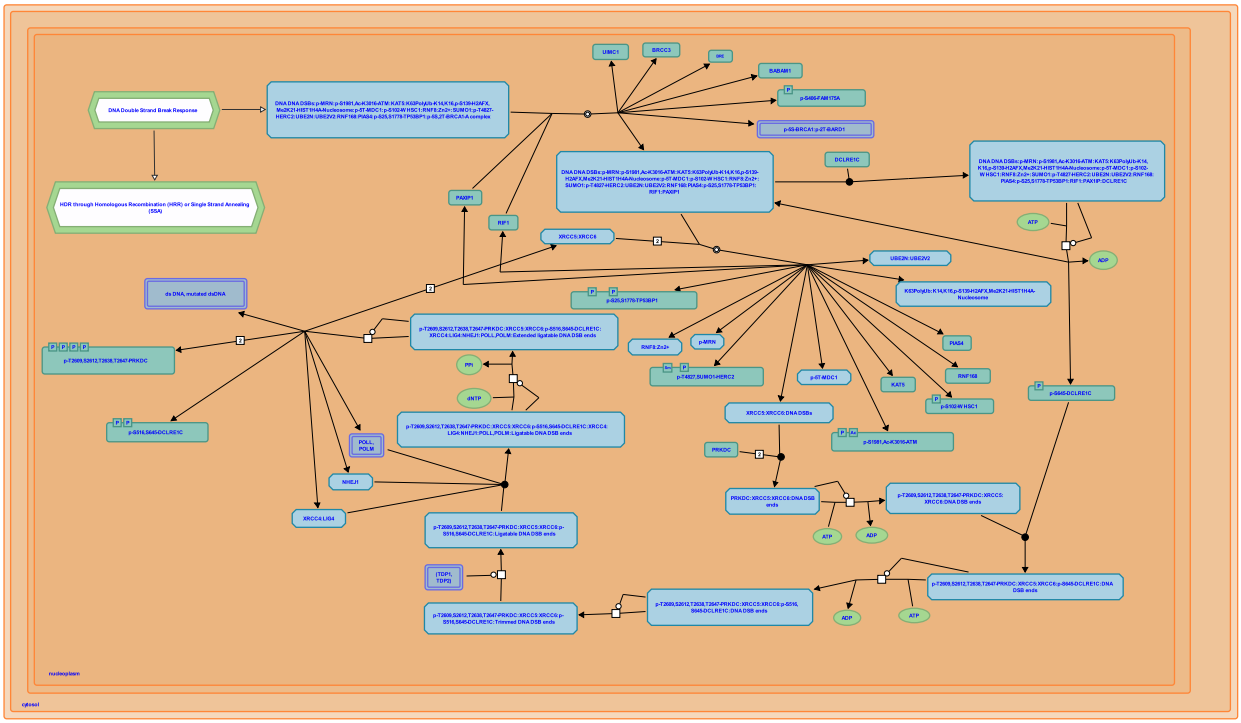
Nonhomologous End-Joining (NHEJ)



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03/05/2024

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. ↗

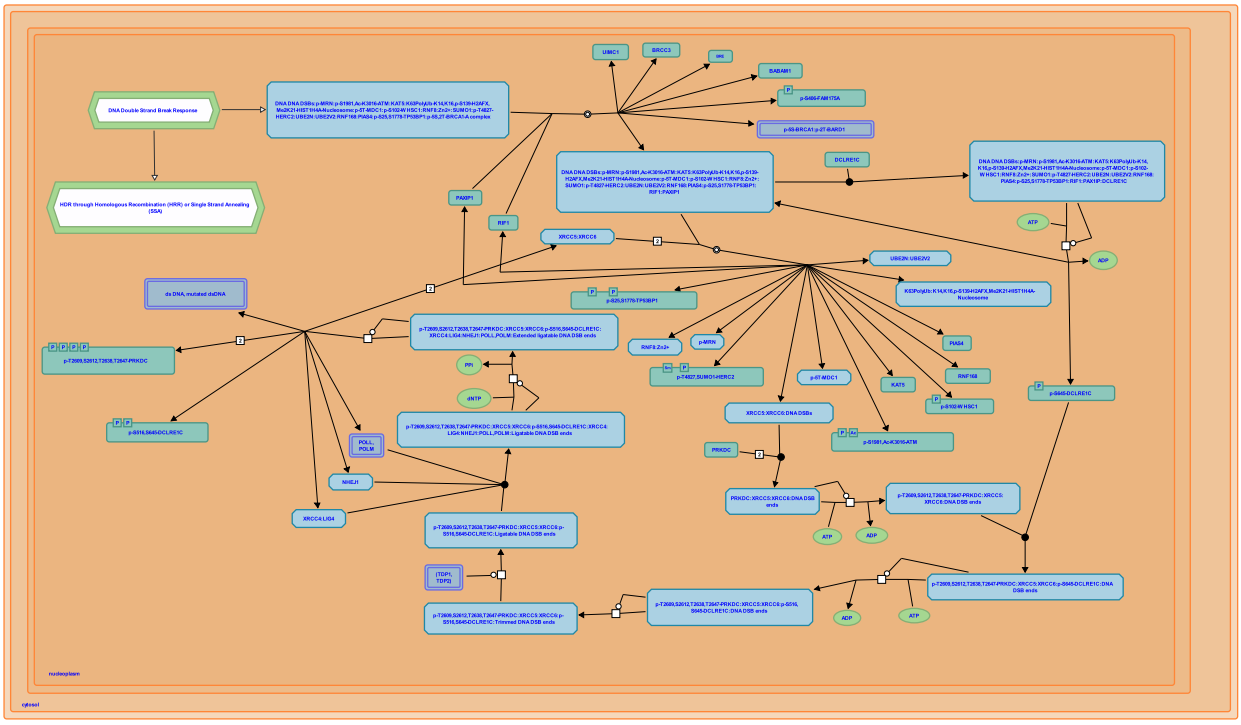
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Nonhomologous End-Joining (NHEJ) ↗

Stable identifier: R-HSA-5693571

Compartments: nucleoplasm



The nonhomologous end joining (NHEJ) pathway is initiated in response to the formation of DNA double-strand breaks (DSBs) induced by DNA-damaging agents, such as ionizing radiation. DNA DSBs are recognized by the MRN complex (MRE11A:RAD50:NBN), leading to ATM activation and ATM-dependent recruitment of a number of DNA damage checkpoint and repair proteins to DNA DSB sites (Lee and Paull 2005). The ATM phosphorylated MRN complex, MDC1 and H2AFX-containing nucleosomes (gamma-H2AX) serve as scaffolds for the formation of nuclear foci known as ionizing radiation induced foci (IRIF) (Gatei et al. 2000, Paull et al. 2000, Stewart et al. 2003, Stucki et al. 2005). Ultimately, both BRCA1:BARD1 heterodimers and TP53BP1 (53BP1) are recruited to IRIF (Wang et al. 2007, Pei et al. 2011, Mallette et al. 2012), which is necessary for ATM-mediated CHEK2 activation (Wang et al. 2002, Wilson et al. 2008). In G1 cells, TP53BP1 promotes NHEJ by recruiting RIF1 and PAX1IP, which displaces BRCA1:BARD1 and associated proteins from the DNA DSB site and prevents resection of DNA DSBs needed for homologous recombination repair (HRR) (Escribano-Diaz et al. 2013, Zimmermann et al. 2013, Callen et al. 2013). TP53BP1 also plays an important role in ATM-mediated phosphorylation of DCLRE1C (ARTEMIS) (Riballo et al. 2004, Wang et al. 2014). 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 (Walker et al. 2001, Sun et al. 2012). 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 (Gottlieb 1993, Yoo and Dynan 2000). DNA-PK complex recruits DCLRE1C (ARTEMIS) to DNA DSB ends (Ma et al. 2002). PRKDC-mediated phosphorylation of DCLRE1C, as well as PRKDC autophosphorylation, enables DCLRE1C to trim 3'- and 5'-overhangs at DNA DSBs, preparing them for ligation (Ma et al. 2002, Ma et al. 2005, Niewolik et al. 2006). The binding of inositol phosphate may additionally stimulate the catalytic activity of PRKDC (Hanakahi et al. 2000). Other factors, such as polynucleotide kinase (PNK), TDP1 or TDP2 may remove unligatable damaged nucleotides from 5'- and 3'-ends of the DSB, converting them to ligatable substrates (Inamdar et al. 2002, Gomez-Herreros et al. 2013). DNA ligase 4 (LIG4) in complex with XRCC4 (XRCC4:LIG4) is recruited to ligatable DNA DSB ends together with the XLF (NHEJ1) homodimer and DNA polymerases mu (POLM) and/or lambda (POLL) (McElhinny et al. 2000, Hsu et al. 2002, Malu et al. 2002, Ahnesorg et al. 2006, Mahajan et al. 2002, Lee et al. 2004, Fan and Wu 2004). After POLL and/or POLM fill 1- or 2-nucleotide long single strand gaps at aligned DNA DSB ends, XRCC4:LIG4 performs the ligation of broken DNA strands, thus completing NHEJ. The presence of NHEJ1 homodimer facilitates the ligation step, especially at mismatched DSB ends (Tsai et al. 2007). Depending on other types of DNA damage present at DNA DSBs, NHEJ can result in error-free products, produce dsDNA with microdeletions and/or mismatched bases, or result in translocations (reviewed by Povrik et al. 2012).

Literature references

Sun, J., Chen, DJ., Davis, AJ., Lee, KJ. (2012). Human Ku70/80 protein blocks exonuclease 1-mediated DNA resection in the presence of human Mre11 or Mre11/Rad50 protein complex. *J. Biol. Chem., 287*, 4936-45. ↗

Sixma, TK., Cui, G., Mer, G., Richard, S., Young, LC., Mallette, FA. et al. (2012). RNF8- and RNF168-dependent degradation of KDM4A/JMJD2A triggers 53BP1 recruitment to DNA damage sites. *EMBO J., 31*, 1865-78. ↗

Spring, K., Lavin, MF., Concannon, P., Gatti, RA., Desai-Mehta, A., Khanna, K. et al. (2000). ATM-dependent phosphorylation of nibrin in response to radiation exposure. *Nat. Genet., 25*, 115-9. ↗

Chen, DJ., Yannone, SM., Hsu, HL. (2002). Defining interactions between DNA-PK and ligase IV/XRCC4. *DNA Repair (Amst.), 1*, 225-35. ↗

Zimmermann, M., Buonomo, SB., de Lange, T., Lottersberger, F., Sfeir, A. (2013). 53BP1 regulates DSB repair using Rif1 to control 5' end resection. *Science, 339*, 700-4. ↗

Editions

2003-07-14	Authored	Lees-Miller, S.
2015-05-12	Edited, Revised	Orlic-Milacic, M.
2015-06-12	Reviewed	Borowiec, JA.
2024-03-06	Edited	Joshi-Tope, G.
2024-03-06	Reviewed	West, SC.

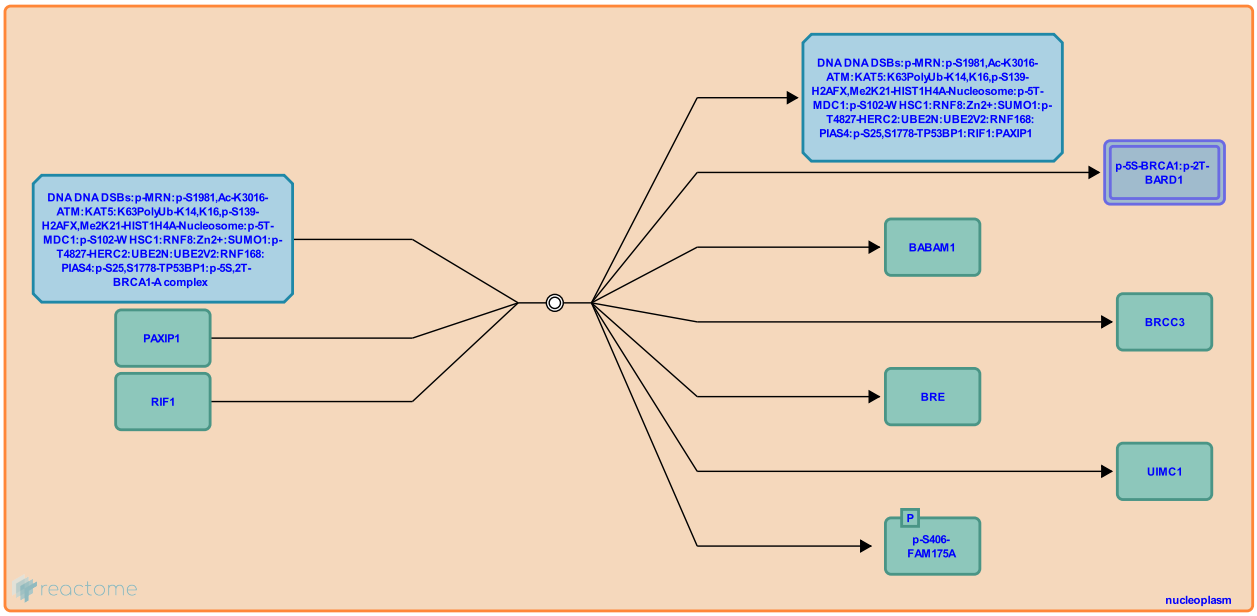
RIF1 and PAX1IP bind TP53BP1 at DNA DSBs ↗

Location: Nonhomologous End-Joining (NHEJ)

Stable identifier: R-HSA-5686685

Type: dissociation

Compartments: nucleoplasm



RIF1 binds TP53BP1 phosphorylated by ATM at DNA double strand breaks (DSBs). RIF1 binding interferes with the accumulation of BRCA1:BARD1 heterodimers and associated proteins at DNA DSBs. Therefore, TP53BP1-mediated recruitment of RIF1 prevents RBBP8 (CtIP) binding to BRCA1:BARD1 and the subsequent resection of DNA DSBs. The action of RIF1 and TP53BP1 promotes non-homologous end joining (NHEJ) of DNA DSBs during G1 phase of the cell cycle, when sister chromatids are not available for homologous recombination-mediated repair (Zimmermann et al. 2013, Escribano-Diaz et al. 2013).

Similar to RIF1, PAX1IP (PTIP) is also recruited to DNA DSBs through interaction with ATM-phosphorylated TP53BP1. Since RIF1 and PAX1IP interact with different phosphorylated sites on TP53BP1, they can simultaneously bind TP53BP1 and colocalize in the majority of TP53BP1 foci. PAX1IP contributes to inhibition of DNA DSB resection mediated by BRCA1-recruited RBBP8 (CtIP) (Callen et al. 2013).

Followed by: Association of Ku heterodimer with ends of DNA double-strand break, TP53BP1 recruits DCLRE1C to ATM

Literature references

Ge, K., Callen, E., Daniel, JA., Polato, F., Alt, FW., Wesemann, DR. et al. (2013). 53BP1 mediates productive and mutagenic DNA repair through distinct phosphoprotein interactions. *Cell, 153*, 1266-80. ↗

Durocher, D., Canny, MD., Fradet-Turcotte, A., Tká?, J., Xing, M., Rosebrock, AP. et al. (2013). A cell cycle-dependent regulatory circuit composed of 53BP1-RIF1 and BRCA1-CtIP controls DNA repair pathway choice. *Mol. Cell, 49*, 872-83. ↗

Zimmermann, M., Buonomo, SB., de Lange, T., Lottersberger, F., Sfeir, A. (2013). 53BP1 regulates DSB repair using Rif1 to control 5' end resection. *Science, 339*, 700-4. ↗

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2015-05-12	Authored, Edited	Orlic-Milacic, M.
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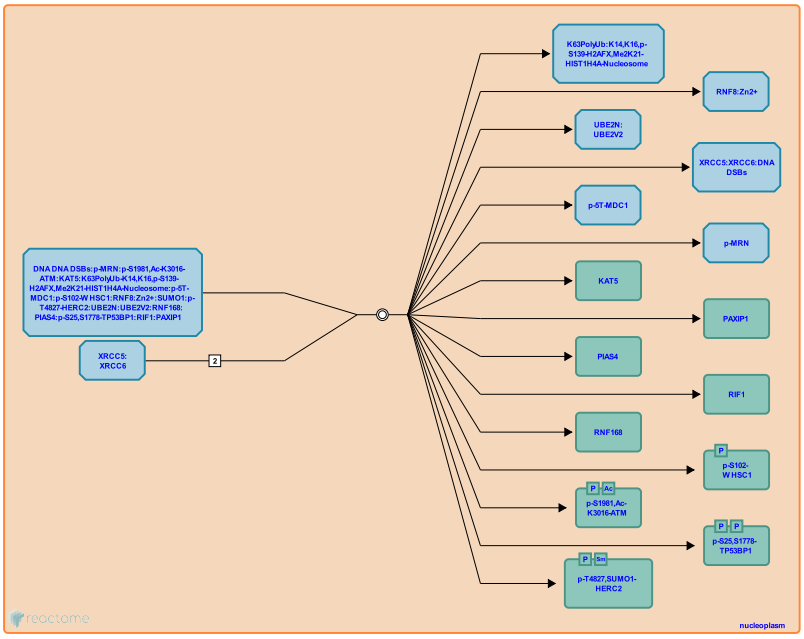
Association of Ku heterodimer with ends of DNA double-strand break ↗

Location: Nonhomologous End-Joining (NHEJ)

Stable identifier: R-HSA-5693599

Type: dissociation

Compartments: nucleoplasm



Ionizing radiation (IR) induces single-strand breaks, i.e., cleavage of the phosphodiester backbone. When two single-strand breaks occur within approximately 10 base pairs, a DNA double-strand break (DSB) results. IR-induced DSBs are complex DNA damage lesions, frequently containing base damage, 5'-OH groups, and 3'-hydroxy or phosphoglycolate groups that must be removed prior to ligation in the final step of NHEJ (Friedberg et al, 1995; Nikjoo et al, 2001; Valerie and Povirk, 2003). The Ku70/80 heterodimer (XRCC5:XRCC6) (Walker et al., 2001) binds to the ends of the double-strand break. Ku can translocate inwards from the site of the break in an ATP-independent manner (reviewed in Dynan and Yoo, 1998). Binding of XRCC5:XRCC6 to DNA DSBs competes away the MRN complex and associated proteins from the DNA DSB (Sun et al. 2012).

Preceded by: RIF1 and PAX1IP bind TP53BP1 at DNA DSBs

Followed by: Association of DNA-PKcs with Ku-bound ends of DNA double-strand breaks - synapsis

Literature references

Valerie, K., Povirk, LF. (2003). Regulation and mechanisms of mammalian double-strand break repair. *Oncogene, 22*, 5792-812. ↗

Sun, J., Chen, DJ., Davis, AJ., Lee, KJ. (2012). Human Ku70/80 protein blocks exonuclease 1-mediated DNA resection in the presence of human Mre11 or Mre11/Rad50 protein complex. *J. Biol. Chem., 287*, 4936-45. ↗

Goodhead, DT., O'Neill, P., Wilson, WE., Nikjoo, H. (2001). Computational approach for determining the spectrum of DNA damage induced by ionizing radiation. *Radiat Res, 156*, 577-83. ↗

Friedberg, EC., Siede, W., Walker, GC. (1995). DNA Repair and Mutagenesis. *ASM Press*.

Dynan, WS., Yoo, S. (1998). Interaction of Ku protein and DNA-dependent protein kinase catalytic subunit with nucleic acids. *Nucleic Acids Res, 26*, 1551-9. ↗

Editions

2003-09-07	Authored	Matthews, L.
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2015-06-12	Reviewed	Borowiec, JA.

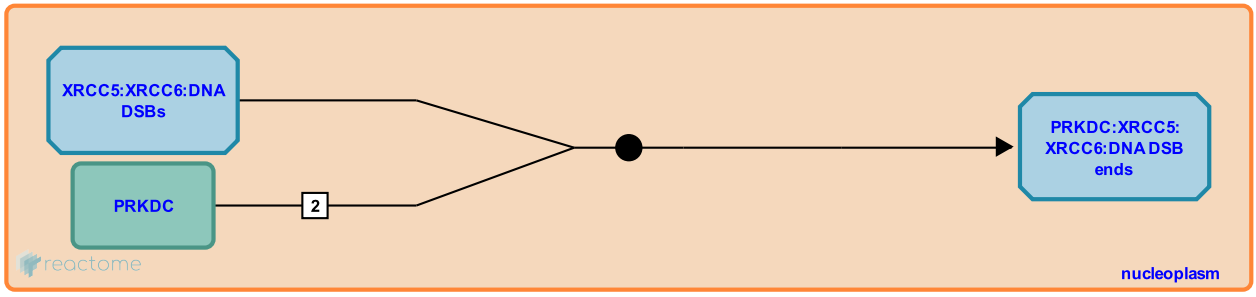
Association of DNA-PKcs with Ku-bound ends of DNA double-strand breaks - synapsis ↗

Location: Nonhomologous End-Joining (NHEJ)

Stable identifier: R-HSA-5693615

Type: binding

Compartments: nucleoplasm



DNA-PKcs (PRKDC) is recruited to the Ku70:Ku80:DNA double strand break ends complex (XRCC5:XRCC6:DNA DSBs) (Gottlieb and Jackson, 1993), causing Ku to translocate inwards (away from the break) approximately 10 bp (Yoo and Dynan, 1999). This forms the DNA-PK complex (DNA-PKcs plus Ku70/Ku80) at each end of the DSB. Two DNA-PK complexes, one on either side of the DSB, interact to bring the DNA ends together.

Preceded by: Association of Ku heterodimer with ends of DNA double-strand break

Followed by: DNA-PKcs autophosphorylates

Literature references

Dynan, WS., Yoo, S. (2000). Geometry of a complex formed by double strand break repair proteins at a single DNA end: recruitment of DNA-PKcs induces inward translocation of Ku protein. *Nucleic Acids Res, 27*, 4679-86. ↗

Gottlieb, TM. (1993). The DNA-dependent protein kinase: requirement for DNA ends and association with Ku antigen . *Cell, 72*, 131-42. ↗

Editions

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2015-06-12	Reviewed	Borowiec, JA.

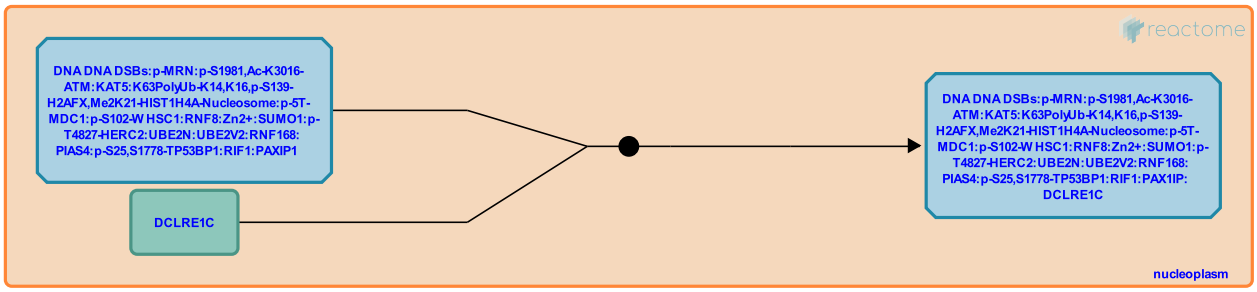
TP53BP1 recruits DCLRE1C to ATM ↗

Location: Nonhomologous End-Joining (NHEJ)

Stable identifier: R-HSA-5686900

Type: binding

Compartments: nucleoplasm



TP53BP1 is required for the recruitment of DCLRE1C (ARTEMIS) to DNA double strand breaks (DSBs) and ATM-mediated phosphorylation of DCLRE1C (Riballo et al. 2004). DCRLE1C directly interacts with the TP53BP1-binding protein PAX1IP (PTIP) (Wang et al. 2014).

Preceded by: RIF1 and PAX1IP bind TP53BP1 at DNA DSBs

Followed by: Activated ATM phosphorylates DCLRE1C

Literature references

Recio, MJ., Löbrich, M., Kühne, M., Jackson, SP., Parker, AR., Doherty, A. et al. (2004). A pathway of double-strand break rejoining dependent upon ATM, Artemis, and proteins locating to gamma-H2AX foci. *Mol. Cell, 16*, 715-24. ↗

Lobrich, M., Aroumougame, A., Gong, Z., Chen, J., Chen, D., Li, Y. et al. (2014). PTIP associates with Artemis to dictate DNA repair pathway choice. *Genes Dev., 28*, 2693-8. ↗

Editions

2015-05-12	Authored, Edited	Orlic-Milacic, M.
2015-06-12	Reviewed	Borowiec, JA.

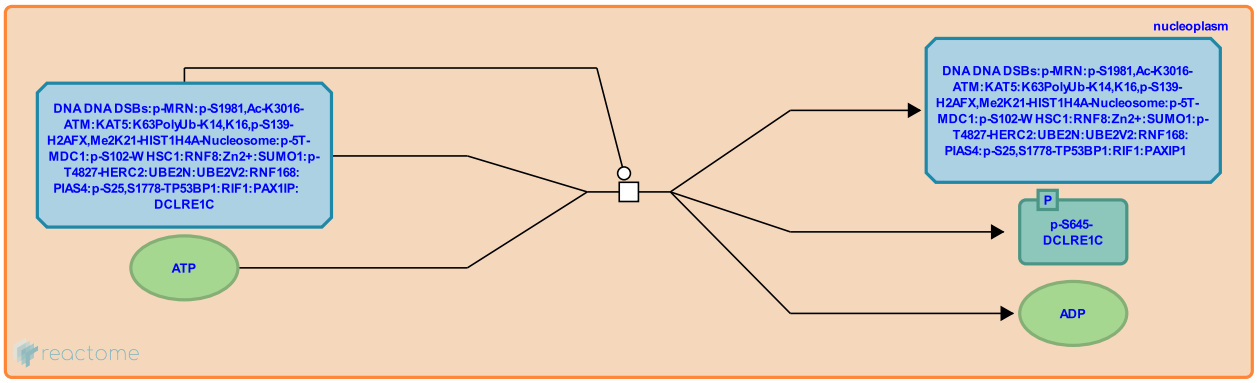
Activated ATM phosphorylates DCLRE1C ↗

Location: Nonhomologous End-Joining (NHEJ)

Stable identifier: R-HSA-5686704

Type: transition

Compartments: nucleoplasm



Activated ATM phosphorylates DCLRE1C (ARTEMIS) at serine residue S645. S645 phosphorylation is necessary for the function of DCLRE1C in non-homologous end joining (NHEJ) (Riballo et al. 2004, Poinsignon et al. 2004, Chen et al. 2005).

Preceded by: TP53BP1 recruits DCLRE1C to ATM

Followed by: DCLRE1C binds PRKDC:XRCC5:XRCC6 at DNA DSBs

Literature references

Fischer, A., Soubeyrand, S., de Chasseval, R., Poinsignon, C., Haché, RJ., de Villartay, JP. et al. (2004). Phosphorylation of Artemis following irradiation-induced DNA damage. *Eur. J. Immunol., 34*, 3146-55. ↗

Delia, D., Nakada, S., Mizutani, S., Chessa, L., Minegishi, Y., Lecis, D. et al. (2005). Ataxia-telangiectasia-mutated dependent phosphorylation of Artemis in response to DNA damage. *Cancer Sci., 96*, 134-41. ↗

Recio, MJ., Löbrich, M., Kühne, M., Jackson, SP., Parker, AR., Doherty, A. et al. (2004). A pathway of double-strand break rejoining dependent upon ATM, Artemis, and proteins locating to gamma-H2AX foci. *Mol. Cell, 16*, 715-24. ↗

Editions

2015-05-12	Authored, Edited	Orlic-Milacic, M.
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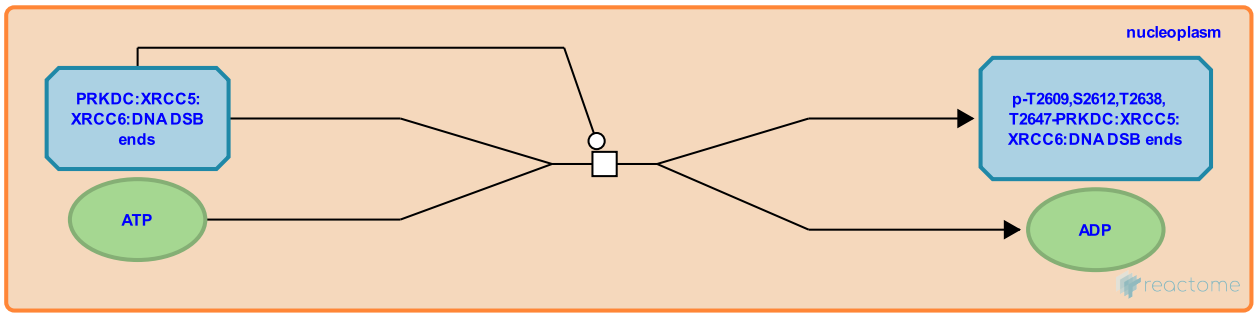
DNA-PKcs autophosphorylates ↗

Location: Nonhomologous End-Joining (NHEJ)

Stable identifier: R-HSA-5693575

Type: transition

Compartments: nucleoplasm



Autophosphorylation of DNA-PKcs (PRKDC) is required for NHEJ in vivo, especially for endonucleolytic processing of DNA double strand break ends, which makes them suitable for ligation (Chan et al, 2002; Ding et al, 2003). In vivo, PRKDC autophosphorylates at threonine residues T2609, T2638 and T2647, and serine residue S2612 (Douglas et al. 2002).

Preceded by: Association of DNA-PKcs with Ku-bound ends of DNA double-strand breaks - synapsis

Followed by: DCLRE1C binds PRKDC:XRCC5:XRCC6 at DNA DSBs

Literature references

Douglas, P., Meek, K., Alessi, DR., Goodarzi, AA., Morrice, N., Yu, Y. et al. (2002). Identification of in vitro and in vivo phosphorylation sites in the catalytic subunit of the DNA-dependent protein kinase. *Biochem J, 368*, 243-51. ↗

Story, MD., Chen, BP., Kurimasa, A., Prithivirajsingh, S., Chan, DW., Chen, DJ. et al. (2002). Autophosphorylation of the DNA-dependent protein kinase catalytic subunit is required for rejoining of DNA double-strand breaks. *Genes Dev, 16*, 2333-8. ↗

Ding, Q., Douglas, P., Meek, K., Ramsden, DA., Woods, T., Lees-Miller, SP. et al. (2003). Autophosphorylation of the catalytic subunit of the DNA-dependent protein kinase is required for efficient end processing during DNA double-strand break repair. *Mol Cell Biol, 23*, 5836-48. ↗

Editions

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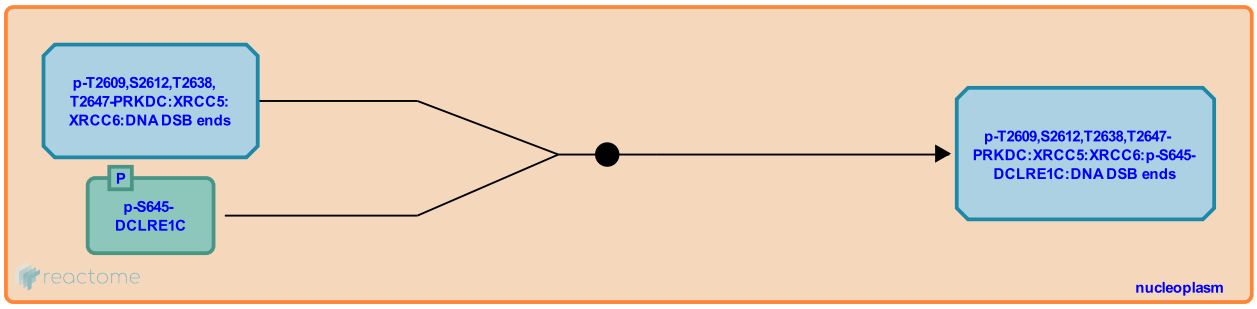
DCLRE1C binds PRKDC:XRCC5:XRCC6 at DNA DSBs ↗

Location: Nonhomologous End-Joining (NHEJ)

Stable identifier: R-HSA-5686924

Type: binding

Compartments: nucleoplasm



DCLRE1C (ARTEMIS) forms a stable complex with PRKDC (DNA-PKcs), even in the absence of DNA ends (Ma et al. 2002). Autophosphorylation of PRKDC as well as ATM-mediated phosphorylation of DCLRE1C are not prerequisites for the interaction of PRKDC and DCLRE1C (Ding et al.2003).

Preceded by: Activated ATM phosphorylates DCLRE1C, DNA-PKcs autophosphorylates

Followed by: PRKDC phosphorylates DCLRE1C at DNA DSBs

Literature references

Schwarz, K., Pannicke, U., Lieber, MR., Ma, Y. (2002). Hairpin opening and overhang processing by an Artemis/DNA-dependent protein kinase complex in nonhomologous end joining and V(D)J recombination. *Cell, 108*, 781-94. ↗

Ding, Q., Douglas, P., Meek, K., Ramsden, DA., Woods, T., Lees-Miller, SP. et al. (2003). Autophosphorylation of the catalytic subunit of the DNA-dependent protein kinase is required for efficient end processing during DNA double-strand break repair. *Mol Cell Biol, 23*, 5836-48. ↗

Editions

2015-05-12	Authored, Edited	Orlic-Milacic, M.
2015-06-12	Reviewed	Borowiec, JA.

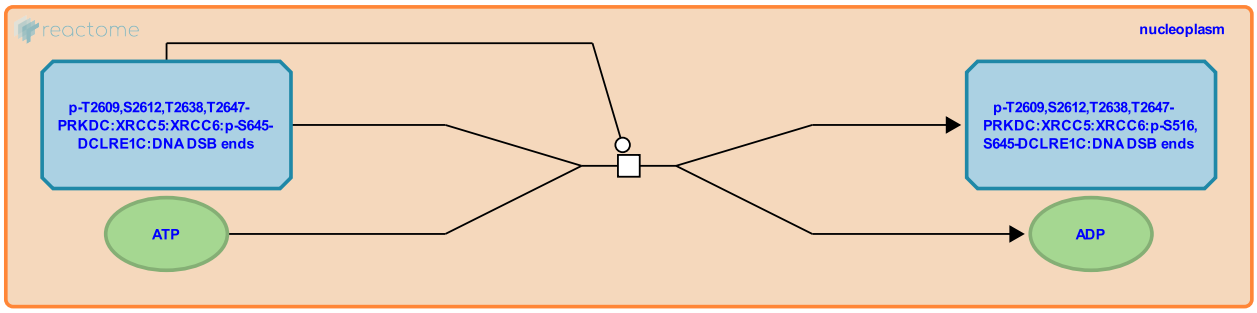
PRKDC phosphorylates DCLRE1C at DNA DSBs ↗

Location: Nonhomologous End-Joining (NHEJ)

Stable identifier: R-HSA-5687183

Type: transition

Compartments: nucleoplasm



PRKDC (DNA-PKcs) phosphorylates DCLRE1C (ARTEMIS) at least on serine residue S516, and this phosphorylation is necessary for the activation of DCLRE1C endonucleolytic activity (Ma et al. 2002, Ma et al. 2005, Soubeyrand et al. 2006) as it relieves an autoinhibitory conformation of DCLRE1C (Niewolik et al. 2006).

Preceded by: DCLRE1C binds PRKDC:XRCC5:XRCC6 at DNA DSBs

Followed by: DCLRE1C (ARTEMIS) processes DNA DSB ends

Literature references

Lieber, MR., Schwarz, K., Lu, H., Pannicke, U., Niewolik, D., Ma, Y. (2005). The DNA-dependent protein kinase catalytic subunit phosphorylation sites in human Artemis. *J. Biol. Chem., 280*, 33839-46. ↗

Kulesza, P., Schwarz, K., Lieber, MR., Lu, H., Wang, LC., Pannicke, U. et al. (2006). DNA-PKcs dependence of Artemis endonucleolytic activity, differences between hairpins and 5' or 3' overhangs. *J. Biol. Chem., 281*, 33900-9. ↗

Schwarz, K., Pannicke, U., Lieber, MR., Ma, Y. (2002). Hairpin opening and overhang processing by an Artemis/DNA-dependent protein kinase complex in nonhomologous end joining and V(D)J recombination. *Cell, 108*, 781-94. ↗

Soubeyrand, S., Dong, F., de Chasseval, R., Pope, L., Haché, RJ., Gosselin, D. et al. (2006). Artemis phosphorylated by DNA-dependent protein kinase associates preferentially with discrete regions of chromatin. *J. Mol. Biol., 358*, 1200-11. ↗

Editions

2015-05-12	Authored, Edited	Orlic-Milacic, M.
2015-06-12	Reviewed	Borowiec, JA.

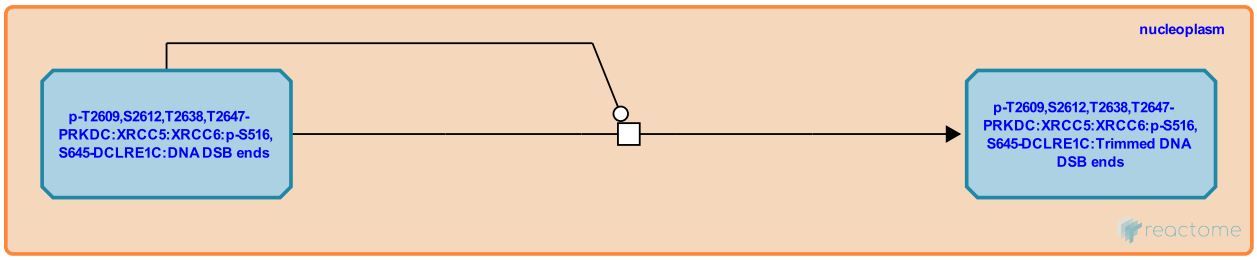
DCLRE1C (ARTEMIS) processes DNA DSB ends ↗

Location: Nonhomologous End-Joining (NHEJ)

Stable identifier: R-HSA-5693533

Type: transition

Compartments: nucleoplasm



DCLRE1C (ARTEMIS) possesses an intrinsic 5' to 3' exonuclease activity. Upon binding to PRKDC (DNA-PKcs) at DNA double strand breaks (DSBs) and undergoing PRKDC-mediated phosphorylation, DCLRE1C acquires endonucleolytic activity towards 5' and 3' overhangs at DNA double strand breaks, and it also acquires a hairpin opening activity (Ma et al. 2002, Ma et al. 2005). Autophosphorylation of PRKDC, although not required for the kinase activity of PRKDC, is needed for the activation of the endonucleolytic activity of DCLRE1C, probably by inducing a conformational change in PRKDC that provides DCLRE1C with access to DNA ends (Goodarzi et al. 2006, Niewolik et al. 2006, Jiang et al. 2015).

Preceded by: PRKDC phosphorylates DCLRE1C at DNA DSBs

Followed by: TDP1 and TDP2 process unligatable DSB ends

Literature references

Zha, S., Crowe, JL., Dubois, RL., Nakajima, S., Lan, L., Liu, C. et al. (2015). Differential Phosphorylation of DNA-PKcs Regulates the Interplay between End-Processing and End-Ligation during Nonhomologous End-Joining. *Mol. Cell , 58*, 172-85. ↗

Ye, R., Härer, C., Walker, SA., Douglas, P., Marchetti, C., Lees-Miller, SP. et al. (2006). DNA-PK autophosphorylation facilitates Artemis endonuclease activity. *EMBO J., 25*, 3880-9. ↗

Lieber, MR., Schwarz, K., Lu, H., Pannicke, U., Niewolik, D., Ma, Y. (2005). The DNA-dependent protein kinase catalytic subunit phosphorylation sites in human Artemis. *J. Biol. Chem., 280*, 33839-46. ↗

Kulesza, P., Schwarz, K., Lieber, MR., Lu, H., Wang, LC., Pannicke, U. et al. (2006). DNA-PKcs dependence of Artemis endonucleolytic activity, differences between hairpins and 5' or 3' overhangs. *J. Biol. Chem., 281*, 33900-9. ↗

Schwarz, K., Pannicke, U., Lieber, MR., Ma, Y. (2002). Hairpin opening and overhang processing by an Artemis/DNA-dependent protein kinase complex in nonhomologous end joining and V(D)J recombination. *Cell, 108*, 781-94. ↗

Editions

2003-07-14	Authored	Lees-Miller, S.
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2015-06-12	Reviewed	Borowiec, JA.

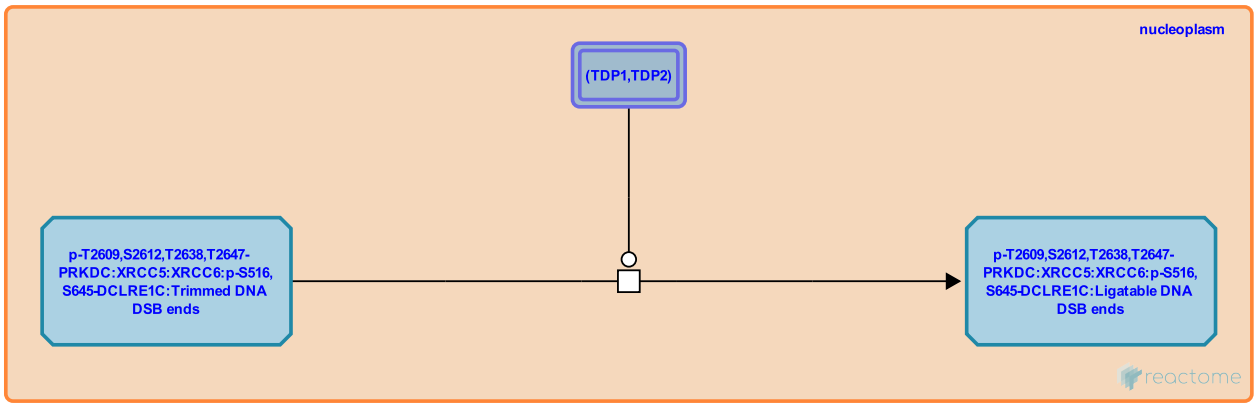
TDP1 and TDP2 process unligatable DSB ends ↗

Location: Nonhomologous End-Joining (NHEJ)

Stable identifier: R-HSA-5693578

Type: transition

Compartments: nucleoplasm



Free radical-induced DNA double strand breaks (DSBs) frequently have unligatable 3'-phosphoglycolate termini, while topoisomerase II (TOP2) inhibition produces unligatable 5'-ends, with a 5'-phosphotyrosil bond between the DNA DSB 5'-end and TOP2 (reviewed by Povirk 2012). Tyrosyl-DNA phosphodiesterase TDP1 is able to remove 3'-phosphoglycolate and plays an important role in non-homologous end joining (NHEJ) (Inamdar et al. 2002, Zhou et al. 2005, Zhou et al. 2009, Heo et al. 2015). Tyrosil-DNA phosphodiesterase TDP2 removes 5'-phosphotyrosine and is also involved in NHEJ (Gomez-Herreros et al. 2013).

Preceded by: DCLRE1C (ARTEMIS) processes DNA DSB ends

Followed by: XRCC4:LIG4, NHEJ1 and POLL or POLM bind DNA DSBs in NHEJ

Literature references

Povirk, LF. (2012). Processing of damaged DNA ends for double-strand break repair in mammalian cells. *ISRN Mol Biol, 2012*. ↗

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Valerie, K., Lin, PS., Ramsden, DA., Mohapatra, S., Lees-Miller, SP., Povirk, LF. et al. (2009). Tyrosyl-DNA phosphodiesterase and the repair of 3'-phosphoglycolate-terminated DNA double-strand breaks. *DNA Repair (Amst.), 8*, 901-11. ↗

Rasouli-Nia, A., Lees-Miller, SP., Inamdar, KV., Povirk, LF., Zhou, T., Pouliot, JJ. (2002). Conversion of phosphoglycolate to phosphate termini on 3' overhangs of DNA double strand breaks by the human tyrosyl-DNA phosphodiesterase hTdp1. *J Biol Chem, 277*, 27162-8. ↗

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Editions

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

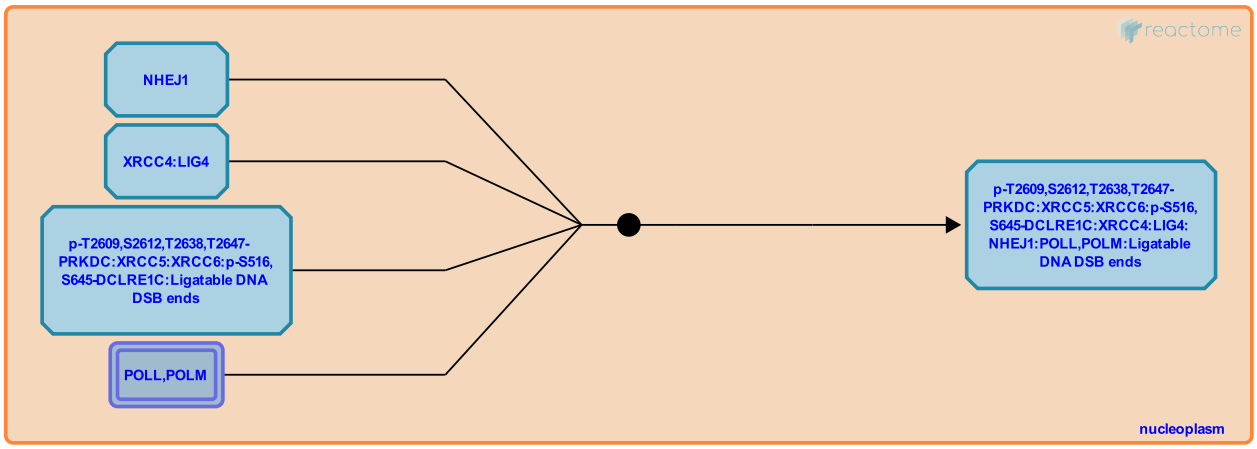
XRCC4:LIG4, NHEJ1 and POLL or POLM bind DNA DSBs in NHEJ ↗

Location: Nonhomologous End-Joining (NHEJ)

Stable identifier: R-HSA-5693574

Type: binding

Compartments: nucleoplasm



A complex consisting of XRCC4 homodimer and DNA ligase IV (LIG4) (Sibanda et al. 2001) is recruited to the synaptic complex consisting of PRKDC (DNA-PKcs), XRCC5, XRCC6, DCLRE1C (ARTEMIS) and ligatable DNA double strand break (DSB) ends (Critchlow and Jackson 1997, Leber et al. 1998, Malu et al. 2012). XRCC4 directly interacts with XRCC5:XRCC6 (McElhinny et al. 2000, Hsu et al. 2002), while LIG4 directly interacts with PRKDC (Hsu et al. 2002) and DCLRE1C (Malu et al. 2012). NHEJ1 (XLF) homodimer binds XRCC4 and is recruited to DNA DSBs together with XRCC4 and LIG4, where it acts as a facilitator of LIG4 activity (Ahnesorg et al. 2006, Buck et al. 2006, Tsai et al. 2007, Li et al. 2008). DNA polymerases mu (POLM) or lambda (POLL) are recruited to DNA DSBs through interaction with the Ku complex (XRCC5:XRCC6) and XRCC4 (Mahajan et al. 2002, Lee et al. 2004, Fan and Wu 2004).

Preceded by: TDP1 and TDP2 process unligatable DSB ends

Followed by: POLL or POLM extends aligned DNA DSB ends to fill gaps

Literature references

Smith, P., Jackson, SP., Ahnesorg, P. (2006). XLF interacts with the XRCC4-DNA ligase IV complex to promote DNA nonhomologous end-joining. *Cell, 124*, 301-13. ↗

Kim, SA., Chu, G., Tsai, CJ. (2007). Cernunnos/XLF promotes the ligation of mismatched and noncohesive DNA ends. *Proc. Natl. Acad. Sci. U.S.A., 104*, 7851-6. ↗

Chen, DJ., Yannone, SM., Hsu, HL. (2002). Defining interactions between DNA-PK and ligase IV/XRCC4. *DNA Repair (Amst.), 1*, 225-35. ↗

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Fischer, A., Sanal, O., Fondanèche, MC., de Chasseval, R., Plebani, A., Le Deist, F. et al. (2006). Cernunnos, a novel nonhomologous end-joining factor, is mutated in human immunodeficiency with microcephaly. *Cell, 124*, 287-99. ↗

Editions

2003-09-07	Authored	Matthews, L.
2015-05-12	Edited, Revised	Orlic-Milacic, M.
2015-06-12	Reviewed	Borowiec, JA.

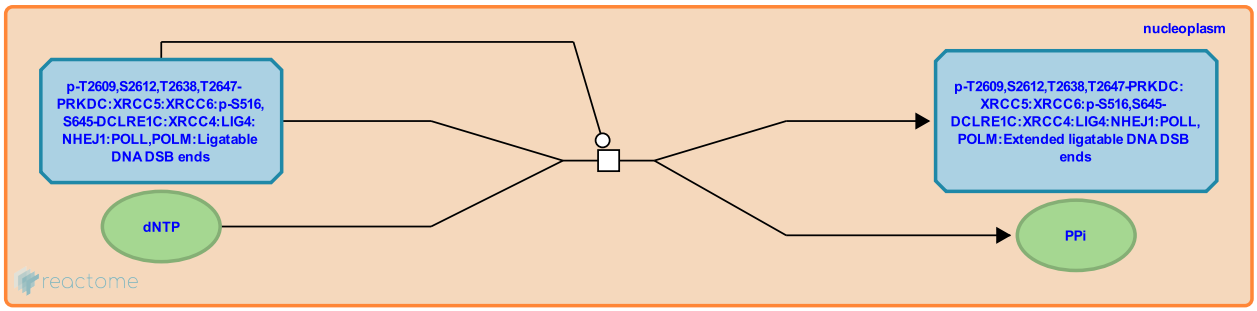
POLL or POLM extends aligned DNA DSB ends to fill gaps ↗

Location: Nonhomologous End-Joining (NHEJ)

Stable identifier: R-HSA-5687360

Type: transition

Compartments: nucleoplasm



DNA polymerases mu (POLM) and lambda (POLL) facilitate non-homologous end joining (NHEJ) of DNA double strand breaks (DSBs) by filling single strand (ss) gaps (usually 1- or 2- nucleotide gaps) present at DNA DSB ends positioned for ligation in the synaptic complex containing XRCC5:XRCC6 (Ku), PRKDC (DNA-PKcs), DCLRE1C (ARTEMIS), XRCC4:LIG4 and NHEJ1 (XLF) (Mahajan et al. 2002, Lee et al. 2004, Fan and Wu 2004, McElhinny et al. 2005, Davis et al. 2008).

Preceded by: XRCC4:LIG4, NHEJ1 and POLL or POLM bind DNA DSBs in NHEJ

Followed by: XRCC4:LIG4 ligates DNA DSB ends during NHEJ

Literature references

Havener, JM., Bebenek, K., Garcia-Diaz, M., Blanco, L., Kee, BL., Ramsden, DA. et al. (2005). A gradient of template dependence defines distinct biological roles for family X polymerases in nonhomologous end joining. *Mol. Cell, 19*, 357-66. ↗

Havener, JM., Davis, BJ., Ramsden, DA. (2008). End-bridging is required for pol mu to efficiently promote repair of noncomplementary ends by nonhomologous end joining. *Nucleic Acids Res., 36*, 3085-94. ↗

Mahajan, KN., Ramsden, DA., Nick McElhinny, SA., Mitchell, BS. (2002). Association of DNA polymerase mu (pol mu) with Ku and ligase IV: role for pol mu in end-joining double-strand break repair. *Mol. Cell. Biol., 22*, 5194-202 . ↗

Fan, W., Wu, X. (2004). DNA polymerase lambda can elongate on DNA substrates mimicking non-homologous end joining and interact with XRCC4-ligase IV complex. *Biochem. Biophys. Res. Commun., 323*, 1328-33. ↗

Lee, JW., Bebenek, K., Garcia-Diaz, M., Blanco, L., Wang, Z., Kunkel, TA. et al. (2004). Implication of DNA polymerase lambda in alignment-based gap filling for nonhomologous DNA end joining in human nuclear extracts. *J. Biol. Chem., 279*, 805-11. ↗

Editions

2015-05-12	Authored, Edited, Revised	Orlic-Milacic, M.
2015-06-12	Reviewed	Borowiec, JA.

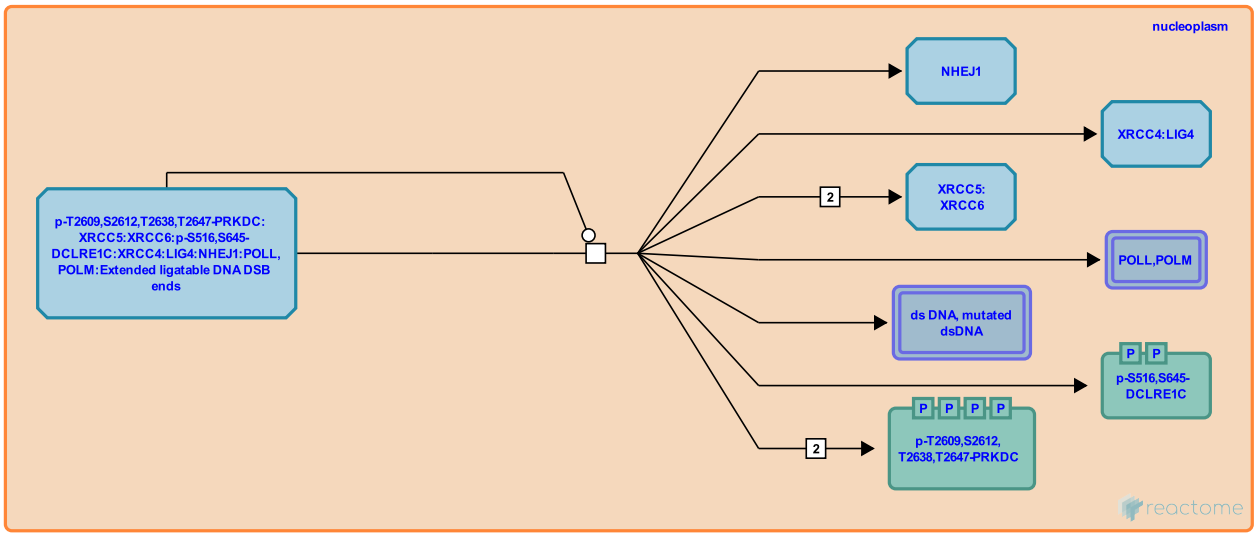
XRCC4:LIG4 ligates DNA DSB ends during NHEJ ↗

Location: Nonhomologous End-Joining (NHEJ)

Stable identifier: R-HSA-5693604

Type: transition

Compartments: nucleoplasm



The DNA ligase complex composed of DNA ligase 4 (LIG4) and the XRCC4 homodimer (Sibanda et al. 2000) catalyzes ligation of DNA double strand break (DSB) ends during non-homologous end joining (NHEJ). The XRCC4:LIG4 complex is recruited to NHEJ sites through interaction of its subunits with XRCC5:XRCC6 (Ku complex), PRKDC (DNA-PKcs) and DCLRE1C (ARTEMIS) (McElhinny et al. 2000, Hsu et al. 2002, Malu et al. 2012). Phosphorylation of XRCC4 by PRKDC may regulate the activity of the ligase complex (Lee et al. 2004). XRCC4:LIG4 can ligate incompatible DNA DSB ends, and may also ligate across single nucleotide gaps (Gu et al. 2007). The presence of the accessory protein NHEJ1 (XLF) facilitates XRCC4:LIG4 ligase activity, especially at mismatched DNA DSB ends (Ahnesorg et al. 2006, Buck et al. 2006, Tsai et al. 2007). Depending on other types of DNA damage present at DNA DSBs, NHEJ can result in error-free products, produce dsDNA with microdeletions and/or mismatched bases, or result in translocations (reviewed by Povirk 2012).

Preceded by: POLL or POLM extends aligned DNA DSB ends to fill gaps

Literature references

Povirk, LF. (2012). Processing of damaged DNA ends for double-strand break repair in mammalian cells. *ISRN Mol Biol, 2012*. ↗

Smith, P., Jackson, SP., Ahnesorg, P. (2006). XLF interacts with the XRCC4-DNA ligase IV complex to promote DNA nonhomologous end-joining. *Cell, 124*, 301-13. ↗

Kim, SA., Chu, G., Tsai, CJ. (2007). Cernunnos/XLF promotes the ligation of mismatched and noncohesive DNA ends. *Proc. Natl. Acad. Sci. U.S.A., 104*, 7851-6. ↗

Hanna, M., Kozlov, M., Greene, M., Malu, S., Tempst, P., Erdjument-Bromage, H. et al. (2012). Artemis C-terminal region facilitates V(D)J recombination through its interactions with DNA Ligase IV and DNA-PKcs. *J. Exp. Med., 209*, 955-63. ↗

Chen, DJ., Yannone, SM., Hsu, HL. (2002). Defining interactions between DNA-PK and ligase IV/XRCC4. *DNA Repair (Amst.), 1*, 225-35. ↗

Editions

2003-09-07	Authored	Matthews, L.
2015-05-12	Edited, Revised	Orlic-Milacic, M.
2015-06-12	Reviewed	Borowiec, JA.

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