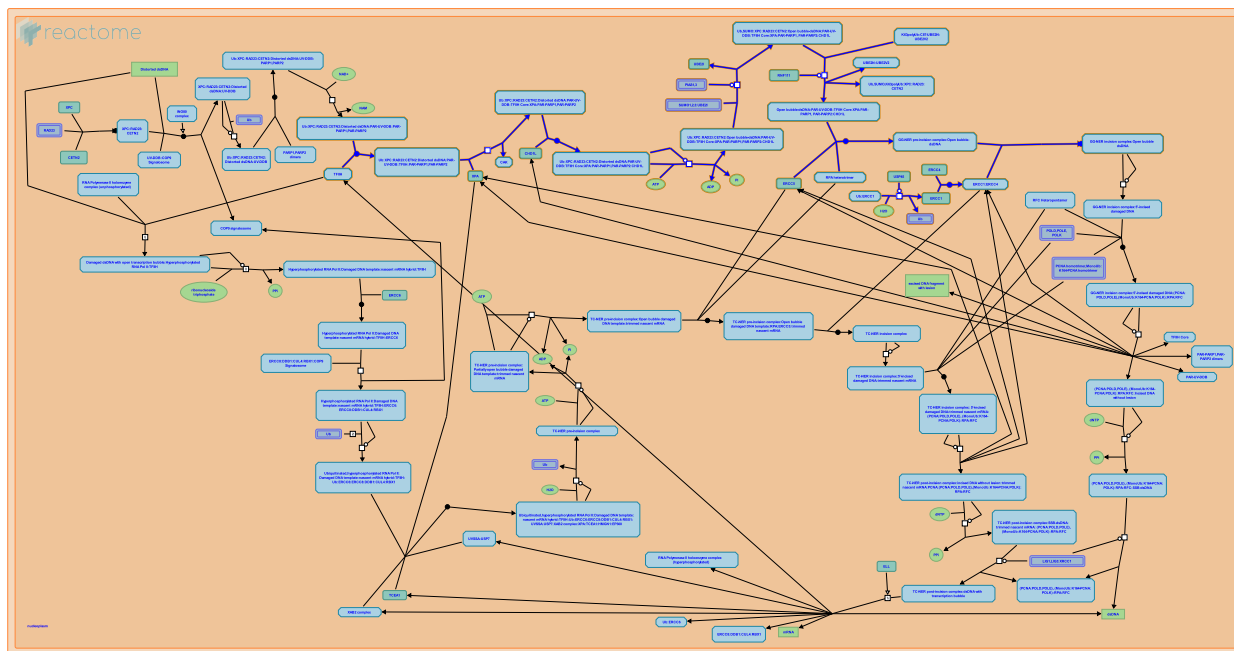


Formation of Incision Complex in GG-NER



Fousteri, M., Gopinathrao, G., Hoeijmakers, JH., Joshi-Tope, G., Orlic-Milacic, M.

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook/).

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.

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Literature references

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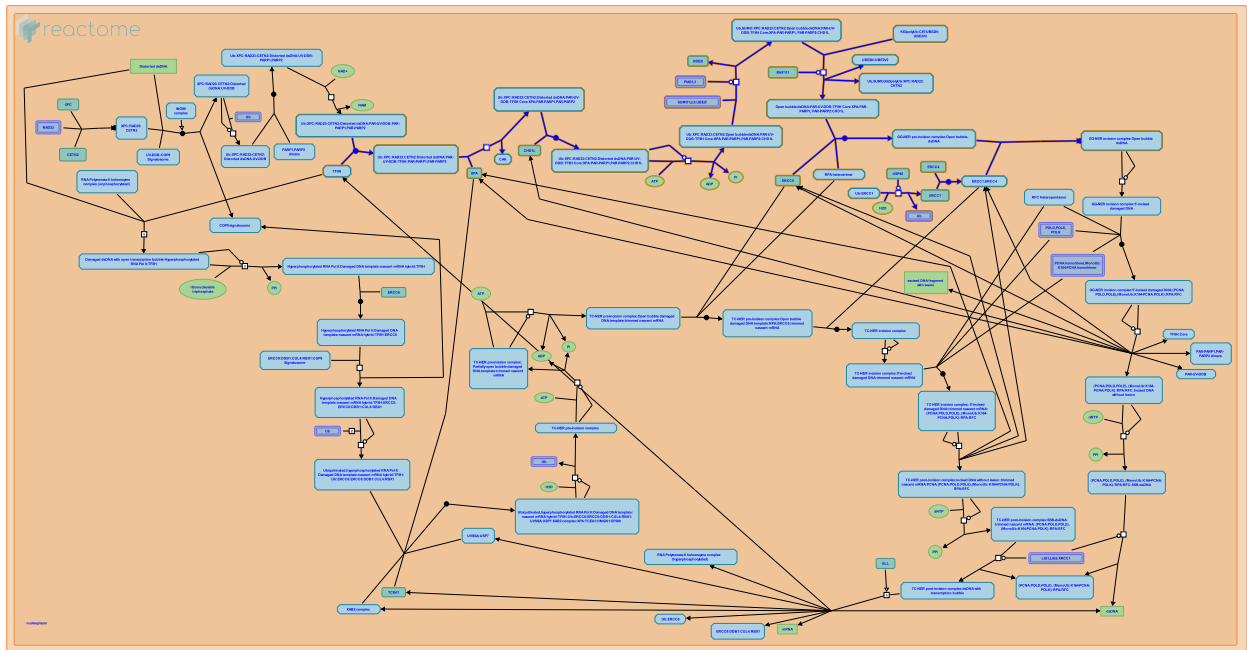
Reactome database release: 88

This document contains 1 pathway and 10 reactions ([see Table of Contents](#))

Formation of Incision Complex in GG-NER ↗

Stable identifier: R-HSA-5696395

Compartments: nucleoplasm



After the XPC complex and the UV-DDB complex bind damaged DNA, a basal transcription factor TFIIH is recruited to the nucleotide excision repair (NER) site (Volker et al. 2001, Riedl et al. 2003). DNA helicases ERCC2 (XPD) and ERCC3 (XPB) are subunits of the TFIIH complex. ERCC2 unwinds the DNA around the damage in concert with the ATPase activity of ERCC3, creating an open bubble (Coin et al. 2007). Simultaneously, the presence of the damage is verified by XPA (Camenisch et al. 2006). The recruitment of XPA is partially regulated by PARP1 and/or PARP2 (King et al. 2012).

Two DNA endonucleases, ERCC5 (XPG) and the complex of ERCC1 and ERCC4 (XPF), are recruited to the open bubble structure to form the incision complex that will excise the damaged oligonucleotide from the affected DNA strand (Dunand-Sauthier et al. 2005, Zotter et al. 2006, Riedl et al. 2003, Tsodikov et al. 2007, Orelli et al. 2010). The RPA heterotrimer coats the undamaged DNA strand, thus protecting it from the endonucleolytic attack (De Laat et al. 1998).

Literature references

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Editions

2003-07-14	Authored	Joshi-Tope, G.
2004-01-29	Authored	Hoeijmakers, JH.
2015-05-04	Authored, Edited, Revised	Orlic-Milacic, M.
2015-08-03	Reviewed	Fousteri, M.

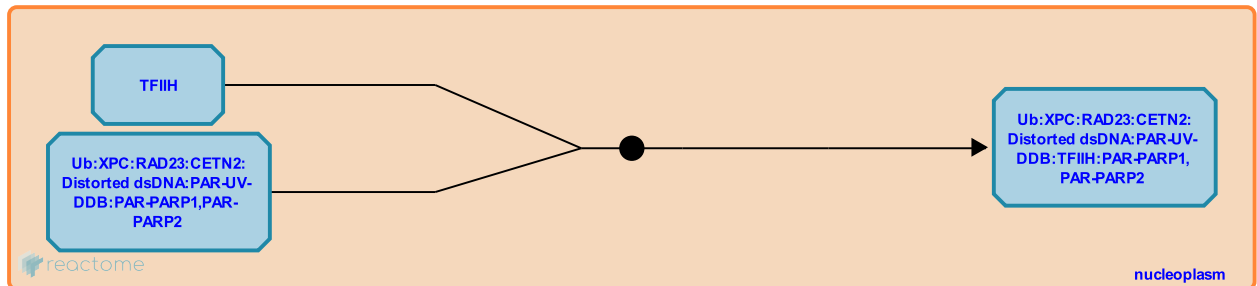
TFIIH binds GG-NER site to form a verification complex ↗

Location: Formation of Incision Complex in GG-NER

Stable identifier: R-HSA-5691000

Type: binding

Compartments: nucleoplasm



Transcription factor II H (TFIIH) complex is recruited to DNA damage sites after the damage is recognized by the XPC:RAD23:CETN2 complex and the UV-DDB complex (DDB1:DDB2) (Volker et al. 2001, Araujo and Wood 1999).

TFIIH consists of ten subunits organized into a ring-like structure (Schultz et al. 2000). The TFIIH core, also forming a ring-like structure, includes a DNA helicase ERCC3 (XPB), GTF2H1 (BTF2-p62), GTF2H2 (BTF2-p44), GTF2H3 (BTF2-p34) and GTF2H4 (BTF2-p52). GTF2H4 directly interacts with ERCC3 and anchors it to the TFIIH complex (Jawhari et al. 2002). Another DNA helicase, ERCC2 (XPD) is anchored to the TFIIH complex by binding to the GTF2H2 subunit (Coin et al. 1998). The CDK-activating kinase (CAK) complex, consisting of CCNH (cyclin H), CDK7 and MNAT1 (MAT1) is included in the TFIIH complex through an interaction with ERCC2 (Reardon et al. 1996, Rossignol et al. 1997). The tenth subunit, GTF2H5 (TTDA, TFB5, BTF2-p5) is important for the stability of the TFIIH complex (Giglia-Mari et al. 2004). The TFIIH complex binds the DNA damage site after XPC:RAD23:CETN2 complex recognizes the damage (Volker et al. 2001, Riedl et al. 2003), and the ERCC3 and GTF2H1 subunits of TFIIH directly interact with XPC (Yokoi et al. 2003).

Followed by: Recruitment of XPA and release of CAK

Literature references

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Editions

2003-07-14	Authored	Joshi-Tope, G.
2004-01-29	Authored	Hoeijmakers, JH.
2015-05-04	Authored, Edited, Revised	Orlic-Milacic, M.
2015-08-03	Reviewed	Fousteri, M.

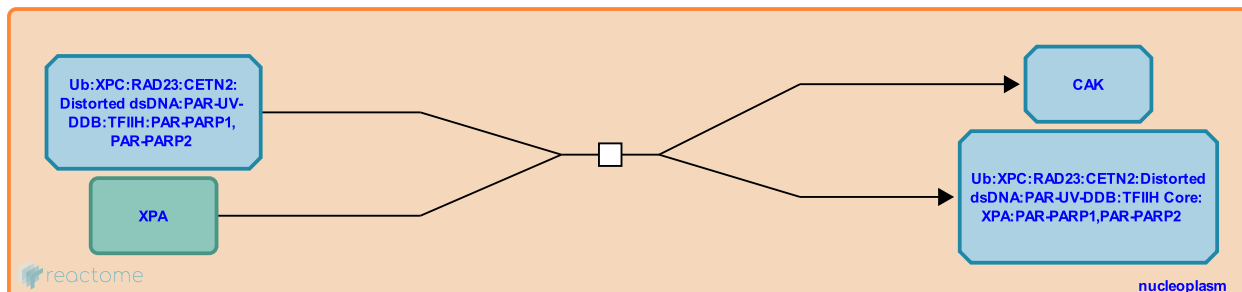
Recruitment of XPA and release of CAK ↗

Location: Formation of Incision Complex in GG-NER

Stable identifier: R-HSA-5689861

Type: transition

Compartments: nucleoplasm



XPA binds the DNA damage site through interaction with the TFIIH complex subunit GTF2H5 (TTDA) (Ziani et al. 2014), and also interacts with the DDB2 subunit of the UV-DDB complex (Wakasugi et al. 2001, Wakasugi et al. 2009, Takedachi et al. 2010). PARylated PARP1 (or possibly PARP2) (King et al. 2012) facilitates XPA association with chromatin. Binding of XPA is accompanied by the release of the CAK subcomplex from the TFIIH complex (Coin et al. 2008).

Preceded by: TFIIH binds GG-NER site to form a verification complex

Followed by: CHD1L is recruited to GG-NER site

Literature references

- King, BS., Liu, KJ., Hudson, LG., Cooper, KL. (2012). Poly(ADP-ribose) contributes to an association between poly(ADP-ribose) polymerase-1 and xeroderma pigmentosum complementation group A in nucleotide excision repair. *J. Biol. Chem.*, 287, 39824-33. ↗
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Editions

2003-07-14	Authored	Joshi-Tope, G.
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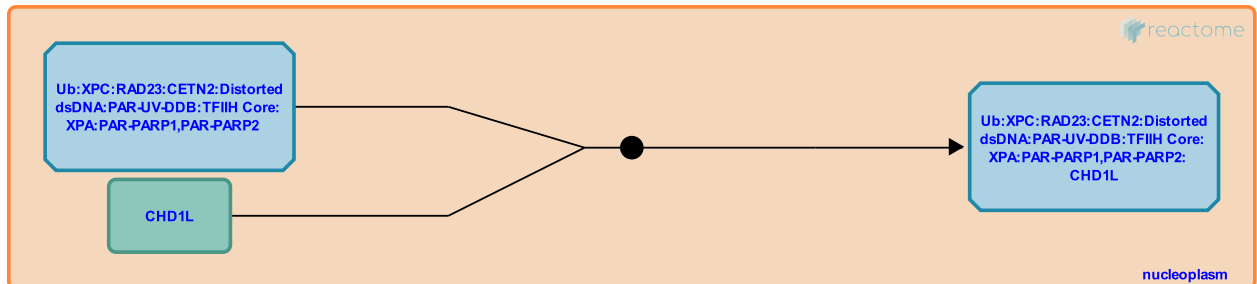
CHD1L is recruited to GG-NER site ↗

Location: [Formation of Incision Complex in GG-NER](#)

Stable identifier: R-HSA-5696670

Type: binding

Compartments: nucleoplasm



A chromatin remodeling enzyme CHD1L (ALC1) is recruited to DNA damage sites through interaction with PARylated PARP1 (or possibly PARP2) (Ahel et al. 2009) or PARylated DDB2 (Pines et al. 2012). CHD1L catalyzes PARP-stimulated nucleosome sliding and is needed for efficient PARP-dependent DNA repair (Ahel et al. 2009). CHD1L depletion or PARP inhibition impair global genomic nucleotide excision repair (GG-NER) of UV-induced DNA damage (Pines et al. 2012).

Preceded by: [Recruitment of XPA and release of CAK](#)

Followed by: [ERCC2 and ERCC3 DNA helicases form an open bubble structure in damaged DNA](#)

Literature references

Luijsterburg, MS., Sugasawa, K., Hensbergen, P., Vrouwe, MG., Mullenders, L., Cansoy, M. et al. (2012). PARP1 promotes nucleotide excision repair through DDB2 stabilization and recruitment of ALC1. *J. Cell Biol.*, 199, 235-49. ↗

Owen-Hughes, T., West, SC., Horejsí, Z., Skehel, M., Flynn, H., Ahel, I. et al. (2009). Poly(ADP-ribose)-dependent regulation of DNA repair by the chromatin remodeling enzyme ALC1. *Science*, 325, 1240-3. ↗

Editions

2015-05-04	Authored, Edited	Orlic-Milacic, M.
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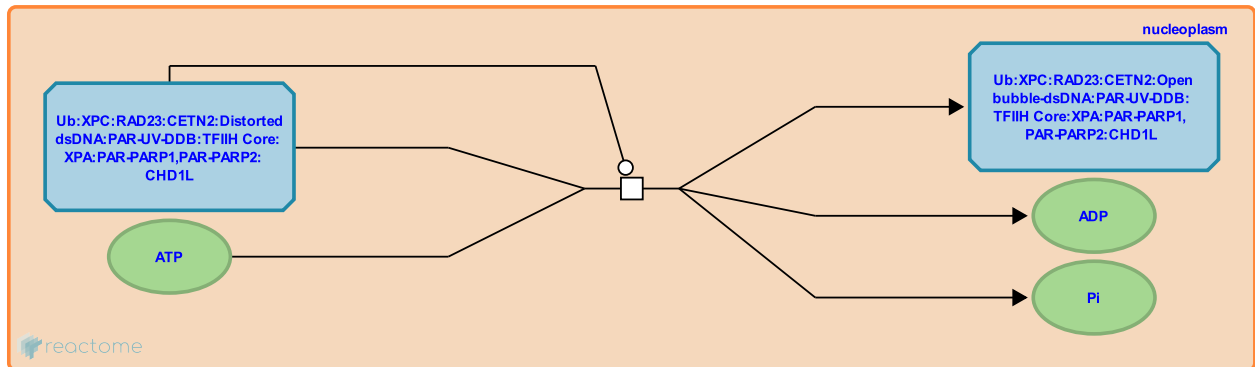
ERCC2 and ERCC3 DNA helicases form an open bubble structure in damaged DNA ↗

Location: Formation of Incision Complex in GG-NER

Stable identifier: R-HSA-5690996

Type: transition

Compartments: nucleoplasm



Two DNA helicases XPB (ERCC3) and XPD (ERCC2), which are part of the TFIIH complex, unwind the distorted DNA duplex around the lesion to form an open bubble structure that exposes the damaged site. The helicase activity of the TFIIH complex is stimulated by the presence of XPA and the XPC:RAD23:CETN2 complex (Winkler et al. 2001). The 5'->3' directed helicase activity of ERCC2 (Kuper et al. 2012) is crucial for unwinding of the distorted dsDNA during nucleotide excision repair (NER) (Coin et al. 2007). The 3'->5' directed DNA helicase ERCC3 contributes to dsDNA unwinding during NER through ATP hydrolysis (Coin et al. 2007). In addition to DNA unwinding, ERCC2 and ERCC3 verify the presence of DNA damage (Oksenysh et al. 2009, Mathieu et al. 2010, Mathieu et al. 2013). Verification of DNA damage also involves XPA (Camenisch et al. 2006). The binding site of XPC determines which DNA strand is selected by ERCC2 to verify the presence of lesions (Sugasawa et al. 2009).

Preceded by: CHD1L is recruited to GG-NER site

Followed by: SUMOylation of XPC

Literature references

- Akagi, J., Iwai, S., Sugasawa, K., Hanaoka, F., Nishi, R. (2009). Two-step recognition of DNA damage for mammalian nucleotide excision repair: Directional binding of the XPC complex and DNA strand scanning. *Mol. Cell*, 36, 642-53. ↗
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Editions

2003-07-14	Authored	Joshi-Tope, G.
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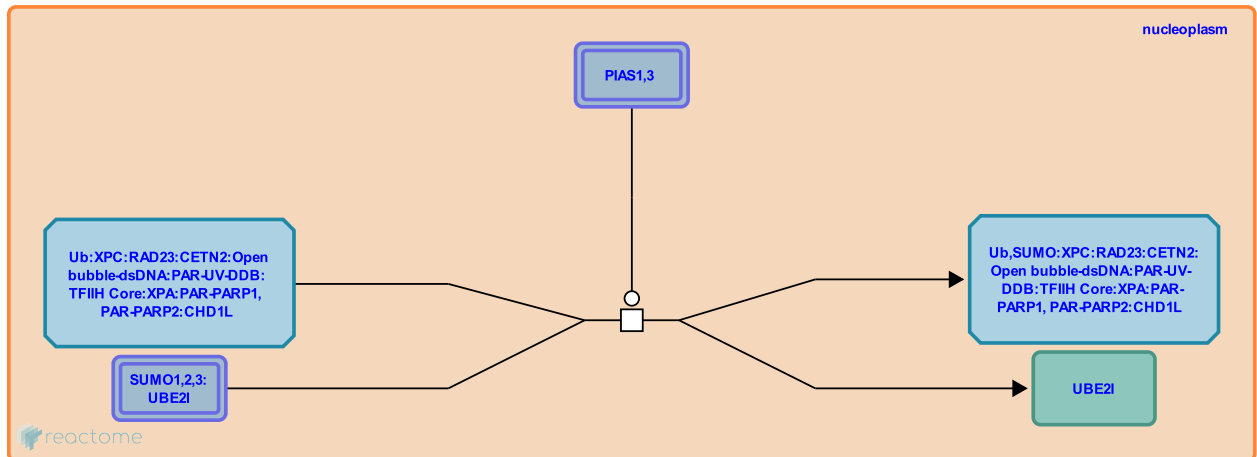
SUMOylation of XPC ↗

Location: [Formation of Incision Complex in GG-NER](#)

Stable identifier: R-HSA-6790454

Type: transition

Compartments: nucleoplasm



XPC undergoes SUMOylation following UV irradiation on several consensus SUMOylation sites (van Cuijk et al. 2015). SUMOylation of XPC probably succeeds the UV-DDB mediated ubiquitination of XPC, as the presence of both DDB2 and XPA is required for SUMOylation (Wang et al. 2005), but it has also been reported that SUMOylation of XPC was DDB2-independent (Akita et al. 2015). It is unclear whether XPC is modified by SUMO1 (Wang et al. 2005, Akita et al. 2015) or poly-SUMO2/3 (Poulsen et al. 2013). SUMO conjugases PIAS1 and PIAS3 both interact with XPC and may catalyze XPC SUMOylation (Akita et al. 2015).

Preceded by: [ERCC2 and ERCC3 DNA helicases form an open bubble structure in damaged DNA](#)

Followed by: [RNF111 ubiquitinates SUMOylated XPC](#)

Literature references

- Mori, T., Tak, YS., Iwai, S., Sugasawa, K., Ikura, T., Shimura, T. et al. (2015). SUMOylation of xeroderma pigmentosum group C protein regulates DNA damage recognition during nucleotide excision repair. *Sci Rep*, 5, 10984. ↗
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- Houtsmuller, AB., Poulsen, SL., Hansen, RK., Wikström, M., van Belle, GJ., Marteijs, JA. et al. (2013). RNF111/Arkadia is a SUMO-targeted ubiquitin ligase that facilitates the DNA damage response. *J. Cell Biol.*, 201, 797-807. ↗

Editions

2015-08-03	Reviewed	Fousteri, M.
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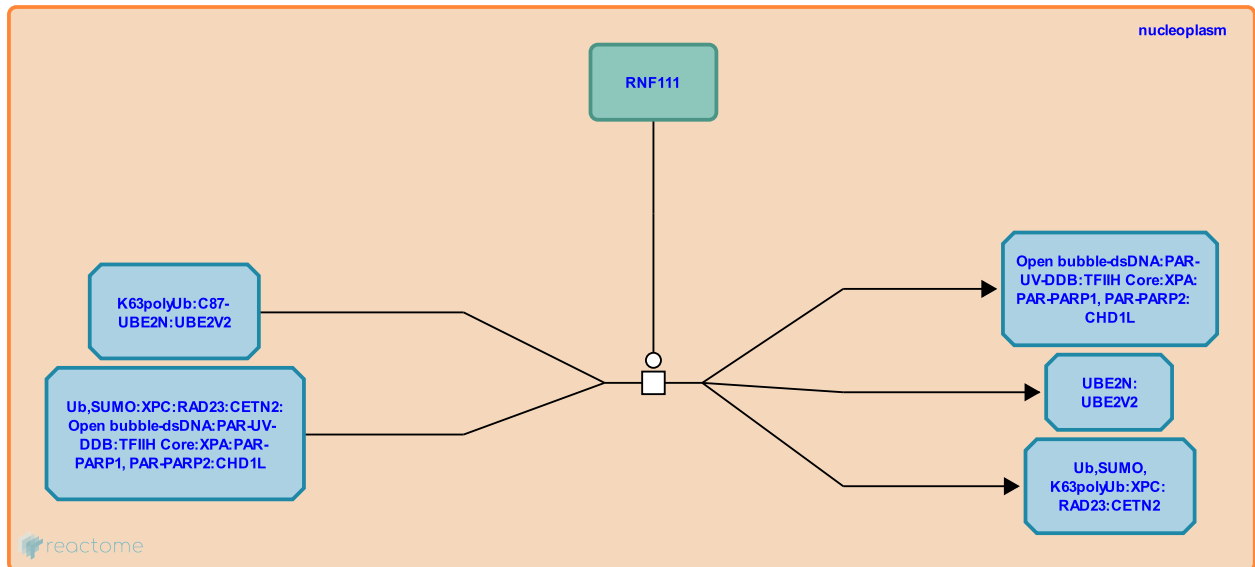
RNF111 ubiquitinates SUMOylated XPC ↗

Location: [Formation of Incision Complex in GG-NER](#)

Stable identifier: R-HSA-6790487

Type: transition

Compartments: nucleoplasm



SUMOylated XPC is recognized by the SUMO-targeted ubiquitin ligase RNF111 (Arcadia) that, together with the E2 ubiquitin conjugating complex of UBE2N (UBC13) and UBE2V2 (MMS2), generates K63-linked polyubiquitin chains on XPC (Poulsen et al. 2013) to efficiently release XPC from UV lesions (van Cuijk et al. 2015). The release of K63-polyubiquitinated XPC occurs from GG-NER pre-incision complexes that contain TFIIH and XPA and promotes optimal access/binding of ERCC5 (XPG) endonuclease to the pre-incision complex (van Cuijk et al. 2015). Successful binding of ERCC5 endonuclease 3' to the damage facilitates binding of the ERCC1:ERCC4 (ERCC1:XPF) endonuclease and progression of the NER reaction.

Preceded by: [SUMOylation of XPC](#)

Followed by: [Formation of the pre-incision complex in GG-NER](#)

Literature references

Houtsmuller, AB., Lans, H., Sabatella, M., Poulsen, SL., Theil, AF., Janssens, RC. et al. (2015). SUMO and ubiquitin-dependent XPC exchange drives nucleotide excision repair. *Nat Commun*, 6, 7499. ↗

Houtsmuller, AB., Poulsen, SL., Hansen, RK., Wikström, M., van Belle, GJ., Marteiijn, JA. et al. (2013). RNF111/Aradia is a SUMO-targeted ubiquitin ligase that facilitates the DNA damage response. *J. Cell Biol.*, 201, 797-807. ↗

Editions

2015-08-03	Reviewed	Fosterer, M.
2015-08-11	Authored, Edited	Orlic-Milacic, M.

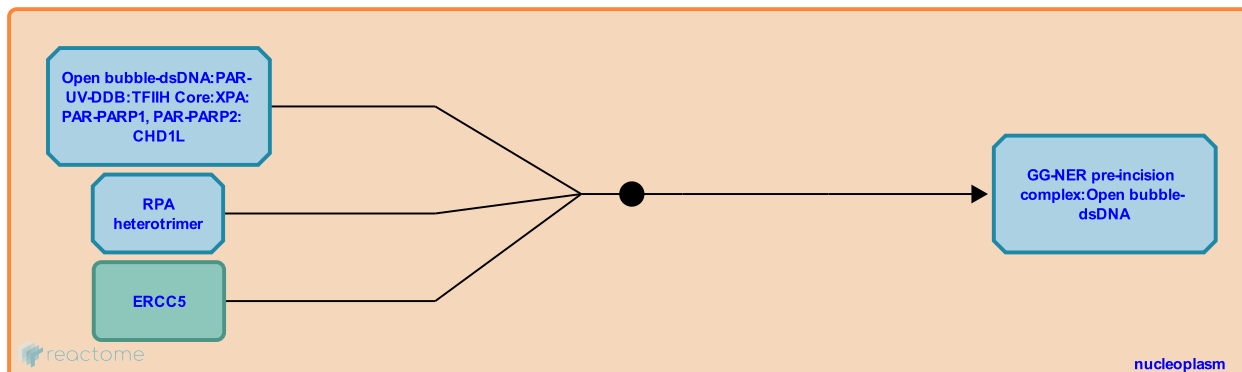
Formation of the pre-incision complex in GG-NER ↗

Location: [Formation of Incision Complex in GG-NER](#)

Stable identifier: R-HSA-5689317

Type: binding

Compartments: nucleoplasm



Once an open bubble structure is generated in damaged dsDNA through a DNA helicase activity of the TFIIH complex, the RPA heterotrimer composed of RPA1, RPA2 and RPA3, coats the undamaged single strand DNA (ssDNA) (de Laat et al. 1998), thereby protecting it from incision and enabling the correct positioning of the NER endonucleases. The interaction of RPA with XPA facilitates RPA recruitment to the global genome nucleotide excision repair (GG-NER) site (He et al. 1995, Ikegami et al. 1998). A DNA endonuclease ERCC5 (XPG) is recruited to the GG-NER site, 3' to the DNA damage, through its interaction with the TFIIH complex (Dunand-Sauthier et al. 2005, Zotter et al. 2006, Ito et al. 2007) and the RPA heterotrimer (de Laat et al. 1998).

Preceded by: [RNF111 ubiquitinates SUMOylated XPC](#)

Followed by: [Binding of ERCC1:ERCC4 \(ERCC1:XPF\) to pre-incision complex in GG-NER](#)

Literature references

Jaspers, NG., Appeldoorn, E., Weterings, E., Sugawara, K., de Laat, WL., Hoeijmakers, JH. (1998). DNA-binding polarity of human replication protein A positions nucleases in nucleotide excision repair. *Genes Dev.*, 12, 2598-609. ↗

Ingles, CJ., Wold, MS., He, Z., Henricksen, LA. (1995). RPA involvement in the damage-recognition and incision steps of nucleotide excision repair. *Nature*, 374, 566-9. ↗

Houtsmuller, AB., van Cappellen, WA., van Driel, R., Luijsterburg, MS., Nigg, A., Zotter, A. et al. (2006). Recruitment of the nucleotide excision repair endonuclease XPG to sites of UV-induced dna damage depends on functional TFIIH. *Mol. Cell. Biol.*, 26, 8868-79. ↗

Kodo, N., Ikegami, T., Saijo, M., Kyogoku, Y., Kuraoka, I., Morikawa, K. et al. (1998). Solution structure of the DNA- and RPA-binding domain of the human repair factor XPA. *Nat. Struct. Biol.*, 5, 701-6. ↗

Kuraoka, I., Tanaka, K., Compe, E., Ito, S., Coin, F., Ishigami, C. et al. (2007). XPG stabilizes TFIIH, allowing trans-activation of nuclear receptors: implications for Cockayne syndrome in XP-G/CS patients. *Mol. Cell*, 26, 231-43. ↗

Editions

2003-07-14	Authored	Joshi-Tope, G.
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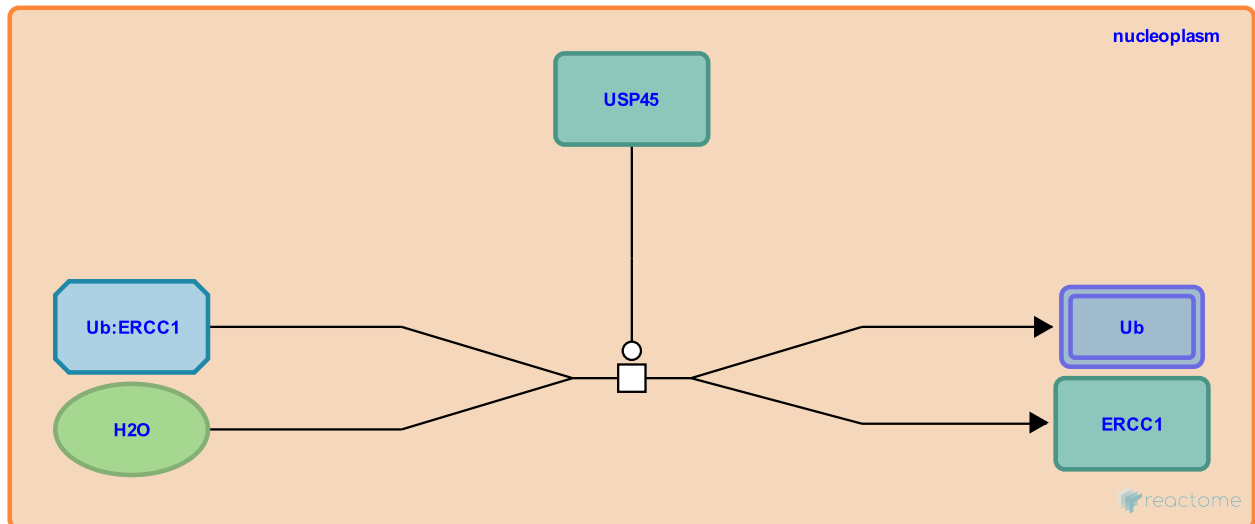
USP45 deubiquitinates ERCC1 ↗

Location: [Formation of Incision Complex in GG-NER](#)

Stable identifier: R-HSA-5696465

Type: transition

Compartments: nucleoplasm



USP45 ubiquitin protease, mutated in prostate cancer and B-cell lymphoma, deubiquitinates ERCC1. While the mechanism and timing of ERCC1 ubiquitination are not known, deubiquitination of ERCC1 by USP45 enables ERCC1 recruitment to DNA damage sites in nucleotide excision repair (NER) and repair of interstrand cross-links (ICLR) (Perez-Oliva et al. 2015).

Followed by: [Formation of ERCC1:XPF heterodimeric complex](#)

Literature references

Hickson, I., Alessi, DR., Lachaud, C., Rouse, J., Szyniarowski, P., Macartney, T. et al. (2015). USP45 deubiquitylase controls ERCC1-XPF endonuclease-mediated DNA damage responses. *EMBO J.*, 34, 326-43. ↗

Editions

2015-05-04	Authored, Edited	Orlic-Milacic, M.
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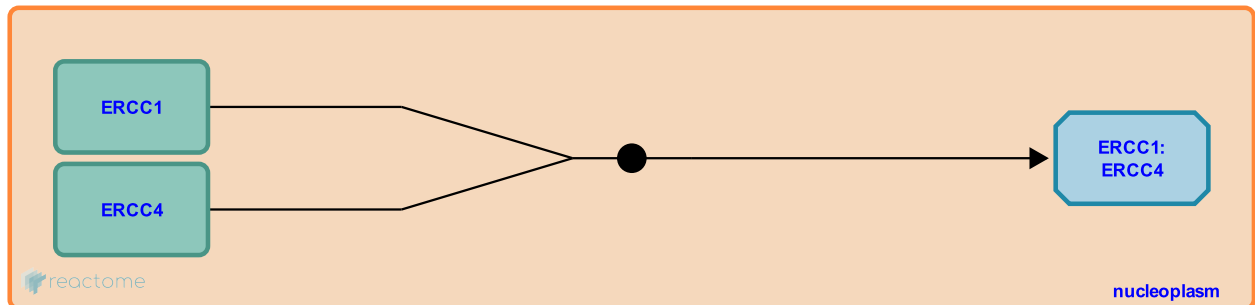
Formation of ERCC1:XPF heterodimeric complex ↗

Location: [Formation of Incision Complex in GG-NER](#)

Stable identifier: R-HSA-109955

Type: binding

Compartments: nucleoplasm



ERCC1 binds ERCC4 (XPF) to form a heterodimeric ERCC1:ERCC4 (ERCC1:XPF) complex with a DNA endonuclease activity, where ERCC4 is the catalytic subunit. Suitable substrates for the ERCC1:ERCC4 endonuclease are single strand DNA (ssDNA) and ssDNA region of a duplex DNA with an open bubble structure (Park et al. 1995).

Preceded by: [USP45 deubiquitinates ERCC1](#)

Followed by: [Binding of ERCC1:ERCC4 \(ERCC1:XPF\) to pre-incision complex in GG-NER](#)

Literature references

Park, CH., Bessho, T., Sancar, A., Matsunaga, T. (1995). Purification and characterization of the XPF-ERCC1 complex of human DNA repair excision nuclease. *J. Biol. Chem.*, 270, 22657-60. ↗

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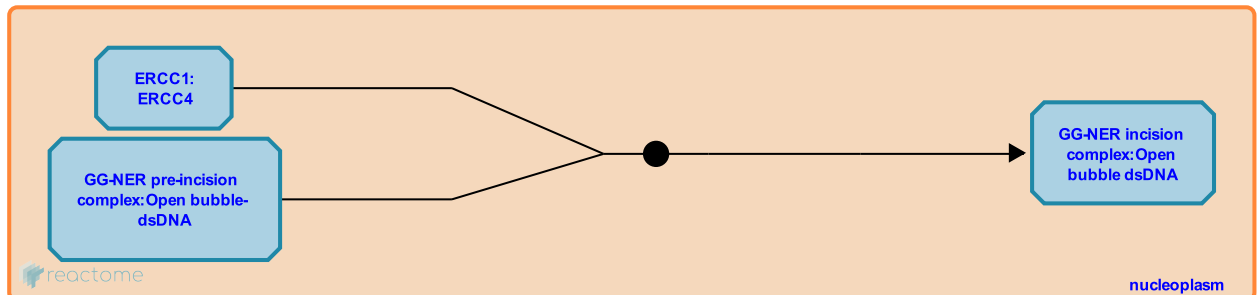
Binding of ERCC1:ERCC4 (ERCC1:XPF) to pre-incision complex in GG-NER ↗

Location: [Formation of Incision Complex in GG-NER](#)

Stable identifier: R-HSA-5690991

Type: binding

Compartments: nucleoplasm



ERCC1:ERCC4 (ERCC1:XPF) DNA endonuclease complex binds 5' to the DNA damage at global genome nucleotide excision repair (GG-NER) sites to form the incision complex. Binding of ERCC5 (XPG) to the NER site precedes the recruitment of ERCC1:ERCC4 (Riedl et al. 2003). ERCC1 directly interacts with XPA, and this interaction is necessary for the loading of ERCC1:ERCC4 to the open bubble structure in damaged dsDNA and the progression of GG-NER (Tsodikov et al. 2007, Orelli et al. 2010).

Preceded by: [Formation of the pre-incision complex in GG-NER](#), [Formation of ERCC1:XPF heterodimeric complex](#)

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