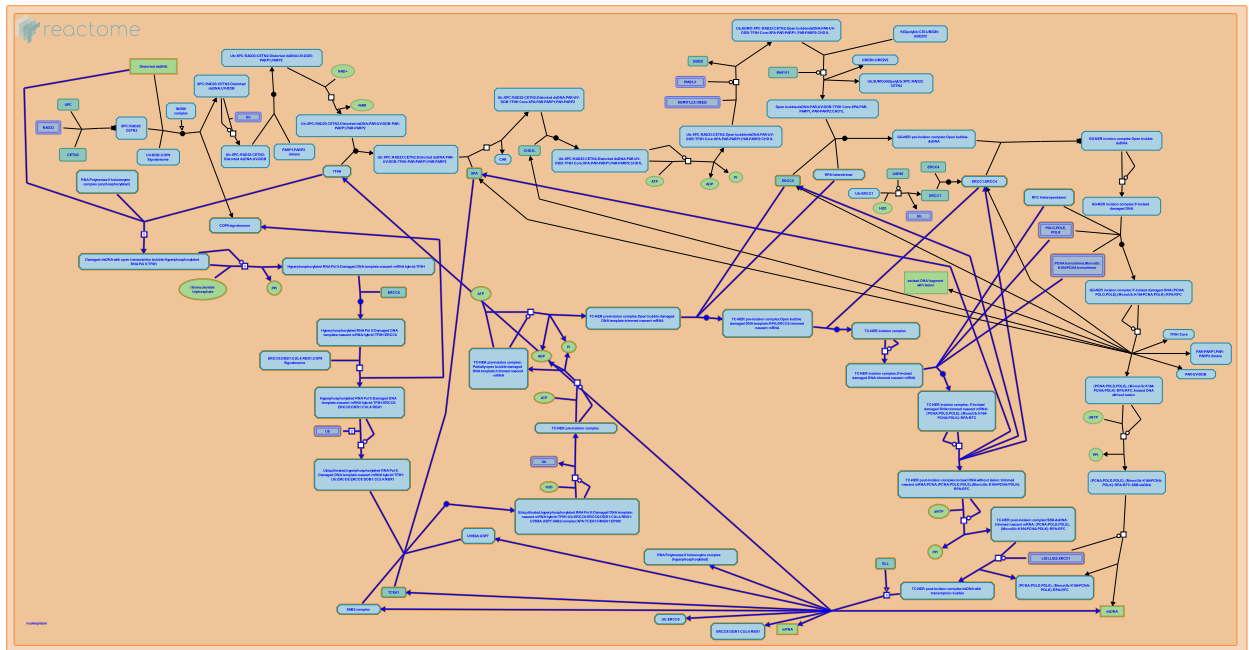


Transcription-Coupled Nucleotide Excision Repair (TC-NER)



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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).

05/05/2024

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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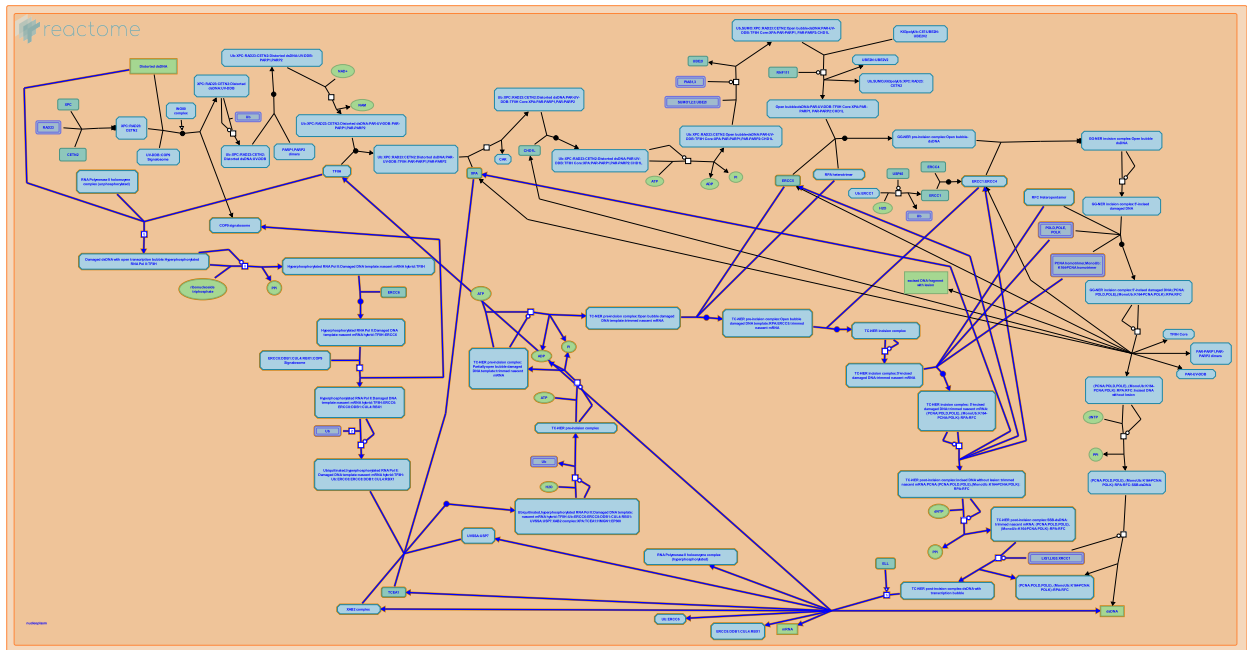
Reactome database release: 88

This document contains 4 pathways and 1 reaction ([see Table of Contents](#))

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

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-precision 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-precision 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.

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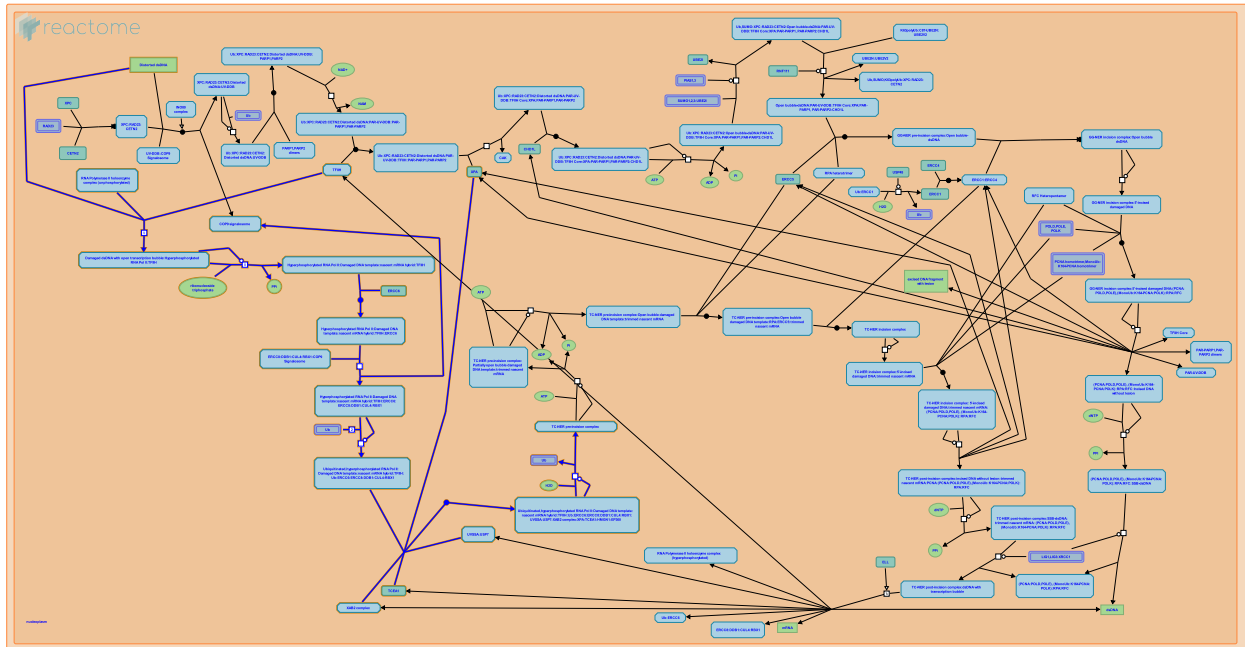
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Formation of TC-NER Pre-Incision Complex ↗

Location: Transcription-Coupled Nucleotide Excision Repair (TC-NER)

Stable identifier: R-HSA-6781823

Compartments: nucleoplasm



Formation of TC-NER pre-incision complex is initiated when the RNA polymerase II (RNA Pol II) complex stalls at a DNA damage site. The stalling is caused by misincorporation of a ribonucleotide opposite to a damaged base (Brueckner et al. 2007). Cockayne syndrome protein B (ERCC6, CSB) binds stalled RNA Pol II and recruits Cockayne syndrome protein A (ERCC8, CSA). ERCC8 is part of an ubiquitin ligase complex that also contains DDB1, CUL4A or CUL4B and RBX1. This complex is implicated in the regulation of TC-NER progression probably by ubiquitinating one or more factors involved in this pathway, which may include RNA Pol II and ERCC6 at the later stages of repair (Bregman et al. 1996, Fousteri et al. 2006, Groisman et al. 2006). XPA is recruited to the TC-NER site through its interaction with the TFIIH complex (Furuta et al. 2002, Ziani et al. 2014). The XAB2 complex, which probably regulates the accessibility of the DNA damage site through its RNA-DNA helicase activity, binds the TC-NER site via the interaction of its XAB2 subunit with RNA Pol II, ERCC6, ERCC8 and XPA (Nakatsu et al. 2000, Sollier et al. 2014). TCEA1 (TFIIS) is a transcription elongation factor that may facilitate backtracking of the stalled RNA Pol II, enabling access of repair proteins to the DNA damage site and promotes partial digestion of the 3' protruding end of the nascent mRNA transcript by the backtracked RNA Pol II, allowing resumption of RNA synthesis after damage removal (Donahue et al. 1994). Access to DNA damage sites in TC-NER was suggested to be facilitated by a chromatin remodeler HMG1 (Birger et al. 2003), but another study found that HMG1 was not needed for human TC-NER (Apelt et al. 2020). UVSSA protein interacts with ubiquitinated ERCC6 and RNA Pol II, recruiting ubiquitin protease USP7 to the TC-NER site and promoting ERCC6 stabilization (Nakazawa et al. 2012, Schwertman et al. 2012, Zhang et al. 2012, Fei and Chen 2012).

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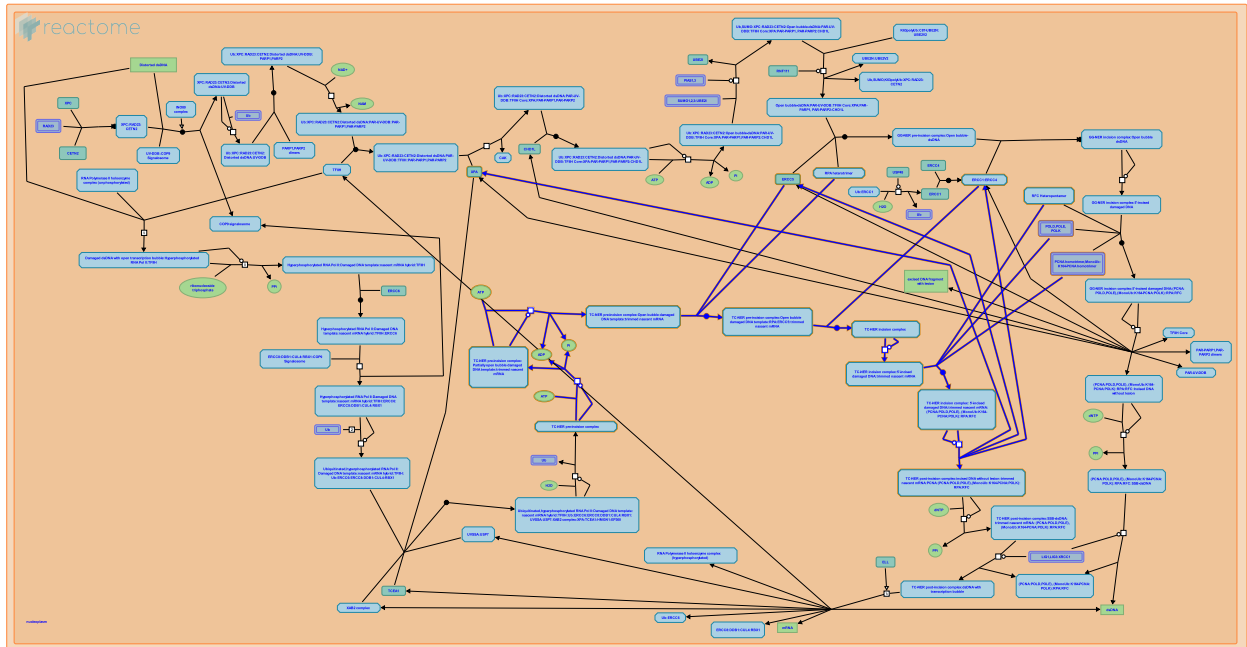
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Dual incision in TC-NER ↗

Location: Transcription-Coupled Nucleotide Excision Repair (TC-NER)

Stable identifier: R-HSA-6782135

Compartments: nucleoplasm



In transcription-coupled nucleotide excision repair (TC-NER), similar to global genome nucleotide excision repair (GG-NER), the oligonucleotide that contains the lesion is excised from the open bubble structure via dual incision of the affected DNA strand. 5' incision by the ERCC1:ERCC4 (ERCC1:XPF) endonuclease precedes 3' incision by ERCC5 (XPG) endonuclease. In order for the TC-NER pre-incision complex to assemble and the endonucleases to incise the damaged DNA strand, the RNA polymerase II (RNA Pol II) complex has to backtrack - reverse translocate from the damage site. Although the mechanistic details of this process are largely unknown in mammals, it may involve ERCC6/ERCC8-mediated chromatin remodelling/ubiquitination events, the DNA helicase activity of the TFIIH complex and TCEA1 (TFIIS)-stimulated cleavage of the 3' protruding end of nascent mRNA by RNA Pol II (Donahue et al. 1994, Lee et al. 2002, Sarker et al. 2005, Vermeulen and Fousteri 2013, Hanawalt and Spivak 2008, Staresincic et al. 2009, Epshtein et al. 2014).

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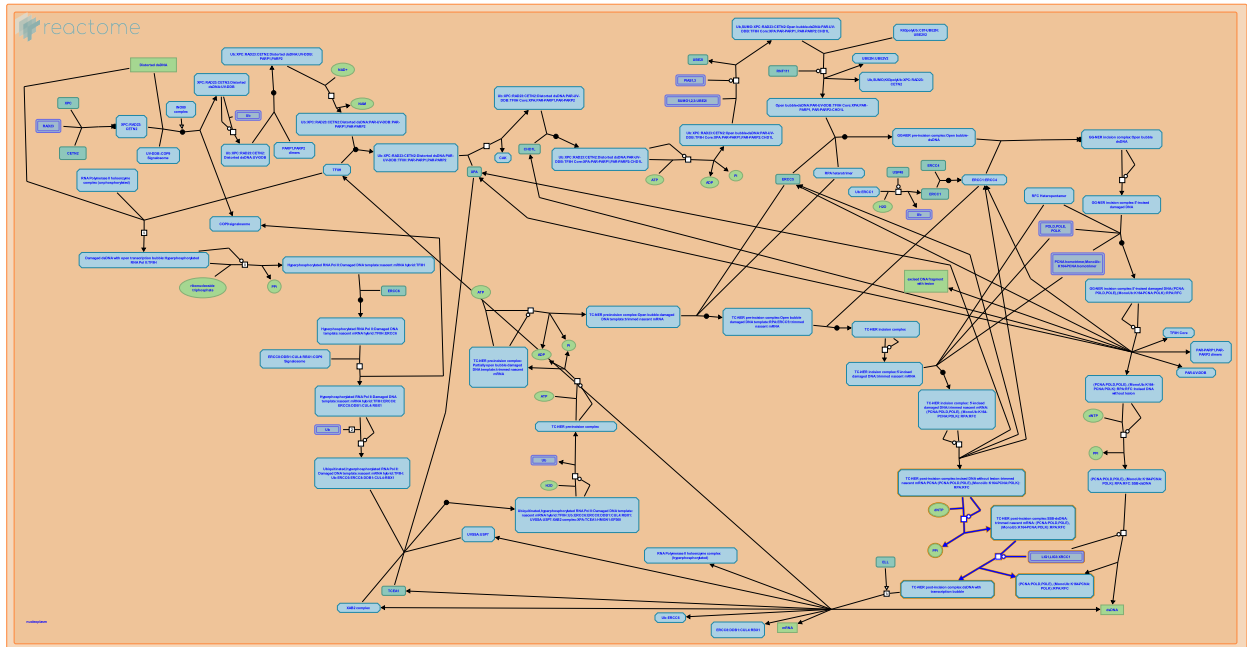
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Gap-filling DNA repair synthesis and ligation in TC-NER ↗

Location: Transcription-Coupled Nucleotide Excision Repair (TC-NER)

Stable identifier: R-HSA-6782210

Compartments: nucleoplasm



In transcription-coupled nucleotide excision repair (TC-NER), similar to global genome nucleotide excision repair (GG-NER), DNA polymerases delta or epsilon, or the Y family DNA polymerase kappa, fill in the single stranded gap that remains after dual incision. DNA ligases LIG1 or LIG3, subsequently seal the single stranded nick by ligating the 3' end of the newly synthesized patch with the 5' end of incised DNA (Staresincic et al. 2009, Ogi et al. 2010, Arakawa et al. 2012, Paul-Konietzko et al. 2015).

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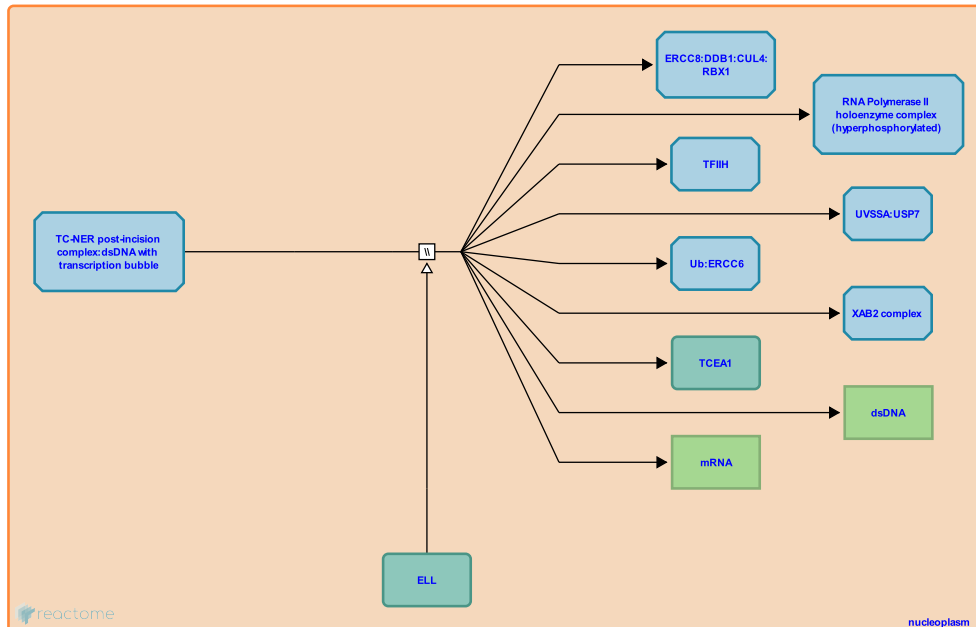
Recovery of RNA synthesis after TC-NER ↗

Location: [Transcription-Coupled Nucleotide Excision Repair \(TC-NER\)](#)

Stable identifier: R-HSA-6782234

Type: omitted

Compartments: nucleoplasm



After DNA repair synthesis is completed at transcription-coupled nucleotide excision repair (TC-NER) sites, transcription resumes. A number of factors have been implicated in this process. ERCC6 (CSB) contains an ubiquitin-binding domain that is indispensable for its function in TC-NER and the restoration of damage-inhibited RNA synthesis (Anindya et al. 2010). The ubiquitin ligase activity of the ERCC8:DDB1:CUL4:RBX1 complex plays an important role in termination of TC-NER, possibly by targeting ERCC6 or its ubiquitinated partner for degradation and promoting dissociation of repair factors from the RNA polymerase II complex (Groisman et al. 2006, Vermeulen and Fousteri 2013). The ubiquitin protease complex composed of UVSSA and USP7 is also implicated in the recovery of RNA synthesis (RRS) (Nakazawa et al. 2012, Scwertman et al. 2012, Zhang et al. 2012, Fei and Chen 2012). ELL protein, recruited to the TFIIH complex, possibly as a component of the little elongation complex, is needed for RRS (Mourgues et al. 2013). Furthermore, histone chaperone FACT promotes accelerated histone exchange at TC-NER sites, allowing efficient progression of TC-NER and restoration of RNA synthesis after the repair of transcription blocking damages is completed (Dinant et al. 2013).

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