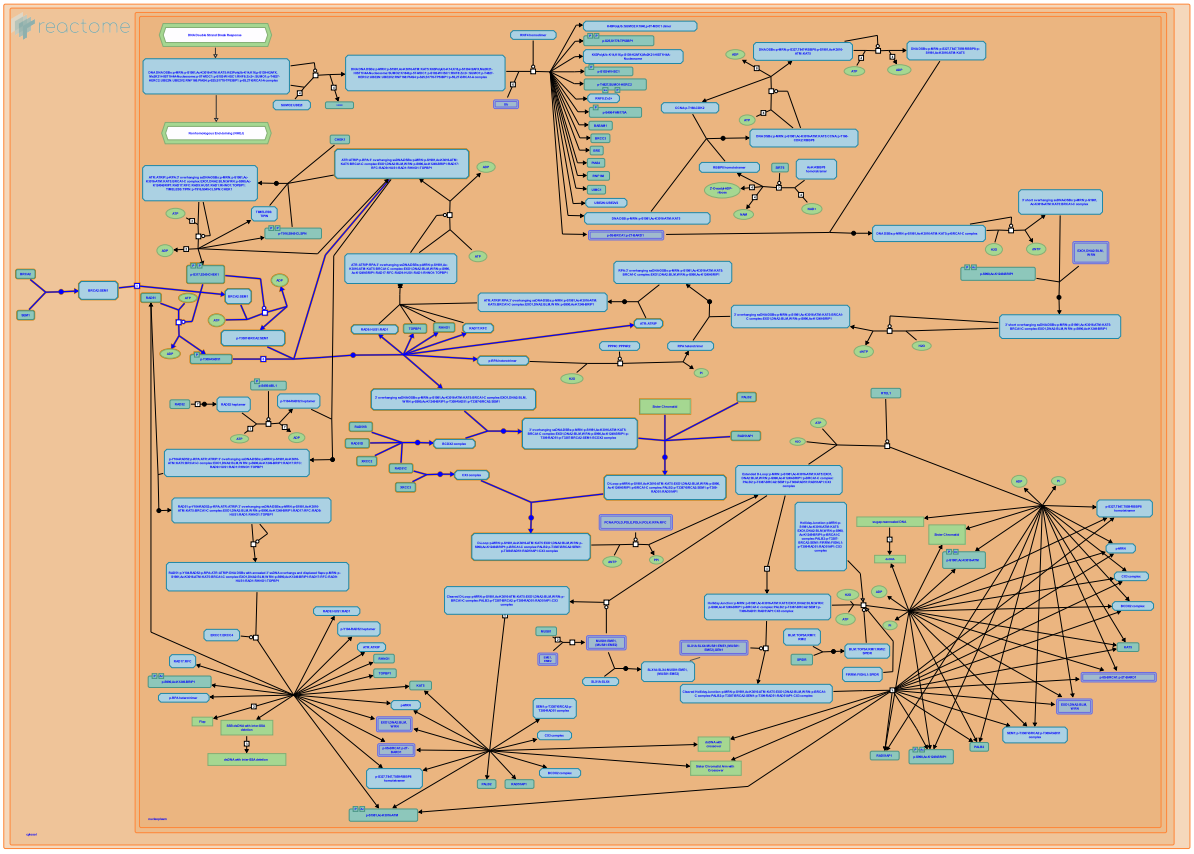
Homologous DNA Pairing and Strand Exchange



Borowiec, JA., Matthews, L., Orlic-Milacic, M., Pospiech, H., Thompson, L., Winqvist, R.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

03/06/2024

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. ↗

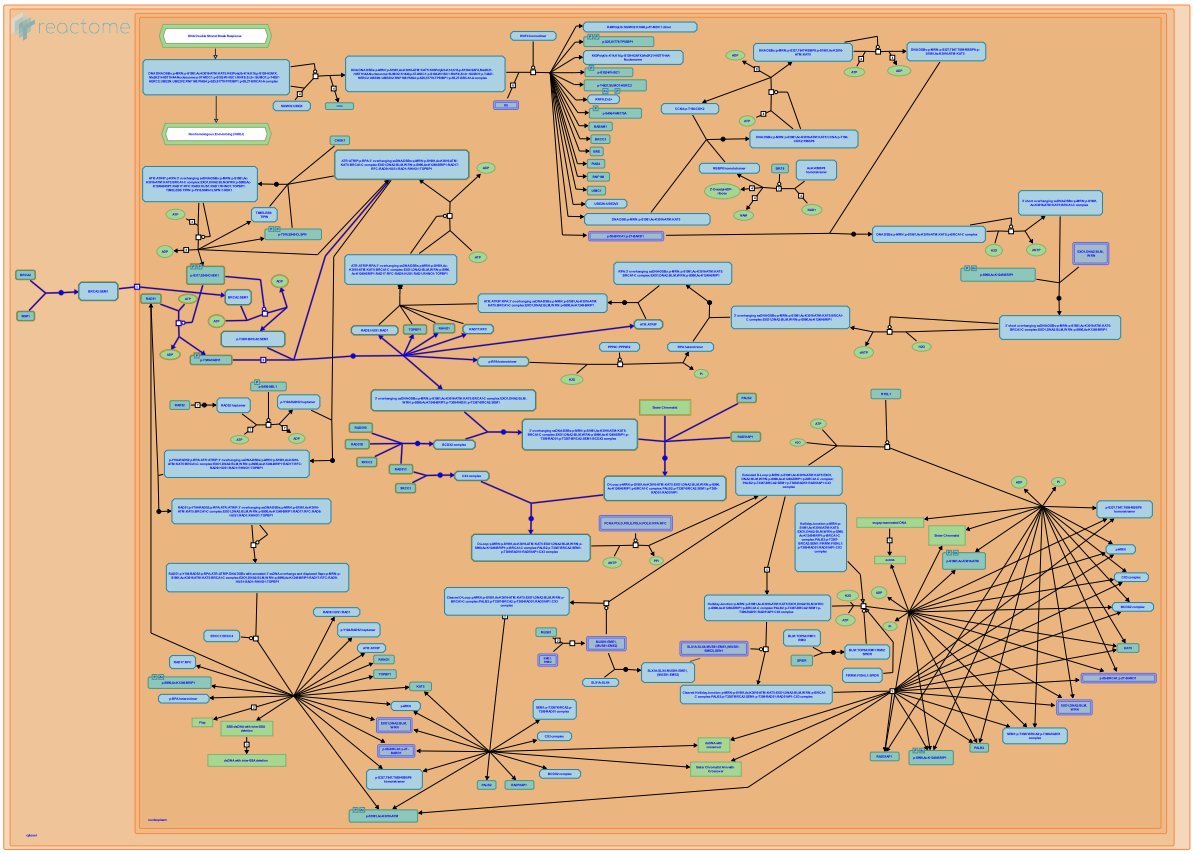
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Homologous DNA Pairing and Strand Exchange ↗

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. ↗

Editions

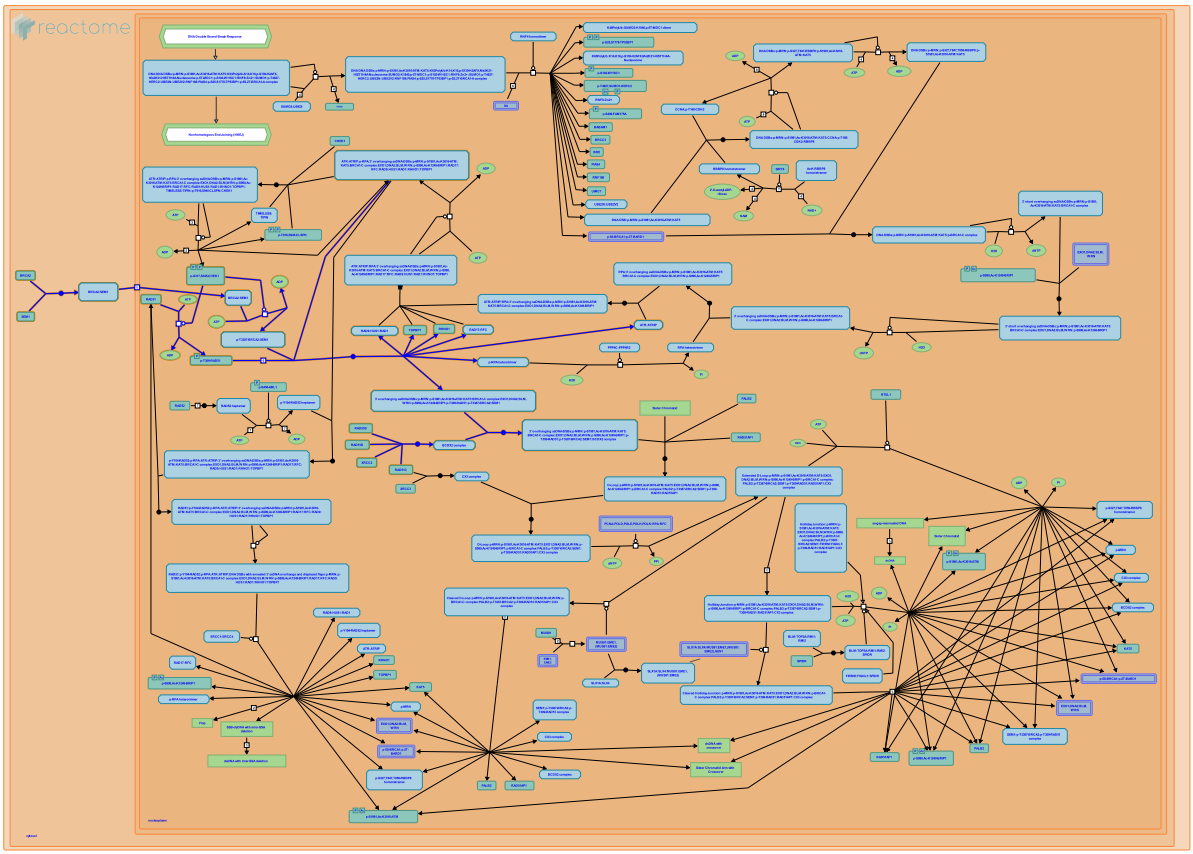
2003-11-23	Authored	Matthews, L.
2015-05-12	Authored, Edited, Revised	Orlic-Milacic, M.
2015-06-12	Reviewed	Borowiec, JA.

Presynaptic phase of homologous DNA pairing and strand exchange ↗

Location: Homologous DNA Pairing and Strand Exchange

Stable identifier: R-HSA-5693616

Compartments: nucleoplasm



The presynaptic phase of homologous DNA pairing and strand exchange during homologous recombination repair (HRR) begins with the displacement of RPA from ssDNA (Thompson and Limoli 2003) by the joint action of RAD51 and BRCA2. CHEK1-mediated phosphorylation of RAD51 and BRCA2 (Sorensen et al. 2005, Bahassi et al. 2008) is needed for BRCA2-mediated nucleation of RAD51 on 3'-ssDNA overhangs, RPA displacement and formation of RAD51 nucleofilaments (Yang et al. 2005, Jensen et al. 2010, Liu et al. 2010, Thorslund et al. 2010). Invasive RAD51 nucleofilaments are stabilized by the BCDX2 complex composed of RAD51B, RAD51C, RAD51D and XRCC2 (Masson et al. 2001, Chun et al. 2013, Amunugama et al. 2013).

Literature references

West, SC., Lekomtsev, S., Compton, SA., McIlwraith, MJ., Petronczki, M., Thorslund, T. et al. (2010). The breast cancer tumor suppressor BRCA2 promotes the specific targeting of RAD51 to single-stranded DNA. *Nat. Struct. Mol. Biol., 17*, 1263-5. ↗

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.

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. ↗

Ovesen, JL., Riesenberg, AL., Bahassi, EM., Stambrook, PJ., Hasty, PE., Bernstein, WZ. (2008). The checkpoint kinases Chk1 and Chk2 regulate the functional associations between hBRCA2 and Rad51 in response to DNA damage. *Oncogene, 27*, 3977-85. ↗

Benson, FE., Shah, R., Masson, JY., West, SC., Stasiak, AZ., Tarsounas, MC. et al. (2001). Identification and purification of two distinct complexes containing the five RAD51 paralogs. *Genes Dev., 15*, 3296-307. ↗

Editions

2003-07-14	Authored	Thompson, L.
2015-05-12	Authored, Edited, Revised	Orlic-Milacic, M.
2015-06-12	Reviewed	Borowiec, JA.

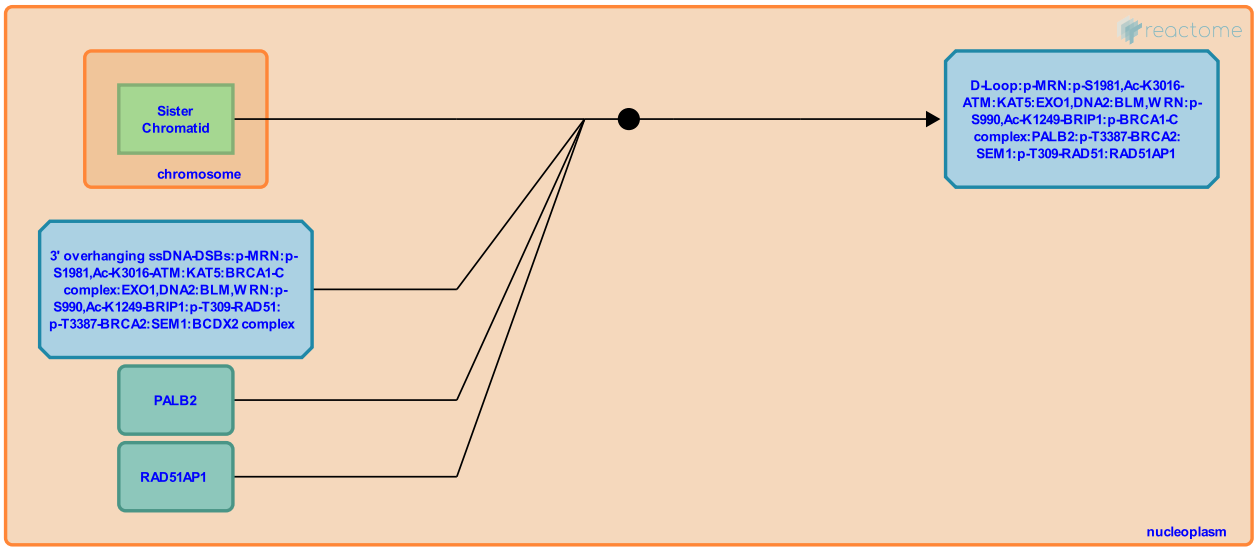
D-loop formation mediated by PALB2, BRCA2 and RAD51 ↗

Location: Homologous DNA Pairing and Strand Exchange

Stable identifier: R-HSA-5693620

Type: binding

Compartments: nucleoplasm, chromosome



A D-loop structure is formed when complementary duplex DNA (sister chromatid) is progressively invaded by the RAD51 nucleoprotein filament, with base pairing of the invading ssDNA and the complementary sister chromatid DNA strand (Sung et al. 2003). PALB2, RAD54, RAD51 paralogs (RAD51B, RAD51C, RAD51D, XRCC2, XRCC3), and RAD51AP1 synergistically stimulate RAD51 recombinase activity, thus enhancing RAD51-mediated strand exchange and promoting the formation of D-loop structures. PALB2 simultaneously interacts with RAD51, BRCA2 and RAD51AP1 (Modesti et al. 2007, Wiese et al. 2007, Buisson et al. 2010, Dray et al. 2010). The direct BRCA1 interaction with PALB2 helps to fine-tune the localization of BRCA2 and RAD51 at DNA double-strand breaks (DSBs) (Zhang et al. 2009, Sy et al. 2009). Phosphorylation of PALB2 by ATR on serine residue S59 promotes BRCA1-PALB2 interaction and the localization of PALB2 to DNA damage sites (Buisson et al. 2017).

Followed by: CX3 complex binds D-loop structures

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. ↗

Shi, I., Tsai, MS., Dray, E., Groesser, T., Williams, GJ., San Filippo, J. et al. (2007). Promotion of homologous recombination and genomic stability by RAD51AP1 via RAD51 recombinase enhancement. *Mol. Cell, 28*, 482-90. ↗

Van Komen, S., Krejci, L., Sehorn, MG., Sung, P. (2003). Rad51 recombinase and recombination mediators. *J Biol Chem, 278*, 42729-32. ↗

Editions

2003-11-23	Authored	Matthews, L.
2015-05-12	Edited, Revised	Orlic-Milacic, M.
2015-06-12	Reviewed	Borowiec, JA.
2021-02-25	Reviewed	Pospiech, H., Winqvist, R.

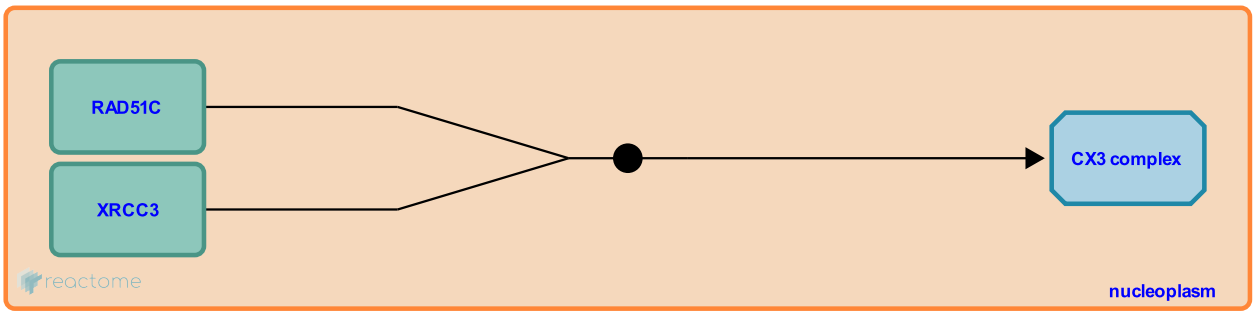
CX3 complex formation ↗

Location: Homologous DNA Pairing and Strand Exchange

Stable identifier: R-HSA-5685319

Type: binding

Compartments: nucleoplasm



RAD51 paralogs RAD51C and XRCC3 form the CX3 complex with 1:1 stoichiometry (Masson et al. 2001, Chun et al. 2013).

Followed by: CX3 complex binds D-loop structures

Literature references

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. ↗

Benson, FE., Shah, R., Masson, JY., West, SC., Stasiak, AZ., Tarsounas, MC. et al. (2001). Identification and purification of two distinct complexes containing the five RAD51 paralogs. *Genes Dev., 15*, 3296-307. ↗

Editions

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

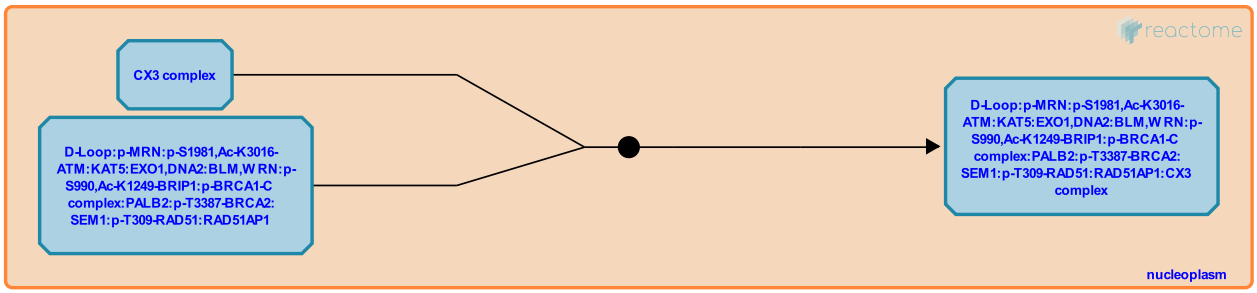
CX3 complex binds D-loop structures ↗

Location: Homologous DNA Pairing and Strand Exchange

Stable identifier: R-HSA-5685838

Type: binding

Compartments: nucleoplasm



The CX3 complex, composed of RAD51 paralogs RAD51C and XRCC3 (Masson, Tarsounas et al. 2001), binds homologous recombination repair sites at a later time point than the BCDX2 complex (Chun et al. 2013). Both RAD51C and XRCC3 can directly interact with PALB2 (Park et al. 2014). CX3 complexes, as well as BCDX2 complexes, multimerize into ring like structures with a central cavity (Masson, Stasiak et al. 2001, Compton et al. 2010). The CX3 complex may be involved in the resolution of Holliday junctions (Liu et al. 2004, Liu et al. 2007).

Preceded by: D-loop formation mediated by PALB2, BRCA2 and RAD51, CX3 complex formation

Literature references

West, SC., Shah, R., O'Regan, P., Masson, JY., Liu, Y. (2004). RAD51C is required for Holliday junction processing in mammalian cells. *Science, 303*, 243-6. ↗

Benson, FE., Masson, JY., West, SC., Stasiak, AZ., Stasiak, A. (2001). Complex formation by the human RAD51C and XRCC3 recombination repair proteins. *Proc. Natl. Acad. Sci. U.S.A., 98*, 8440-6. ↗

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. ↗

Ozgür, S., Compton, SA., Griffith, JD. (2010). Ring-shaped Rad51 paralog protein complexes bind Holliday junctions and replication forks as visualized by electron microscopy. *J. Biol. Chem., 285*, 13349-56. ↗

Benson, FE., Shah, R., Masson, JY., West, SC., Stasiak, AZ., Tarsounas, MC. et al. (2001). Identification and purification of two distinct complexes containing the five RAD51 paralogs. *Genes Dev., 15*, 3296-307. ↗

Editions

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

Table of Contents