

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. [↗](#)

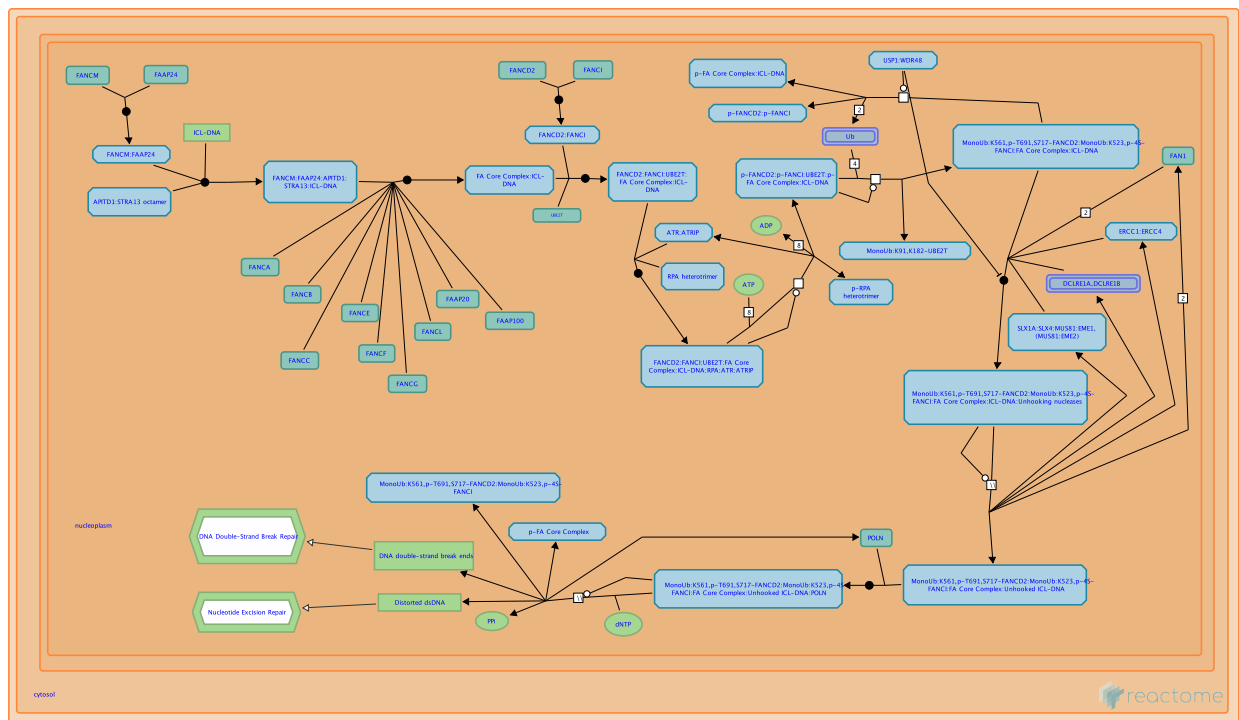
Reactome database release: 77

This document contains 1 pathway and 13 reactions ([see Table of Contents](#))

Fanconi Anemia Pathway ↗

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, 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 (FANCL) (reviewed by Deans and West 2011, Kottmann

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).

Literature references

- Kottemann, MC., Smogorzewska, A. (2013). Fanconi anaemia and the repair of Watson and Crick DNA crosslinks. *Nature*, 493, 356-63. [↗](#)
- Jiang, Q., Greenberg, RA. (2015). Deciphering the BRCA1 Tumor Suppressor Network. *J. Biol. Chem.*, 290, 17724-32. [↗](#)
- Deans, AJ., West, SC. (2011). DNA interstrand crosslink repair and cancer. *Nat. Rev. Cancer*, 11, 467-80. [↗](#)
- Cohn, MA., Kowal, P., Yang, K., Haas, W., Huang, TT., Gygi, SP. et al. (2007). A UAF1-containing multisubunit protein complex regulates the Fanconi anemia pathway. *Mol Cell*, 28, 786-97. [↗](#)
- Evans, MK., Longo, DL. (2014). PALB2 mutations and breast-cancer risk. *N. Engl. J. Med.*, 371, 566-8. [↗](#)

Editions

2009-05-02	Authored	Matthews, L.
2009-05-20	Reviewed	Huang, TT.
2009-05-20	Edited	Matthews, L.
2015-06-11	Authored, Edited, Revised	Orlic-Milacic, M.
2015-08-20	Reviewed	Fugger, K.

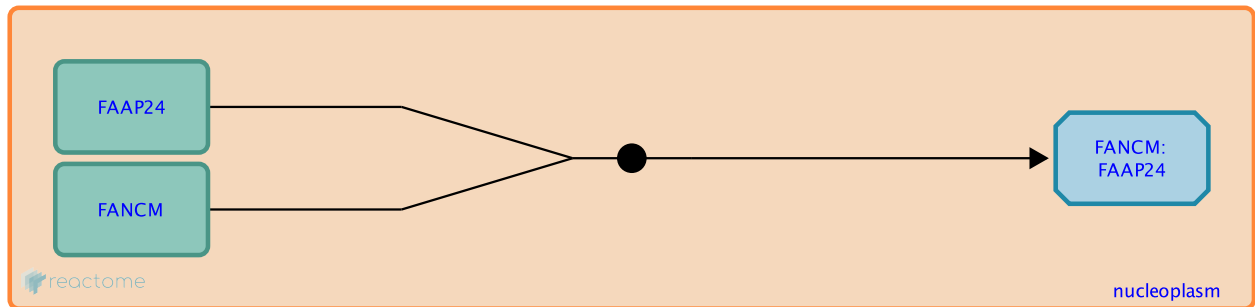
FANCM binds FAAP24 ↗

Location: [Fanconi Anemia Pathway](#)

Stable identifier: R-HSA-6785607

Type: binding

Compartments: nucleoplasm



FANCM binds FAAP24, forming a complex that recognizes DNA interstrand crosslinks, thus triggering the Fanconi anemia repair pathway (Ciccia et al. 2007, Kim et al. 2008).

Followed by: [FANCM:FAAP24 and APITD1:STRA13 bind ICL-DNA](#)

Literature references

Ciccia, A., Ling, C., Coulthard, R., Yan, Z., Xue, Y., Meetei, AR. et al. (2007). Identification of FAAP24, a Fanconi anemia core complex protein that interacts with FANCM. *Mol. Cell*, 25, 331-43. ↗

Kim, JM., Kee, Y., Gurtan, A., D'Andrea, AD. (2008). Cell cycle-dependent chromatin loading of the Fanconi anemia core complex by FANCM/FAAP24. *Blood*, 111, 5215-22. ↗

Editions

2015-06-29	Authored, Edited	Orlic-Milacic, M.
2015-08-20	Reviewed	Fugger, K.

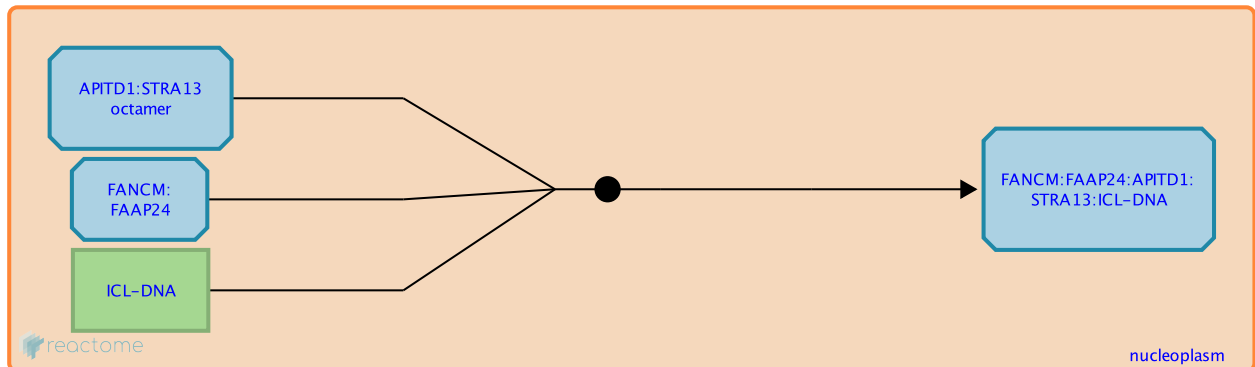
FANCM:FAAP24 and APITD1:STRA13 bind ICL-DNA ↗

Location: [Fanconi Anemia Pathway](#)

Stable identifier: R-HSA-6785087

Type: binding

Compartments: nucleoplasm



A complex composed of FANCM and FAAP24 is constitutively associated with chromatin (Ciccia et al. 2007, Kim et al. 2008). Chromatin localization of the FANCM:FAAP24 complex is facilitated by the octameric MHF complex (Tao et al. 2012) composed of four dimers of two histone-like proteins: APITD1 (MHF1, FAAP16) and STRA13 (MHF2, FAAP10) (Singh et al. 2010). The complex of FANCM, FAAP24, APITD1 and STRA13 may constitute a molecular machine that preferentially binds to replication forks stalled at DNA interstrand crosslinks (ICL-DNA), with FANCM preferentially binding to the branch point, FAAP24 to the single strand DNA (ssDNA) and the MHF complex to the double strand DNA (Yan et al. 2010).

Preceded by: [FANCM binds FAAP24](#)

Followed by: [FA core complex assembles at DNA interstrand crosslinks \(ICLs\)](#)

Literature references

- Yan, Z., Delannoy, M., Ling, C., Daege, D., Osman, F., Muniandy, PA. et al. (2010). A histone-fold complex and FANCM form a conserved DNA-remodeling complex to maintain genome stability. *Mol. Cell*, 37, 865-78. ↗
- Singh, TR., Saro, D., Ali, AM., Zheng, XF., Du, CH., Killen, MW. et al. (2010). MHF1-MHF2, a histone-fold-containing protein complex, participates in the Fanconi anemia pathway via FANCM. *Mol. Cell*, 37, 879-86. ↗
- Tao, Y., Jin, C., Li, X., Qi, S., Chu, L., Niu, L. et al. (2012). The structure of the FANCM-MHF complex reveals physical features for functional assembly. *Nat Commun*, 3, 782. ↗
- Ciccia, A., Ling, C., Coulthard, R., Yan, Z., Xue, Y., Meetei, AR. et al. (2007). Identification of FAAP24, a Fanconi anemia core complex protein that interacts with FANCM. *Mol. Cell*, 25, 331-43. ↗
- Kim, JM., Kee, Y., Gurtan, A., D'Andrea, AD. (2008). Cell cycle-dependent chromatin loading of the Fanconi anemia core complex by FANCM/FAAP24. *Blood*, 111, 5215-22. ↗

Editions

2015-06-29	Authored, Edited	Orlic-Milacic, M.
2015-08-20	Reviewed	Fugger, K.

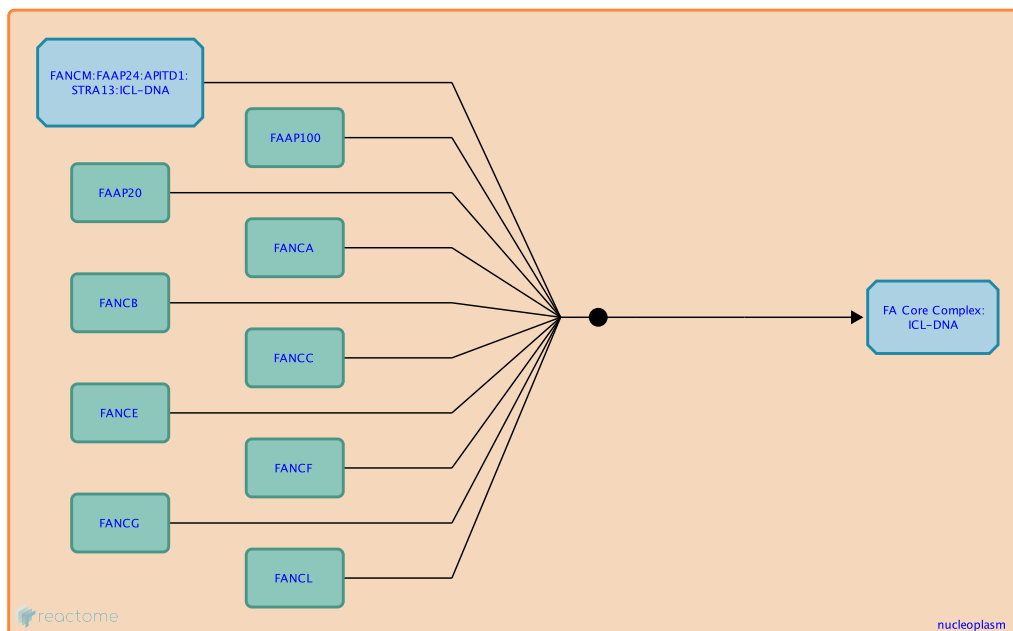
FA core complex assembles at DNA interstrand crosslinks (ICLs) ↗

Location: [Fanconi Anemia Pathway](#)

Stable identifier: R-HSA-6785126

Type: binding

Compartments: nucleoplasm



In addition to FANCM, FAAP24, APITD1 (MHF1) and STRA13 (MHF2), the FA core complex also includes FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, FAAP20 and FAAP100 (Singh et al. 2010, Yan et al. 2010, Leung et al. 2012). While FANCA, FANCB, FANCC, FANCE, FANCF, FANCG and FANCL, and probably FAAP20 and FAAP100, can assemble a complex in the nucleoplasm, they are unable to load onto DNA in the absence of FANCM and FAAP24 (Kim et al. 2008, Yan et al. 2010, Leung et al. 2012).

Preceded by: [FANCM:FAAP24 and APITD1:STRA13 bind ICL-DNA](#)

Followed by: [FANCD2:FANCI complex and UBE2T bind ICL-DNA associated with the FA core complex](#)

Literature references

- Yan, Z., Delannoy, M., Ling, C., Daele, D., Osman, F., Muniandy, PA. et al. (2010). A histone-fold complex and FANCM form a conserved DNA-remodeling complex to maintain genome stability. *Mol. Cell*, 37, 865-78. ↗
- Singh, TR., Saro, D., Ali, AM., Zheng, XF., Du, CH., Killen, MW. et al. (2010). MHF1-MHF2, a histone-fold-containing protein complex, participates in the Fanconi anemia pathway via FANCM. *Mol. Cell*, 37, 879-86. ↗
- Kim, JM., Kee, Y., Gurtan, A., D'Andrea, AD. (2008). Cell cycle-dependent chromatin loading of the Fanconi anemia core complex by FANCM/FAAP24. *Blood*, 111, 5215-22. ↗
- Leung, JW., Wang, Y., Fong, KW., Huen, MS., Li, L., Chen, J. (2012). Fanconi anemia (FA) binding protein FAAP20 stabilizes FA complementation group A (FANCA) and participates in interstrand cross-link repair. *Proc. Natl. Acad. Sci. U.S.A.*, 109, 4491-6. ↗

Editions

2015-06-29	Authored, Edited	Orlic-Milacic, M.
2015-08-20	Reviewed	Fugger, K.

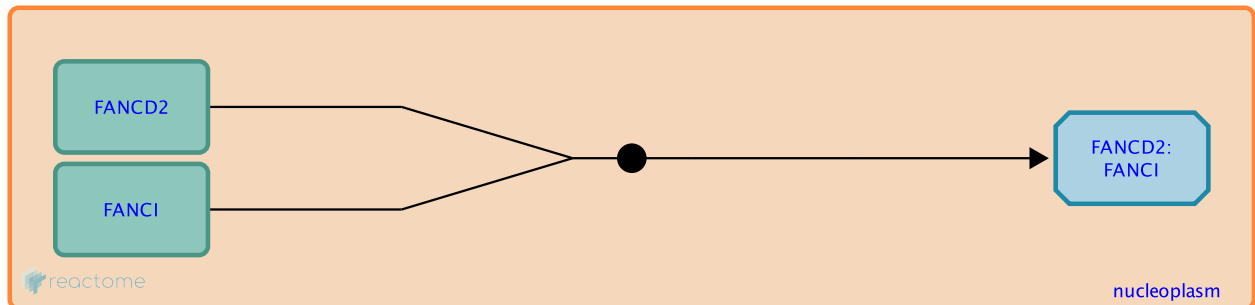
FANCD2 binds FANCI ↗

Location: [Fanconi Anemia Pathway](#)

Stable identifier: R-HSA-6785594

Type: binding

Compartments: nucleoplasm



FANCD2 binds FANCI, forming the ID2 complex (Yuan et al. 2009, Joo et al. 2011). The ID2 complex plays an important role in the repair of DNA interstrand crosslinks (the Fanconi anemia pathway).

Followed by: [FANCD2:FANCI complex and UBE2T bind ICL-DNA associated with the FA core complex](#)

Literature references

Joo, W., Xu, G., Persky, NS., Smogorzewska, A., Rudge, DG., Buzovetsky, O. et al. (2011). Structure of the FANCI-FANCD2 complex: insights into the Fanconi anemia DNA repair pathway. *Science*, 333, 312-6. ↗

Yuan, F., El Hokayem, J., Zhou, W., Zhang, Y. (2009). FANCI protein binds to DNA and interacts with FANCD2 to recognize branched structures. *J. Biol. Chem.*, 284, 24443-52. ↗

Editions

2015-06-29	Authored, Edited	Orlic-Milacic, M.
2015-08-20	Reviewed	Fugger, K.

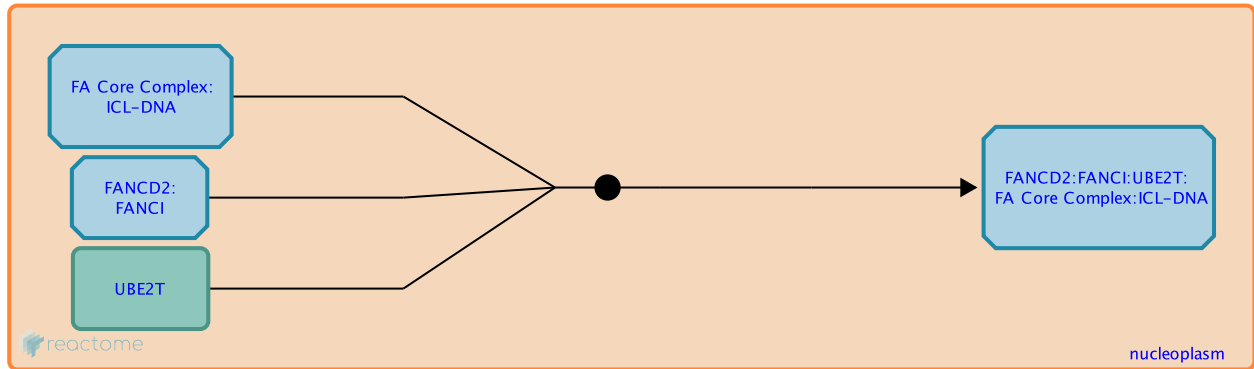
FANCD2:FANCI complex and UBE2T bind ICL-DNA associated with the FA core complex ↗

Location: Fanconi Anemia Pathway

Stable identifier: R-HSA-6785342

Type: binding

Compartments: nucleoplasm



The ID2 complex, composed of FANCD2 and FANCI, binds to branched DNA structures, such as stalled replication forks at DNA interstrand crosslinks (ICL-DNA) (Yuan et al. 2009, Longerich et al. 2009, Joo et al. 2011). The ID2 complex also interacts with the FA core complex component FANCL, activating the E3 ubiquitin ligase activity of FANCL (Rajendra et al. 2014, Longerich et al. 2014). Up to fifty FANCD2 molecules (ID2 complexes) may be recruited per one ICL, probably spreading to surrounding DNA (Douwel et al. 2014). The E2 ubiquitin ligase UBE2T is recruited to ICL-DNA by binding to the FANCL subunit of the FA core complex independently of the ID2 complex (Machida et al. 2006, Alpi et al. 2007, Hodson et al. 2014).

Preceded by: FA core complex assembles at DNA interstrand crosslinks (ICLs), FANCD2 binds FANCI

Followed by: The complex of ATR and ATRIP is recruited to ICL-DNA

Literature references

- Longerich, S., Kwon, Y., Tsai, MS., Hlaing, AS., Kupfer, GM., Sung, P. (2014). Regulation of FANCD2 and FANCI monoubiquitination by their interaction and by DNA. *Nucleic Acids Res.*, 42, 5657-70. ↗
- Hodson, C., Purkiss, A., Miles, JA., Walden, H. (2014). Structure of the human FANCL RING-Ube2T complex reveals determinants of cognate E3-E2 selection. *Structure*, 22, 337-44. ↗
- Longerich, S., San Filippo, J., Liu, D., Sung, P. (2009). FANCI binds branched DNA and is monoubiquitinated by UBE2T-FANCL. *J. Biol. Chem.*, 284, 23182-6. ↗
- Alpi, A., Langevin, F., Mosedale, G., Machida, YJ., Dutta, A., Patel, KJ. (2007). UBE2T, the Fanconi anemia core complex, and FANCD2 are recruited independently to chromatin: a basis for the regulation of FANCD2 monoubiquitination. *Mol. Cell. Biol.*, 27, 8421-30. ↗
- Machida, YJ., Machida, Y., Chen, Y., Gurtan, AM., Kupfer, GM., D'Andrea, AD. et al. (2006). UBE2T is the E2 in the Fanconi anemia pathway and undergoes negative autoregulation. *Mol Cell*, 23, 589-96. ↗

Editions

2015-06-29	Authored, Edited	Orlic-Milacic, M.
2015-08-20	Reviewed	Fugger, K.

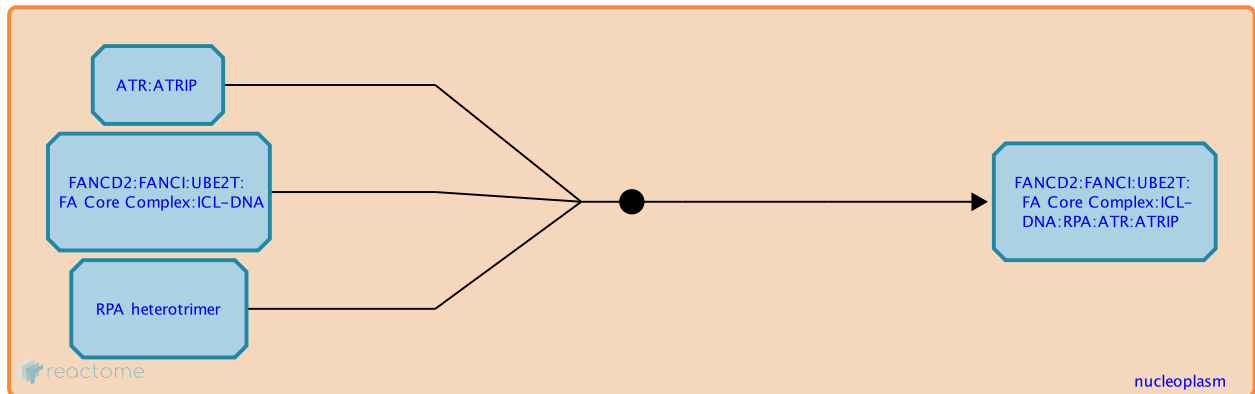
The complex of ATR and ATRIP is recruited to ICL-DNA ↗

Location: [Fanconi Anemia Pathway](#)

Stable identifier: R-HSA-6788385

Type: binding

Compartments: nucleoplasm



The complex of ATR and ATRIP (ATR:ATRIP) is recruited to replication forks blocked by DNA interstrand crosslinks (ICL-DNA) through interaction with the RPA complex and the Fanconi anemia (FA) core complex. The RPA heterotrimer associates both with single strand DNA (ssDNA) that is produced by DNA resection at ICL-DNA-stalled replication forks and with the FANCM and FAAP24 components of the FA core complex (Huang et al. 2010). ATRIP directly interacts with the FANCL component of the FA core complex (Tomida et al. 2013). The presence of RAD17 and TOPBP1, which is required for ATR activation at DNA double strand breaks (DSBs), is not needed for ATR activation at ICL-DNA (Tomida et al. 2013).

Preceded by: [FANCD2:FANCI complex and UBE2T bind ICL-DNA associated with the FA core complex](#)

Followed by: [ATR phosphorylates RPA2, FANCI, FANCD2 and FANCM at ICL-DNA](#)

Literature references

Huang, M., Kim, JM., Shiotani, B., Yang, K., Zou, L., D'Andrea, AD. (2010). The FANCM/FAAP24 complex is required for the DNA interstrand crosslink-induced checkpoint response. *Mol. Cell*, 39, 259-68. ↗

Tomida, J., Itaya, A., Shigechi, T., Unno, J., Uchida, E., Ikura, M. et al. (2013). A novel interplay between the Fanconi anemia core complex and ATR-ATRIP kinase during DNA cross-link repair. *Nucleic Acids Res.*, 41, 6930-41. ↗

Editions

2015-06-29	Authored, Edited	Orlic-Milacic, M.
2015-08-20	Reviewed	Fugger, K.

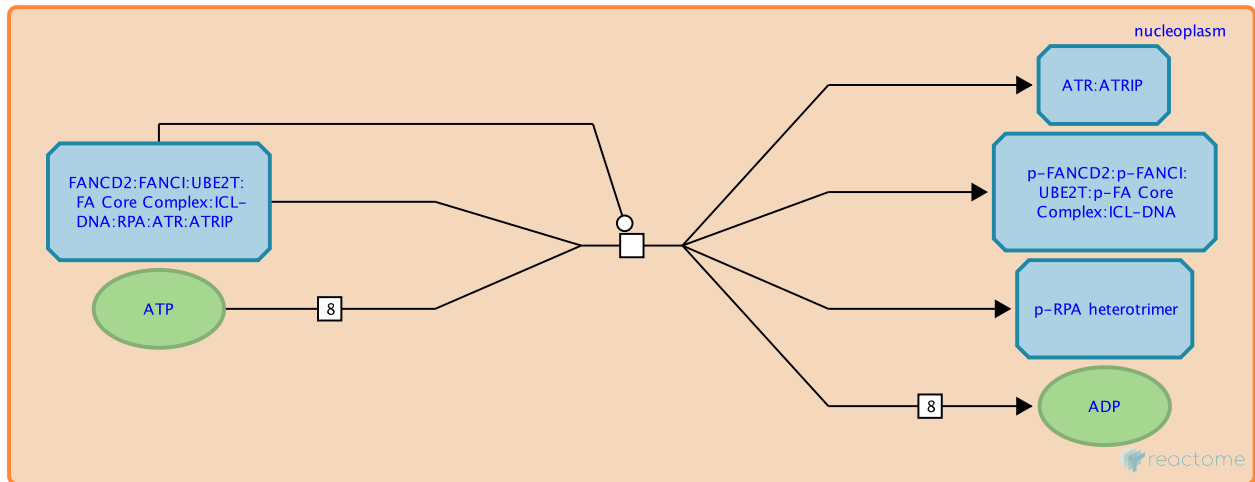
ATR phosphorylates RPA2, FANCI, FANCD2 and FANCM at ICL-DNA ↗

Location: [Fanconi Anemia Pathway](#)

Stable identifier: R-HSA-6788392

Type: transition

Compartments: nucleoplasm



ATR phosphorylates several proteins at DNA interstrand crosslinks (ICL-DNA), with ATR activity at ICL-DNA being independent of the presence of RAD17 and TOPBP1 (Shigechi et al. 2012, Tomida et al. 2013). Besides phosphorylating the RPA2 subunit of the RPA heterotrimeric complex (Huang et al. 2010), activated ATR also phosphorylates the Fanconi anemia core complex component FANCM on serine residue S1045 (Singh et al. 2013). ATR-mediated phosphorylation of FANCM is thought to be important for the progression of ICL repair, although the mechanism is not known. The critical ATR substrate at ICL-DNA is considered to be FANCI component of the ID2 complex. ATR-mediated phosphorylation of FANCI, at least on serine residues S556, S559, S565 and S617, is a prerequisite for FANCD2 monoubiquitination (Ishiai et al. 2008, Shigechi et al. 2012). FANCD2 itself is also phosphorylated by ATR on threonine residue T691 and serine residue S717, which promotes FANCD2 monoubiquitination and enhances cellular resistance to DNA crosslinking agents (Ho et al. 2006).

Preceded by: [The complex of ATR and ATRIP is recruited to ICL-DNA](#)

Followed by: [Monoubiquitination of FANCD2:FANCI](#)

Literature references

- Tomida, J., Itaya, A., Shigechi, T., Unno, J., Uchida, E., Ikura, M. et al. (2013). A novel interplay between the Fanconi anemia core complex and ATR-ATRIP kinase during DNA cross-link repair. *Nucleic Acids Res.*, 41, 6930-41. ↗
- Shigechi, T., Tomida, J., Sato, K., Kobayashi, M., Eykelenboom, JK., Pessina, F. et al. (2012). ATR-ATRIP kinase complex triggers activation of the Fanconi anemia DNA repair pathway. *Cancer Res.*, 72, 1149-56. ↗
- Huang, M., Kim, JM., Shiotani, B., Yang, K., Zou, L., D'Andrea, AD. (2010). The FANCM/FAAP24 complex is required for the DNA interstrand crosslink-induced checkpoint response. *Mol. Cell*, 39, 259-68. ↗
- Singh, TR., Ali, AM., Paramasivam, M., Pradhan, A., Wahengbam, K., Seidman, MM. et al. (2013). ATR-dependent phosphorylation of FANCM at serine 1045 is essential for FANCM functions. *Cancer Res.*, 73, 4300-10. ↗
- Ishiai, M., Kitao, H., Smogorzewska, A., Tomida, J., Kinomura, A., Uchida, E. et al. (2008). FANCI phosphorylation functions as a molecular switch to turn on the Fanconi anemia pathway. *Nat Struct Mol Biol*, 15, 1138-46. ↗

Editions

2009-05-02	Authored	Matthews, L.
2009-05-20	Reviewed	Huang, TT.
2009-05-20	Edited	Matthews, L.
2015-06-29	Edited	Orlic-Milacic, M.
2015-07-21	Authored, Revised	Orlic-Milacic, M.
2015-08-20	Reviewed	Fugger, K.

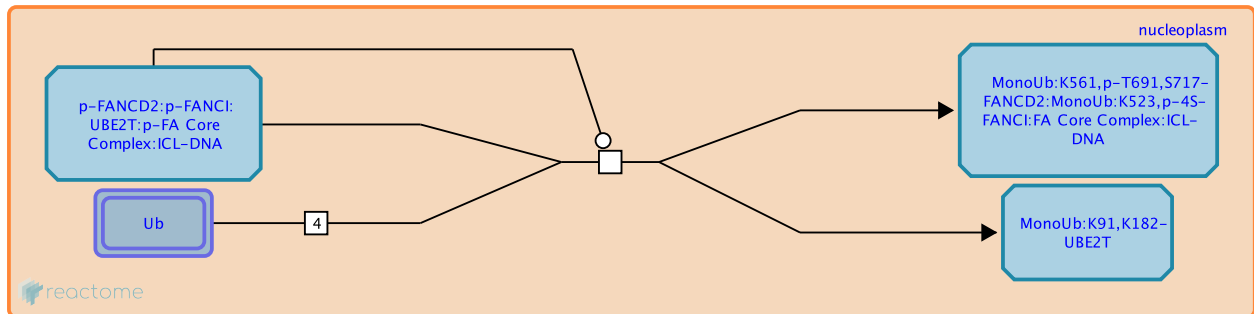
Monoubiquitination of FANCD2:FANCI ↗

Location: [Fanconi Anemia Pathway](#)

Stable identifier: R-HSA-6785361

Type: transition

Compartments: nucleoplasm



FANCD2 and FANCI, the components of the ID2 complex, are monoubiquitinated at DNA interstrand crosslinks (ICL-DNA) by the coordinated action of the E2 ubiquitin ligase UBE2T and the E3 ubiquitin ligase FANCL (Machida et al. 2006, Alpi et al. 2007, Sims et al. 2007, Smogorzewska et al. 2007, Longerich et al. 2009, Sato et al. 2012, Hodson et al. 2014). FANCL achieves the maximal catalytic activity as part of the ICL-DNA-bound FA core complex, and requires the presence of at least FANCB and FAAP100 subunits of the FA core complex to monoubiquitinate the ID2 complex (Rajendra et al. 2014, Longerich et al. 2014). FANCD2 is monoubiquitinated on lysine residue K561, while FANCI is monoubiquitinated on lysine residue K523 (Alpi et al. 2008, Longerich et al. 2014). In the absence of FANCD2, a DNA-bound FANCI can be monoubiquitinated in a FANCL-independent manner (Longerich et al. 2014).

UBE2T is also monoubiquitinated by FANCL on lysine residues K91 and K182 during the process of ID2 monoubiquitination. Monoubiquitination of UBE2T may serve as a self-inactivating mechanism that negatively regulates the Fanconi anemia pathway (Machida et al. 2006).

FANCD2 monoubiquitination promotes stability of the ID2 complex and its retention at ICL-DNA, and enables recruitment of additional proteins that participate in the repair of ICL-DNA (Garcia-Higuera et al. 2001, Smogorzewska et al. 2007, Alpi et al. 2008, Joo et al. 2011).

Preceded by: [ATR phosphorylates RPA2, FANCI, FANCD2 and FANCM at ICL-DNA](#)

Followed by: [FANCD2 deubiquitination by USP1:WDR48, DNA nucleases bind monoubiquitinated ID2 complex](#)

Literature references

- Garcia-Higuera, I., Taniguchi, T., Ganesan, S., Meyn, MS., Timmers, C., Hejna, J. et al. (2001). Interaction of the Fanconi anemia proteins and BRCA1 in a common pathway. *Mol Cell*, 7, 249-62. ↗
- Machida, YJ., Machida, Y., Chen, Y., Gurtan, AM., Kupfer, GM., D'Andrea, AD. et al. (2006). UBE2T is the E2 in the Fanconi anemia pathway and undergoes negative autoregulation. *Mol Cell*, 23, 589-96. ↗
- Sims, AE., Spiteri, E., Sims RJ, 3rd., Arita, AG., Lach, FP., Landers, T. et al. (2007). FANCI is a second monoubiquitinated member of the Fanconi anemia pathway. *Nat Struct Mol Biol*, 14, 564-7. ↗
- Smogorzewska, A., Matsuoka, S., Vinciguerra, P., McDonald ER, 3rd., Hurov, KE., Luo, J. et al. (2007). Identification of the FANCI protein, a monoubiquitinated FANCD2 paralog required for DNA repair. *Cell*, 129, 289-301. ↗
- Sato, K., Toda, K., Ishiai, M., Takata, M., Kurumizaka, H. (2012). DNA robustly stimulates FANCD2 monoubiquitylation in the complex with FANCI. *Nucleic Acids Res.*, 40, 4553-61. ↗

Editions

2009-05-02	Authored	Matthews, L.
2009-05-20	Reviewed	Huang, TT.
2009-05-20	Edited	Matthews, L.
2015-06-29	Edited, Revised	Orlic-Milacic, M.
2015-08-20	Reviewed	Fugger, K.

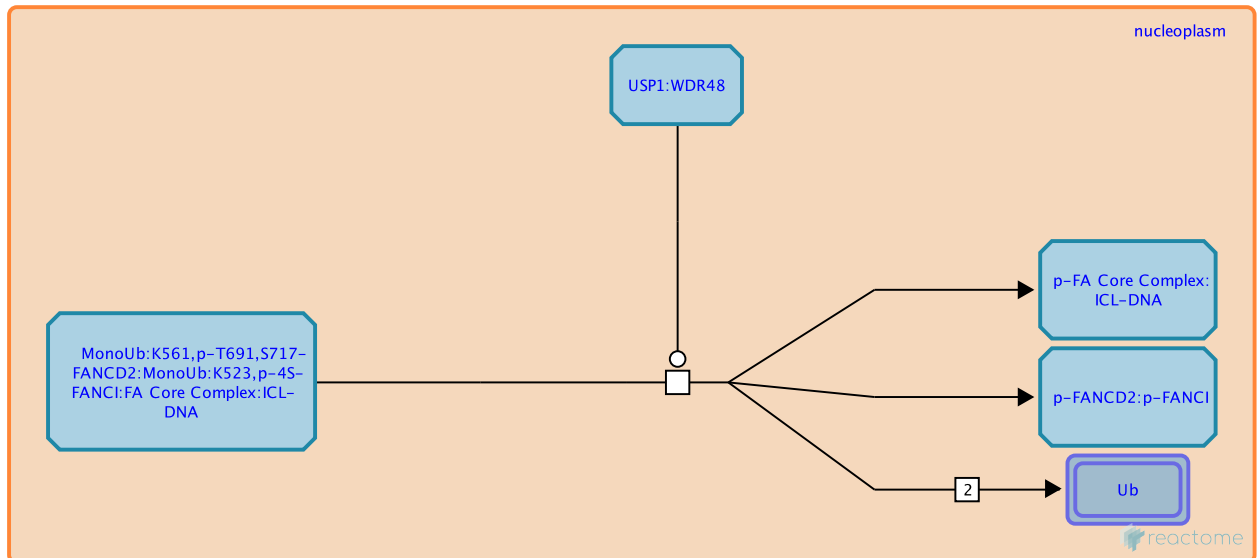
FANCD2 deubiquitination by USP1:WDR48 ↗

Location: [Fanconi Anemia Pathway](#)

Stable identifier: R-HSA-6786171

Type: transition

Compartments: nucleoplasm



The FA pathway is negatively regulated through the USP1:WDR48-mediated deubiquitination of FANCD2 (Nijman et al. 2005). WDR48 (UAF1) forms a complex with and activates USP1 (Cohn et al. 2007).

Preceded by: [Monoubiquitination of FANCD2:FANCI](#)

Literature references

Cohn, MA., Kowal, P., Yang, K., Haas, W., Huang, TT., Gygi, SP. et al. (2007). A UAF1-containing multisubunit protein complex regulates the Fanconi anemia pathway. *Mol Cell*, 28, 786-97. ↗

Editions

2009-05-02	Authored	Matthews, L.
2009-05-20	Reviewed	Huang, TT.
2009-05-20	Edited	Matthews, L.
2015-08-20	Reviewed	Fugger, K.

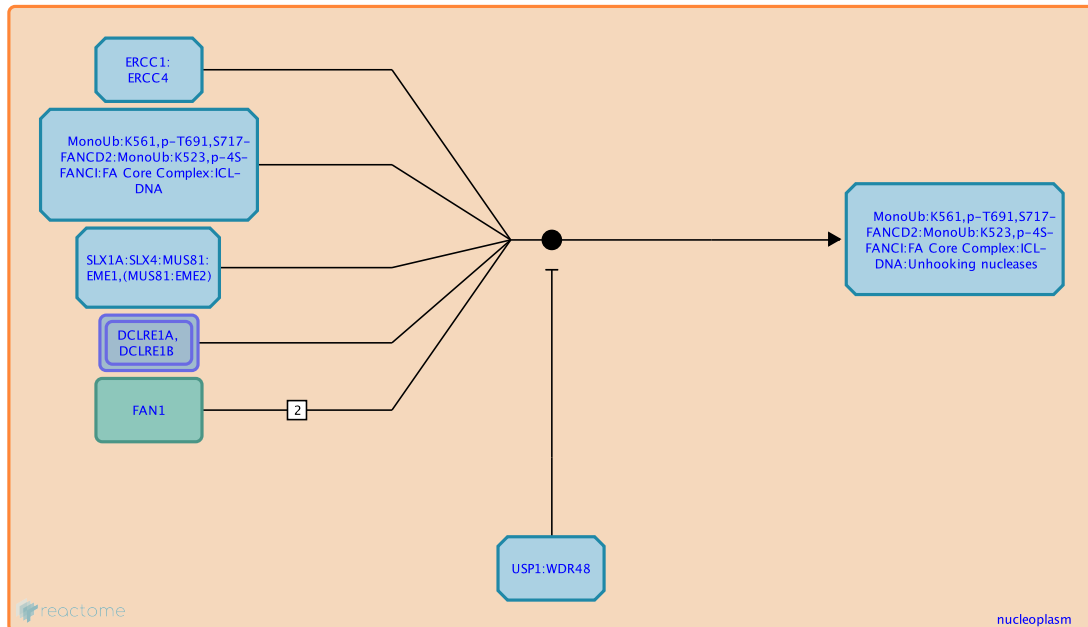
DNA nucleases bind monoubiquitinated ID2 complex ↗

Location: [Fanconi Anemia Pathway](#)

Stable identifier: R-HSA-6785732

Type: binding

Compartments: nucleoplasm



Several DNA nucleases bind to interstrand crosslinks (ICL-DNA) and participate in ICL "unhooking". The ubiquitin-binding zinc finger (UBZ) domain of the DNA nuclease FAN1 binds to monoubiquitinated FANCD2, enabling the recruitment of FAN1 to the ICL-DNA repair site (Liu et al. 2010, MacKay et al. 2010, Smogorzewska et al. 2010, Kratz et al. 2010). Once recruited to ICL-DNA, FAN1 forms head-to-tail homodimers. Homodimerization is important for the endonucleolytic activity of FAN1 (Zhao et al. 2014). SLX4 (FANCP) serves as a docking platform for recruitment of SLX1A, MUS81 and EME1 or EME2, resulting in formation of the SLX1A:SLX4:MUS81:EME1 (or SLX1A:SLX4:MUS81:EME2) endonucleolytic complex (Fekairi et al. 2009, Wyatt et al. 2013). SLX4 can also bind the endonucleolytic complex composed of ERCC1 and ERCC4 (XPF) (Fekairi et al. 2009). SLX4 is recruited to ICL-DNA through interaction of the UBZ domain of SLX4 with monoubiquitinated FANCD2 (Yamamoto et al. 2011). Targeted deletion of the UBZ domain of SLX4 confers sensitivity to ICL-inducing agents, but the UBZ domain seems to be dispensable for the role of SLX4 in homologous recombination repair (Yamamoto et al. 2011).

DNA exonucleases DCLRE1A (SNM1A) and DCLRE1B (SNM1B) likely function redundantly in ICL repair. Similar to FAN1, they are able to digest the DNA past the ICL, thereby unhooking one of the DNA strands (Wang et al. 2011, Sengerova et al. 2012). Monoubiquitination of the PCNA subunit of the stalled replicative polymerase complex by RAD18 may provide the docking site for DCLRE1A (or DCLRE1B) (Yang et al. 2010). In addition, PIAS1 may facilitate loading of DCLRE1A (or DCLRE1B) to ICL sites (Ishiai et al. 2004).

Preceded by: [Monoubiquitination of FANCD2:FANCI](#)

Followed by: [DNA nucleases unhook the interstrand crosslink \(ICL\)](#)

Literature references

Liu, T., Ghosal, G., Yuan, J., Chen, J., Huang, J. (2010). FAN1 acts with FANCI-FANCD2 to promote DNA interstrand cross-link repair. *Science*, 329, 693-6. ↗

- MacKay, C., Déclais, AC., Lundin, C., Agostinho, A., Deans, AJ., Macartney, TJ. et al. (2010). Identification of KIAA1018/FAN1, a DNA repair nuclease recruited to DNA damage by monoubiquitinated FANCD2. *Cell*, 142, 65-76. [↗](#)
- Smogorzewska, A., Desetty, R., Saito, TT., Schlabach, M., Lach, FP., Sowa, ME. et al. (2010). A genetic screen identifies FAN1, a Fanconi anemia-associated nuclease necessary for DNA interstrand crosslink repair. *Mol. Cell*, 39, 36-47. [↗](#)
- Kratz, K., Schöpf, B., Kaden, S., Sandoel, A., Eberhard, R., Lademann, C. et al. (2010). Deficiency of FANCD2-associated nuclease KIAA1018/FAN1 sensitizes cells to interstrand crosslinking agents. *Cell*, 142, 77-88. [↗](#)
- Zhao, Q., Xue, X., Longerich, S., Sung, P., Xiong, Y. (2014). Structural insights into 5' flap DNA unwinding and incision by the human FAN1 dimer. *Nat Commun*, 5, 5726. [↗](#)

Editions

2015-06-29	Authored, Edited	Orlic-Milacic, M.
2015-08-20	Reviewed	Fugger, K.

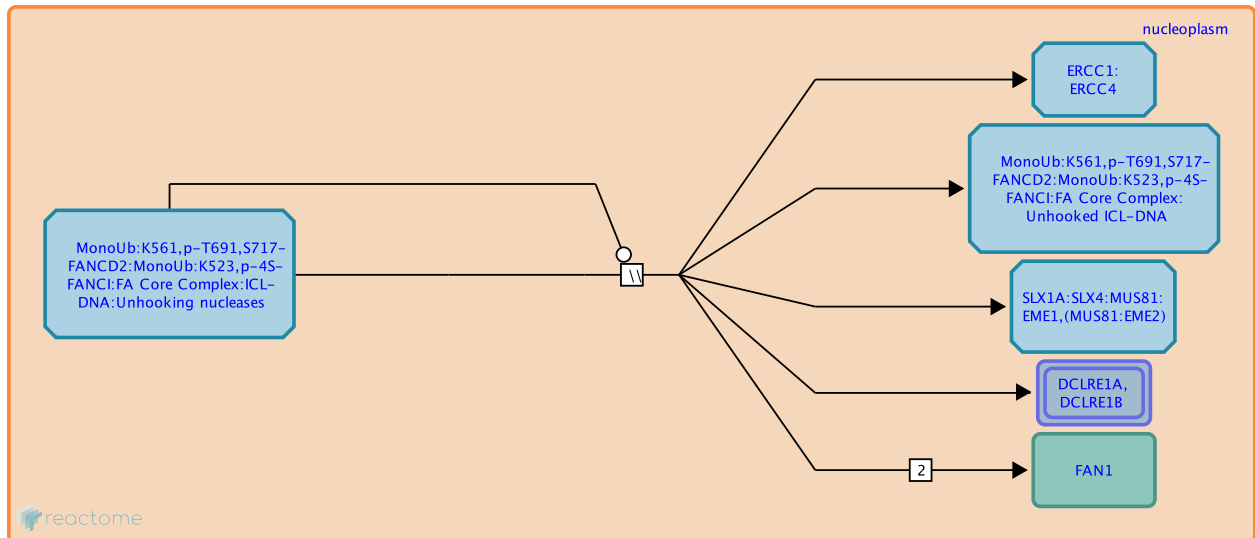
DNA nucleases unhook the interstrand crosslink (ICL) ↗

Location: [Fanconi Anemia Pathway](#)

Stable identifier: R-HSA-6785986

Type: omitted

Compartments: nucleoplasm



Unhooking of interstrand crosslinks (ICLs) from damaged DNA (ICL-DNA) involves coordinated action of several DNA nucleases: FAN1, DCLRE1A or DCLRE1B, the complex of ERCC1 and ERCC4 (XPF), and the complex of SLX4 (FANCP), SLX1A, MUS81 and EME1 or EME2. These DNA nucleases incise ICL-DNA at both sides of the ICL, thus removing the covalent bond between the two DNA strands. The exact sequence of incision steps has not been determined and it is possible that some of the implicated nucleases act in a redundant manner.

FAN1 exhibits 5'→3' endonuclease activity, as well as 5'→3' exonuclease activity, with a preference for 5' flaps and branched DNA structures (Smogorzewska et al. 2010, Kratz et al. 2010, MacKay et al. 2010, Liu et al. 2010). The FAN1 head-to-tail homodimer recognizes the lesion, orients and unwinds the 5' flap (Zhao et al. 2014). FAN1 requires a 5' terminal phosphate anchor and successively cleaves the DNA at every third nucleotide (Wang et al. 2014). This suggests that an incision 5' to the ICL precedes the action of FAN1.

ERCC4 (XPF) in complex with ERCC1 may perform the first endonucleolytic incision 5' to the ICL (Wang et al. 2011), while MUS81 in complex with EME1 or EME2 may act as a backup endonuclease. DCLRE1A (SNM1A) exhibits a 5'→3' exonuclease activity and can digest past the ICL, thereby unhooking it from one DNA strand after the ERCC1:ERCC4 complex does the initial incision 5' to the ICL (Wang et al. 2011). DCLRE1A functions redundantly with DCLRE1B (SNM1B) in ICL repair (Ishiai et al. 2004, Sangerova et al. 2012).

Preceded by: [DNA nucleases bind monoubiquitinated ID2 complex](#)

Followed by: [POLN binds ICL-DNA](#)

Literature references

Liu, T., Ghosal, G., Yuan, J., Chen, J., Huang, J. (2010). FAN1 acts with FANCI-FANCD2 to promote DNA interstrand cross-link repair. *Science*, 329, 693-6. ↗

- MacKay, C., Déclais, AC., Lundin, C., Agostinho, A., Deans, AJ., Macartney, TJ. et al. (2010). Identification of KIAA1018/FAN1, a DNA repair nuclease recruited to DNA damage by monoubiquitinated FANCD2. *Cell*, 142, 65-76. [↗](#)
- Smogorzewska, A., Desetty, R., Saito, TT., Schlabach, M., Lach, FP., Sowa, ME. et al. (2010). A genetic screen identifies FAN1, a Fanconi anemia-associated nuclease necessary for DNA interstrand crosslink repair. *Mol. Cell*, 39, 36-47. [↗](#)
- Kratz, K., Schöpf, B., Kaden, S., Sandoel, A., Eberhard, R., Lademann, C. et al. (2010). Deficiency of FANCD2-associated nuclease KIAA1018/FAN1 sensitizes cells to interstrand crosslinking agents. *Cell*, 142, 77-88. [↗](#)
- Zhao, Q., Xue, X., Longerich, S., Sung, P., Xiong, Y. (2014). Structural insights into 5' flap DNA unwinding and incision by the human FAN1 dimer. *Nat Commun*, 5, 5726. [↗](#)

Editions

2015-06-29	Authored, Edited	Orlic-Milacic, M.
2015-08-20	Reviewed	Fugger, K.

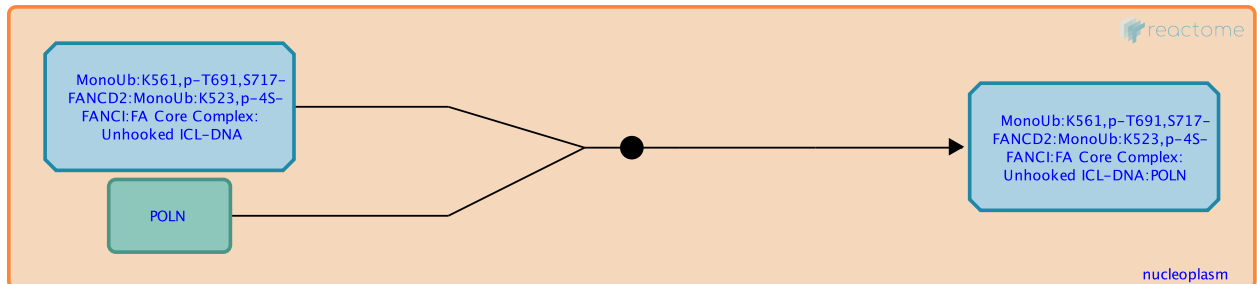
POLN binds ICL-DNA ↗

Location: [Fanconi Anemia Pathway](#)

Stable identifier: R-HSA-6786155

Type: binding

Compartments: nucleoplasm



An error-prone DNA polymerase nu (POLN) is recruited to the interstrand crosslink (ICL) repair site through interaction with monoubiquitinated FANCD2 and probably the PCNA subunit of the stalled replication complex (Moldovan et al. 2010).

Preceded by: [DNA nucleases unhook the interstrand crosslink \(ICL\)](#)

Followed by: [Translesion synthesis across unhooked ICL by POLN](#)

Literature references

Moldovan, GL., Madhavan, MV., Mirchandani, KD., McCaffrey, RM., Vinciguerra, P., D'Andrea, AD. (2010). DNA polymerase POLN participates in cross-link repair and homologous recombination. *Mol. Cell. Biol.*, 30, 1088-96. ↗

Editions

2015-06-29	Authored, Edited	Orlic-Milacic, M.
2015-08-20	Reviewed	Fugger, K.

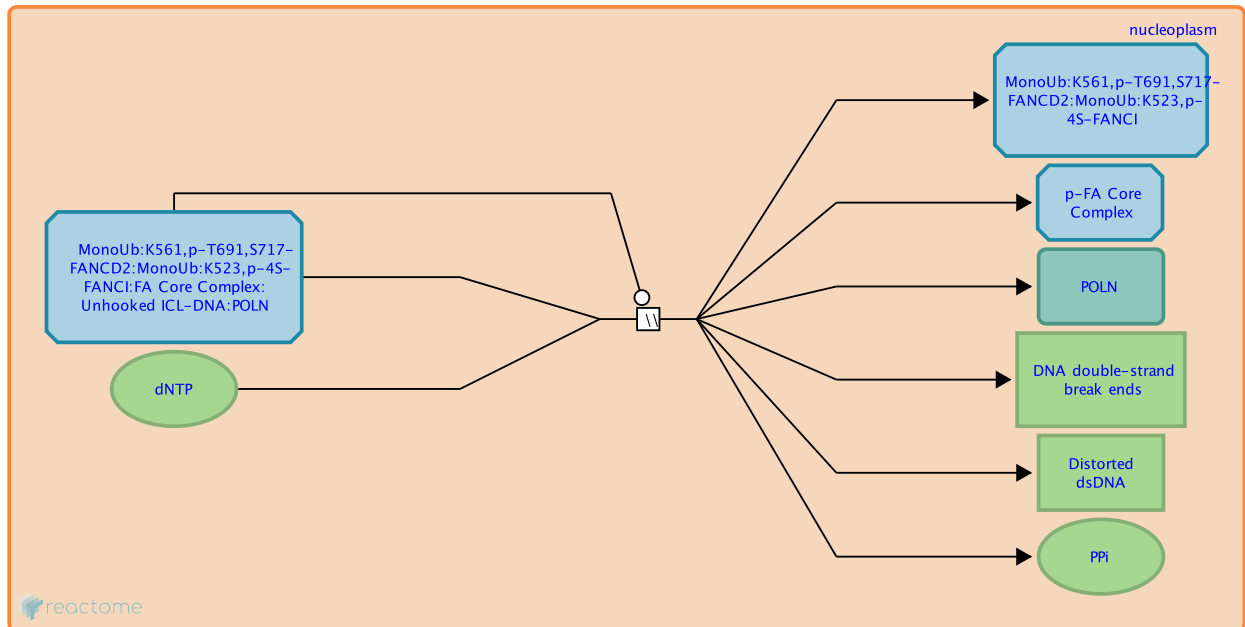
Translesion synthesis across unhooked ICL by POLN ↗

Location: [Fanconi Anemia Pathway](#)

Stable identifier: R-HSA-6786166

Type: omitted

Compartments: nucleoplasm



The error-prone DNA polymerase nu (POLN) performs translesion DNA synthesis using the DNA strand with unhooked interstrand crosslink (ICL) as a template, thereby bypassing the unhooked ICL (Moldovan et al. 2010, Yamanaka et al. 2010). The DNA strand with unhooked ICL is subsequently repaired via nucleotide excision repair (NER), while the double strand break (DSB) generated by incision of the stalled replication fork during the unhooking step is repaired via homologous recombination repair (HRR) (reviewed by Kottemann and Smogorzewska 2013, Deans and West 2011).

Preceded by: [POLN binds ICL-DNA](#)

Literature references

Moldovan, GL., Madhavan, MV., Mirchandani, KD., McCaffrey, RM., Vinciguerra, P., D'Andrea, AD. (2010). DNA polymerase POLN participates in cross-link repair and homologous recombination. *Mol. Cell. Biol.*, 30, 1088-96. ↗

Yamanaka, K., Minko, IG., Takata, K., Kolbanovskiy, A., Kozekov, ID., Wood, RD. et al. (2010). Novel enzymatic function of DNA polymerase nu in translesion DNA synthesis past major groove DNA-peptide and DNA-DNA crosslinks. *Chem. Res. Toxicol.*, 23, 689-95. ↗

Kottemann, MC., Smogorzewska, A. (2013). Fanconi anaemia and the repair of Watson and Crick DNA crosslinks. *Nature*, 493, 356-63. ↗

Deans, AJ., West, SC. (2011). DNA interstrand crosslink repair and cancer. *Nat. Rev. Cancer*, 11, 467-80. ↗

Editions

2015-06-29	Authored, Edited	Orlic-Milacic, M.
2015-08-20	Reviewed	Fugger, K.

Table of Contents

Introduction	1
☰ Fanconi Anemia Pathway	2
↳ FANCM binds FAAP24	4
↳ FANCM:FAAP24 and APITD1:STRA13 bind ICL-DNA	5
↳ FA core complex assembles at DNA interstrand crosslinks (ICLs)	6
↳ FANCD2 binds FANCI	7
↳ FANCD2:FANCI complex and UBE2T bind ICL-DNA associated with the FA core complex	8
↳ The complex of ATR and ATRIP is recruited to ICL-DNA	9
↳ ATR phosphorylates RPA2, FANCI, FANCD2 and FANCM at ICL-DNA	10
↳ Monoubiquitination of FANCD2:FANCI	12
↳ FANCD2 deubiquitination by USP1:WDR48	14
↳ DNA nucleases bind monoubiquitinated ID2 complex	15
↳ DNA nucleases unhook the interstrand crosslink (ICL)	17
↳ POLN binds ICL-DNA	19
↳ Translesion synthesis across unhooked ICL by POLN	20
Table of Contents	21