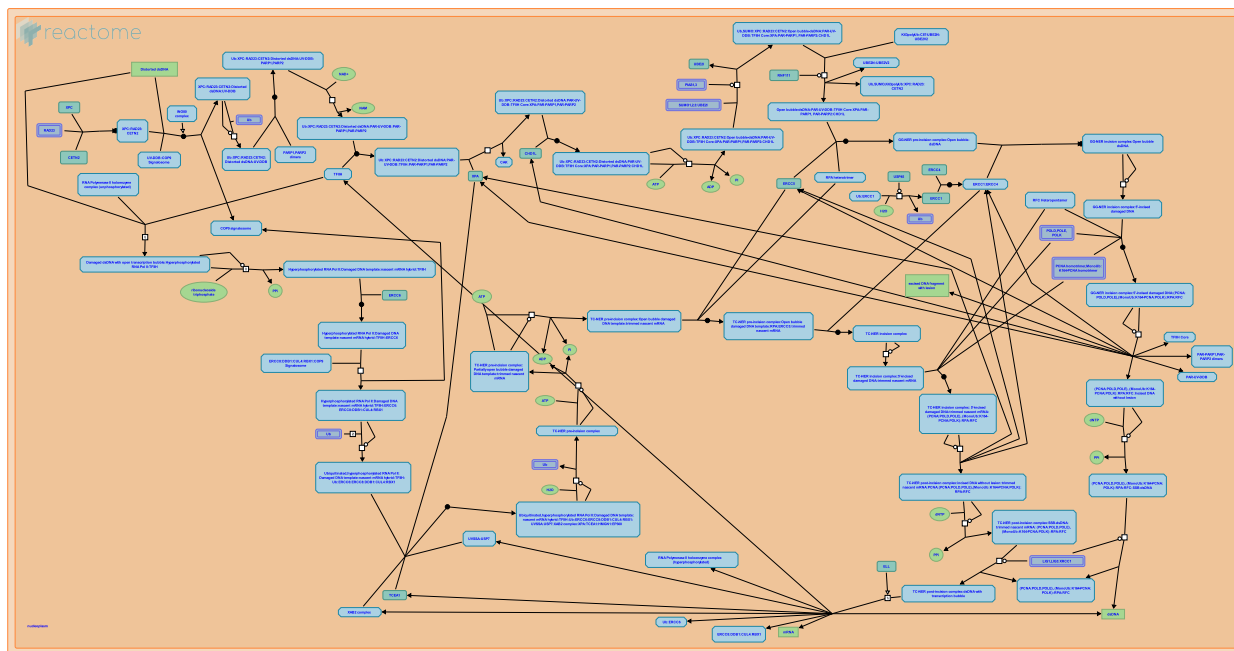


# Nucleotide Excision Repair



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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/).

08/05/2024

## 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. [↗](#)

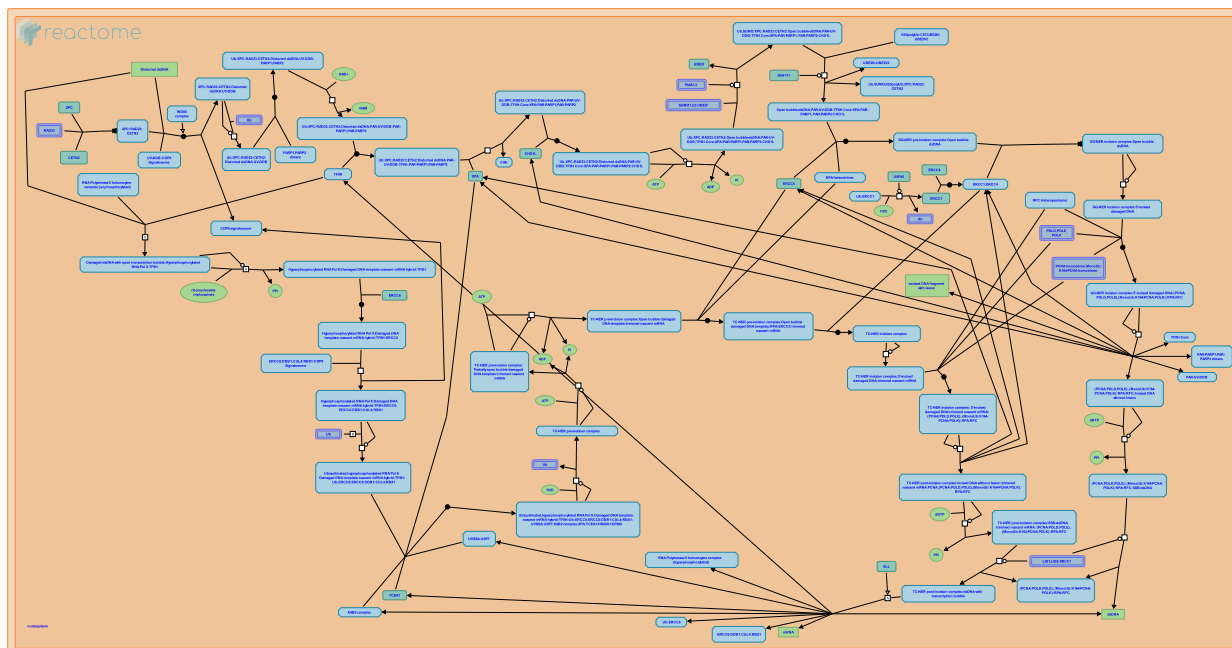
Reactome database release: 88

This document contains 3 pathways ([see Table of Contents](#))

# Nucleotide Excision Repair ↗

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

**Compartments:** nucleoplasm



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

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

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

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

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

## Literature references

- Fousteri, M., Vermeulen, W. (2013). Mammalian transcription-coupled excision repair. *Cold Spring Harb Perspect Biol*, 5, a012625. ↗
- Tomicic, MT., Roos, WP., Christmann, M., Kaina, B. (2003). Mechanisms of human DNA repair: an update. *Toxicology*, 193, 3-34. ↗
- Lans, H., Marteijn, JA., Hoeijmakers, JH., Vermeulen, W. (2014). Understanding nucleotide excision repair and its roles in cancer and ageing. *Nat. Rev. Mol. Cell Biol.*, 15, 465-81. ↗
- Lindahl, T., Wood, RD. (1999). Quality control by DNA repair. *Science*, 286, 1897-905. ↗

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

**Editions**

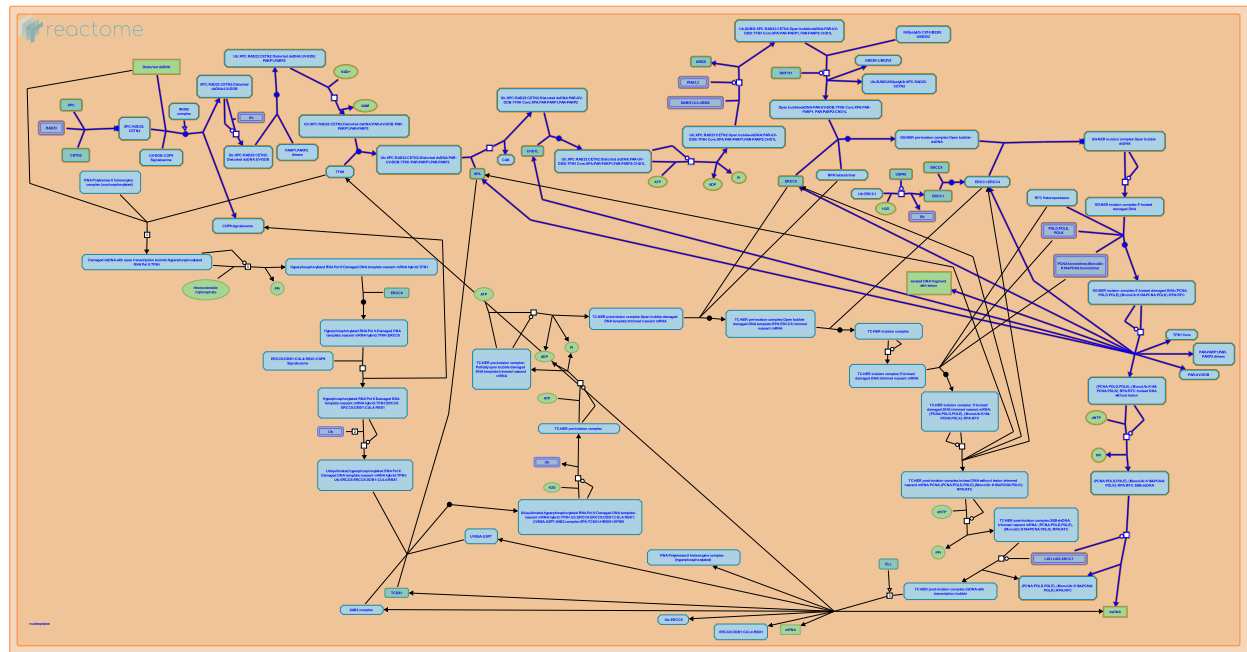
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Global Genome Nucleotide Excision Repair (GG-NER) ↗

Location: Nucleotide Excision Repair

Stable identifier: R-HSA-5696399

Compartments: nucleoplasm



The DNA damage in GG-NER is recognized by the joint action of two protein complexes. The first complex is composed of XPC, RAD23A or RAD23B and CETN2. The second complex, known as the UV-DDB complex, is an ubiquitin ligase composed of DDB1, CUL4A or CUL4B, RBX1 and a GG-NER specific protein DDB2. In vitro, the UV-DDB complex is only necessary for GG-NER mediated repair of UV-induced pyrimidine dimers. In vivo, however, where DNA repair occurs in the chromatin context, the UV-DDB complex likely facilitates GG-NER mediated repair irrespective of the DNA damage type.

After DNA damage recognition, the TFIIH complex, together with XPA, verifies the DNA damage and unwinds the DNA helix around the damage, creating an open bubble. Two DNA endonucleases, ERCC5 (XPG) and the complex of ERCC1 and ERCC4 (XPF), excise the oligonucleotide that contains damaged base(s) from the affected DNA strand. DNA polymerases delta, epsilon and/or kappa perform DNA repair synthesis, followed by DNA ligation, thus completing GG-NER.

For a recent review, please refer to Marteiijn et al. 2014.

Literature references

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

Editions

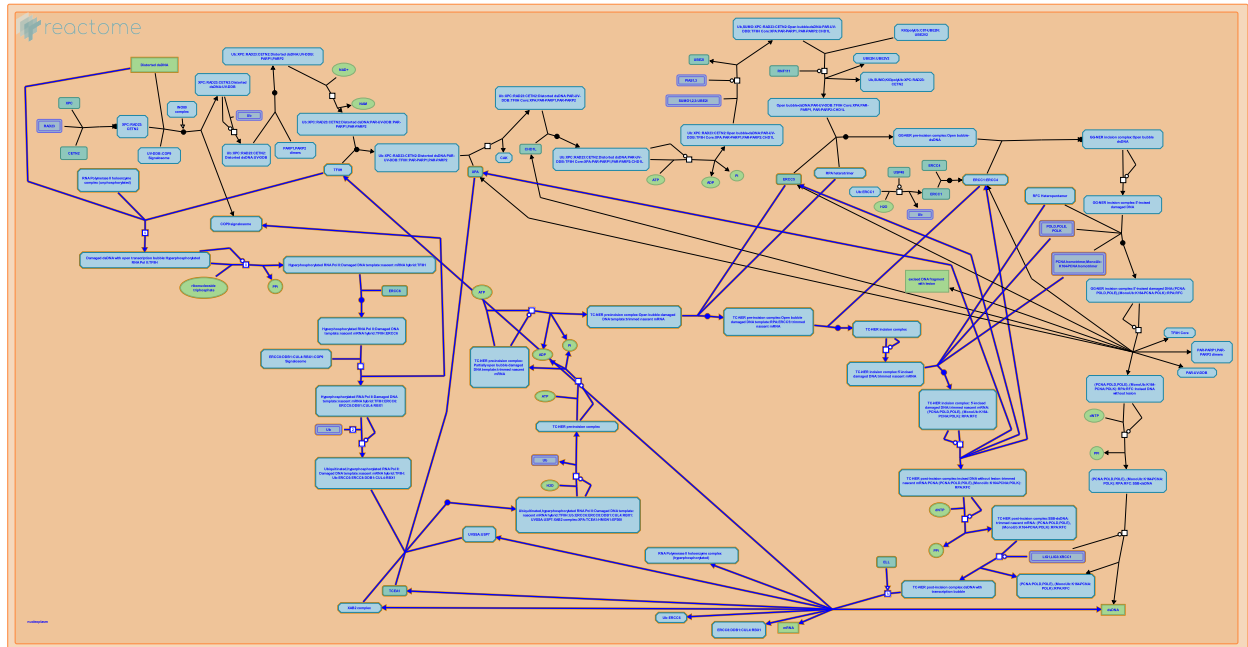
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## Transcription-Coupled Nucleotide Excision Repair (TC-NER) ↗

**Location:** Nucleotide Excision Repair

**Stable identifier:** R-HSA-6781827

**Compartments:** nucleoplasm



DNA damage in transcribed strands of active genes is repaired through a specialized nucleotide excision repair (NER) pathway known as transcription-coupled nucleotide excision repair (TC-NER). TC-NER impairment is the underlying cause of a severe hereditary disorder Cockayne syndrome, an autosomal recessive disease characterized by hypersensitivity to UV light.

TC-NER is triggered by helix distorting lesions that block the progression of elongating RNA polymerase II (RNA Pol II). Stalled RNA Pol II complex triggers the recruitment of ERCC6. ERCC6, commonly known as CSB (Cockayne syndrome protein B) recruits ERCC8, commonly known as CSA (Cockayne syndrome protein A). ERCC8 has 7 WD repeat motifs and is part of the ubiquitin ligase complex that also includes DDB1, CUL4A or CUL4B and RBX1. The ERCC8 ubiquitin ligase complex is one of the key regulators of TC-NER that probably exerts its role by ubiquitinating one or more factors involved in this repair process, including the RNA Pol II complex and ERCC6.

In addition to RNA Pol II, ERCC6 and the ERCC8 complex, the transcription elongation factor TFIIH, which is also involved in global genome nucleotide excision repair (GG-NER), is recruited to sites of TC-NER. The TC-NER pre-incision complex also includes XPA, XAB2 complex, TCEA1 (TFIIS), HMG1, UVSSA in complex with USP7, and EP300 (p300). XPA probably contributes to the assembly and stability of the pre-incision complex, similar to its role in GG-NER. The XAB2 complex is involved in pre-mRNA splicing and may modulate the structure of the nascent mRNA hybrid with template DNA through its RNA-DNA helicase activity, allowing proper processing of DNA damage. TCEA1 may be involved in RNA Pol II backtracking, which allows repair proteins to gain access to the damage site. It also facilitates trimming of the 3' end of protruding nascent mRNA from the stalled RNA Pol II, enabling recovery of RNA synthesis after repair.

Deubiquitinating activity of the UVSSA:USP7 complex is needed for ERCC6 stability at repair sites. Non-histone nucleosomal binding protein HMG1 and histone acetyltransferase p300 (EP300) remodel the chromatin around the damaged site, thus facilitating repair.

Dual incision of the lesion-containing oligonucleotide from the affected DNA strand is performed by two DNA endonucleases, the ERCC1:ERCC4 (ERCC1:XPF) complex and ERCC5 (XPG), which also participate in GG-NER. DNA polymerases delta, epsilon or kappa fill in the single stranded gap after dual incision and the remaining single strand nick is sealed by DNA ligases LIG1 or LIG3 (the latter in complex with XRCC1), similar to GG-NER. After the repair of DNA damage is complete, RNA Pol II resumes RNA synthesis.

For past and recent reviews, see Mellon et al. 1987, Svejstrup 2002, Hanawalt and Spivak 2008, Vermeulen and Fousteri 2013 and Marteijn et al. 2014.

## Literature references

- Fousteri, M., Vermeulen, W. (2013). Mammalian transcription-coupled excision repair. *Cold Spring Harb Perspect Biol*, 5, a012625. [↗](#)
- Lans, H., Marteijn, JA., Hoeijmakers, JH., Vermeulen, W. (2014). Understanding nucleotide excision repair and its roles in cancer and ageing. *Nat. Rev. Mol. Cell Biol.*, 15, 465-81. [↗](#)
- Svejstrup, JQ. (2002). Mechanisms of transcription-coupled DNA repair. *Nat Rev Mol Cell Biol*, 3, 21-9. [↗](#)
- Mellon, I., Bohr, VA., Smith, CA., Hanawalt, PC. (1987). Preferential DNA repair of an active gene in human cells. *Proc Natl Acad Sci U S A*, 83, 8878-82. [↗](#)
- Hanawalt, PC., Spivak, G. (2008). Transcription-coupled DNA repair: two decades of progress and surprises. *Nat. Rev. Mol. Cell Biol.*, 9, 958-70. [↗](#)

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