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The role of Transcription Factor IIH complex in nucleotide excision repair

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Abstract

DNA damage occurs throughout life from a variety of sources, and it is imperative to repair damage in a timely manner to maintain genome stability. Thus, DNA repair mechanisms are a fundamental part of life. Nucleotide excision repair (NER) plays an important role in the removal of bulky DNA adducts, such as cyclobutane pyrimidine dimers from ultraviolet light or DNA crosslinking damage from platinum-based chemotherapeutics, such as cisplatin. A main component for the NER pathway is transcription factor IIH (TFIIH), a multifunctional, 10-subunit protein complex with crucial roles in both transcription and NER. In transcription, TFIIH is a component of the pre-initiation complex and is important for promoter opening and the phosphorylation of RNA Polymerase II (RNA Pol II). During repair, TFIIH is important for DNA unwinding, recruitment of downstream repair factors, and verification of the bulky lesion. Several different disease states can arise from mutations within subunits of the TFIIH complex. Most strikingly are xeroderma pigmentosum (XP), XP combined with Cockayne syndrome (CS), and trichothiodystrophy (TTD). Here, we summarize the recruitment and functions of TFIIH in the two NER subpathways, global genomic (GG-NER) and transcription-coupled NER (TC-NER). We will also discuss how TFIIH's roles in the two subpathways lead to different genetic disorders.

Keywords

DNA damage; genome stability; GG-NER; TC-NER; transcription factor IIH

1 | INTRODUCTION

DNA damage occurs frequently throughout all aspects of life from a variety of sources. Exogenous DNA damaging sources include physical or chemical agents, such as ionizing radiation, UV light, environmental mutagens, or chemotherapeutic treatments. These exogenous agents induce DNA strand breaks, helix-distorting photolesions, and intra- or inter-strand crosslinks (Chatterjee & Walker, 2017). There are also many damaging agents residing in cells. The most common one is reactive oxygen species, which is generated during cell metabolism and can induce a high amount of oxidative damage in DNA (Cooke

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et al., 2003). Additionally, cytosine deamination (loss of an amino group), depurination (loss of a base), and nucleotide misincorporation during replication or recombination also occur at high frequency to form endogenous DNA damage (Ciccia & Elledge, 2010). These lesions may cause a variety of structural alterations within the DNA, thereby representing a major threat to the integrity of the genome.

DNA damage can trigger a wide range of cellular responses, including gene transcription, checkpoint activation, DNA repair, and others (Giglia-Mari et al., 2011; Wang, 1998). Among these responses, DNA repair plays particularly important roles in maintaining genome stability (Sancar et al., 2004). This is because many types of DNA lesions are genotoxic by blocking DNA replication or gene transcription. Failure to repair them may lead to apoptosis (Wang, 2001). Alternatively, if the cell does not die, the unrepaired damage can lead to mutations, which can cause several disease states, such as cancer or neurodegeneration (Chatterjee & Walker, 2017; Cooke et al., 2003; Giglia-Mari et al., 2011; Martin, 2008; Sancar et al., 2004).

Corresponding to the different types of DNA damage, cells are equipped with different repair pathways and are able to utilize the right repair mechanism for damage removal. There are several DNA repair pathways currently identified in the cell, including direct damage reversal, mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER), single strand break repair (SSBR), and double strand break repair (DSBR; Chatterjee & Walker, 2017; Martin, 2008). Direct reversal repair enzymes include UV photolyase that repairs UV damage, O^6-methylguanine-DNA-methyltransferase that repairs O^6-alkylated bases, and the AlkB family that reverses *N*-alkylated base adducts (Yi & He, 2013). MMR corrects mismatches between base pairs (i.e., non-A:T or G:C pairing) and insertions or deletions accumulated during replication and recombination (Li, 2008). BER repairs small base damage in the nucleus and the mitochondria, such as oxidation, deamination, abasic sites, and alkylation lesions that do not cause distortions to the DNA helix (Krokan & Bjørås, 2013). SSBR and DSBR are responsible for the repair of single-stranded and double-stranded breaks, respectively. In SSBR, breaks are recognized by the Poly (ADP-ribose) polymerase 1 (PARP1) protein and repair is conducted similar to the BER pathway (Ray Chaudhuri & Nussenzweig, 2017). DSBR has two major pathways to resolve double strand breaks: non-homologous end joining and homologous recombination (Lieber, 2010; Scully et al., 2019).

NER is a versatile repair mechanism that removes a wide range of DNA adducts and plays a critical role for maintaining genome stability (Marteijn et al., 2014). Somewhat similar to BER, NER also conducts the “cut-and-patch” type repair process; however, NER mainly removes helix-distorting lesions from the genome, such as UV photoproducts—cyclobutane pyrimidine dimers (CPDs) and 6–4 photoproducts (6–4PPs), DNA adducts induced by benzopyrene in cigarettes, and intrastrand crosslinks formed by cancer chemotherapeutics, such as cisplatin (Marteijn et al., 2014). These adducts can present different chemical modifications within the DNA; however, they are all bulky and helical distorting and can impede the progression of replication and transcription. As detailed below, NER performs “dual incision” on both 5’ and 3’ sides of the damage to remove approximately 25–30 bases (Huang et al., 1992). The resulting gap on the damaged strand is subsequently filled by

DNA polymerase and ligase (Marteijn et al., 2014; Prakash & Prakash, 2000; Schärer, 2013; Spivak, 2015).

Transcription factor IIH (TFIIH) is a multifunctional 10-subunit protein complex integral to both transcription initiation and NER (Compe & Egly, 2012). The TFIIH complex includes a 7-subunit core, which consists of XPB, XPD, p52, p8, p62, p34, and p44, and a three-subunit cyclin activated kinase (CAK) module, which consists of CDK7, cyclin H, and MAT1 (Tsutakawa et al., 2020; Figure 1). During transcription, TFIIH is a component of the RNAP II transcription initiation machinery, known as the pre-initiation complex (PIC). TFIIE in PIC interacts directly with both RNAP II and TFIIH, thus helping assemble and orient TFIIH in PIC (Schilbach et al., 2017). The XPB subunit in TFIIH, an ATP-dependent DNA translocase, functions as a wedge to open the promoter DNA at the transcription start site (Tirode et al., 1999). The TFIIH-mediated promoter opening allows the single-stranded template DNA to engage the RNAP II active site for transcription initiation. TFIIH is also important for RNAP II escape from the promoter, elongation, mRNA processing and termination, mainly through its kinase activity in phosphorylating Ser5 residue of the C-terminal domain of RNAP II (Rimel & Taatjes, 2018). TFIIH has some similar functions in DNA repair; however, its role in repair is significantly different from what it does in transcription. TFIIH mainly performs the helicase function to unwind damaged DNA and keep the DNA bubble open, and facilitate recruitment of downstream repair proteins (Compe & Egly, 2012). The helicase function is solely dependent on the 7-subunit core complex, but does not require the CAK kinase module. Interestingly, it has been shown that CAK needs to be displaced from TFIIH by XPA, and the displacement activates the repair function of TFIIH (Coin et al., 2008). CAK has been shown to negatively regulate the helicase activity of XPD and phosphorylate one or more TFIIH and NER components (Araújo et al., 2000). Therefore, dissociation of the CAK complex from the TFIIH core can stimulate the helicase and ATPase activities of other subunits, allowing for the DNA strand to be opened and enlarged around the site of damage (Winkler et al., 2001). On the other hand, the p44 subunit interacts with XPD and can enhance XPD's ATPase activity in vitro (Dubaele et al., 2003). Additionally, TFIIH plays an important role in damage verification before the step of strand incision (Mu et al., 2018; Zurita & Cruz-Becerra, 2016). Here, we will discuss detailed functions of TFIIH in NER and summarize human genetic disorders associated with TFIIH deficiency.

2 | MECHANISMS OF TFIIH IN REGULATING NER

2.1 | The two subpathways in NER

NER has two subpathways—global genome (GG-NER) and transcription coupled NER (TC-NER; Schärer, 2013; Spivak, 2015). GG-NER utilizes surveillance proteins such as XPC and UV-DDB to recognize DNA damage. Therefore, it repairs damage across the whole genome, including transcribed and untranscribed regions (Kusakabe et al., 2019). In contrast, TC-NER is specific for repair on the transcribed strand of active genes, when elongating RNA Pol II is stalled by the damage. While TC-NER only repairs a small fraction of the human genome, it is more efficient than GG-NER and can rapidly respond to Pol II stalling for repair (Duan et al., 2021; Fousteri & Mullenders, 2008). There are

four main steps in NER: damage recognition, DNA unwinding, dual incision, and repair synthesis. Although there is a key difference in the damage recognition step between the two subpathways, the damage recognition is followed by the recruitment of TFIIH in both of them, and the steps after TFIIH are believed to be the same as well (Okuda et al., 2017; Tsutakawa et al., 2020). As GG- and TC-NER are initiated by XPC/UV-DDB and RNA Pol II, respectively, the mechanism for TFIIH recruitment in the two sub-pathways is found to be significantly different (see below for more details).

Once TFIIH is recruited, it functions as a DNA helicase to promote the pre-incision complex formation together with other NER factors, such as XPA and RPA (Coin et al., 2008; Kuper et al., 2014; Topolska-Woś et al., 2020). After the DNA strands have been unwound, TFIIH retains the open DNA conformation (Kokic et al., 2019). ERCC1-XPF and XPG, two repair endonucleases, nick the damaged strand on the 5’ and 3’ side, respectively. XPF and XPG cut the DNA strand asymmetrically relative to the lesion. ERCC1-XPF cleaves DNA 20 nt ± 5 nt upstream of the damage site, whereas XPG cleaves DNA 6 nt ± 3 nt downstream of the lesion (Hu et al., 2015), evicting an oligonucleotide of ~30 nt containing the damage. Of note, the size of the dual incision product varies slightly between different species, despite high conservation of the protein complex (Li et al., 2018). A recent study shows that the Rad5-related DNA translocase HLTF facilitates release of the incised DNA fragment (van Toorn et al., 2022). Once the damage has been excised, DNA polymerase can synthesize the new DNA strand, followed by ligation to seal the nick. This restores the nucleotide sequence for transcription and replication, and the factors then disassociate from the strand (Schärer, 2013).

As NER plays a critical role in the repair of a variety of DNA damage, genetic defects and mutations that occur in TFIIH and other NER proteins are associated with a variety of human disorders (Coin et al., 1998; Lehann, 2001). These will be discussed more in detail later in this paper.

2.2 | TFIIH recruitment and functions in GG-NER

GG-NER is responsible for the repair of bulky adducts across the genome, and is particularly important for the suppression of mutations and potential carcinogenesis associated with UV lesions and other bulky adducts. In GG-NER, damage, such as a CPD lesion, is first recognized by the UV-DDB protein and then transferred to XPC, through UV-DDB-mediated XPC polyubiquitylation (Sugasawa et al., 2005). XPC forms a heterodimer with RAD23 and binds to thermodynamically destabilized DNA (Min & Pavletich, 2007), instead of a specific type of lesion. This low lesion specificity allows GG-NER to repair a broad range of lesions, such as UV photolesions, cisplatin-induced intrastrand crosslinks, benzopyrene adducts, and other helix-distorting lesions. However, the low specificity may enable XPC to bind to other types of damage not commonly repaired by NER, including DNA mismatch bubbles (Chen et al., 2015; Krasikova et al., 2013). Thus, the importance of TFIIH’s damage verification function is inexplicably tied to the role of XPC to avoid incisions at sites without bulky adducts.

TFIIH is directly recruited by XPC in GG-NER. Biochemical data indicate that the p62 and XPB subunits of TFIIH physically interact with XPC (Uchida et al., 2002; Yokoi et

al., 2000). This finding is further supported by the structural data for the yeast and human XPC-TFIIH-DNA complexes. The yeast data show that the N-terminus of XPC contacts with the pleckstrin homology (PH) domain of p62, while the XPC C-terminal domain interacts with the C-terminal helix of XPB (van Eeuwen et al., 2021). The more recent human study indicates that DNA damage recognized by XPC is handed over to the TFIIH core complex and XPA. The binding location of XPA between XPB and XPD positions the damage-containing DNA strand for damage verification by XPD (Kim et al., 2023).

After recruitment by XPC, TFIIH plays two major roles in GGN-ER: DNA unwinding and damage verification, both of which are mainly dependent on the XPD subunit (Figure 2). XPD is the major helicase to unwind the two strands in the NER pathway. While XPB was initially suggested as another helicase with an opposite polarity to XPD (Fuss & Tainer, 2011), other studies show that XPB's ATPase, but not the helicase function, is required for DNA repair (Coin et al., 2007). This raises an interesting model that XPB functions as an ATPase for the initial unwinding and anchoring TFIIH to the DNA strand, resulting in a helix opening action and engagement of XPD to the DNA. In agreement with this model, Cryo-EM analysis of the yeast XPC-TFIIH-DNA complex has provided structural insights into the coordinated action between XPB and XPC in initiating DNA unwinding (van Eeuwen et al., 2021). The data show that XPB binds to the 5' side relative to the damage, whereas XPC holds the 3' side. XPB uses its ATP-dependent DNA translocase activity to generate torsion stress and unwind DNA. XPC holds the other side as an anchor to avoid DNA free rotation. Hence, XPB and XPC function in a cooperative manner to initiate DNA unwinding. The partially opened DNA state promoted by XPB and XPC is then delivered to XPD for further bubble formation and damage verification. These structural data thus suggest that XPB and XPD act sequentially to promote formation of the NER bubble structure. Defects in either XPB or XPD can result in failure of strand separation around the damage and incomplete repair. In line with this notion, yeast genetics evidence has shown that truncation of the C-terminal portion of XPB or point mutations deactivating XPD's heli-case activity leads to extremely high UV sensitivity and low or even undetectable GG-NER (Duan et al., 2020; van Eeuwen et al., 2021).

XPD also performs a sliding function to verify if a genuine NER damage is present. This damage verification function is carried out by sliding a single-stranded DNA (ssDNA) through the central tunnel of XPD protein formed by an iron-sulfur cluster and an arch domain (Kuper et al., 2014). This sliding function will stop or be impeded if the DNA has a bulky lesion and can aid in the translocation of the TFIIH complex to the location of the damage. The stalling of XPD by a bulky lesion thus serves as a critical damage verification mechanism before NER initiates strand excision. Mutations of several amino acids near XPD's central tunnel abolishes the damage verification function, but does not impact the DNA helicase activity (Mathieu et al., 2013), suggesting that DNA unwinding and damage verification are conducted by different functional domains in XPD. Once the DNA has been opened and the damage verified, it allows for further proteins of the preincision complex to be recruited at the lesion site to excise the damaged nucleotides. A critical protein for the preincision complex assembly is XPA. XPA binds to the 5' end of the damage and facilitates the recruitments of replication protein A (RPA) and repair endonuclease XPF-ERCC1 (Sugitani et al., 2016). RPA is a single-stranded DNA binding protein that

binds approximately 30 nucleotides on the undamaged strand. It functions together with XPA as the central scaffold to ensure proper positioning of the two repair endonucleases, XPF and XPG, at the site of damage in the DNA (Schärer, 2013).

2.3 | TFIIH recruitment and functions in TC-NER

TC-NER only repairs damage on the transcribed strand of active genes and is considered more efficient than GG-NER (Hu et al., 2015). A key difference that distinguishes TC-NER from GG-NER is the presence of damage-stalled RNA Pol II that serves as the signal for TC-NER initiation (Lainé & Egly, 2006). The first protein responding to Pol II stalling is Cockayne syndrome B (CSB), a SWI2-SNF2 type ATPase (Selby & Sancar, 1997). CSB normally binds to DNA upstream of Pol II to promote transcription elongation (Kokic et al., 2021; Xu et al., 2017). Upon transcription stalling, CSB quickly moves to Pol II and functions in recruiting downstream TC-NER proteins, including Cockayne syndrome A (CSA) (van der Weegen et al., 2020), a component of an E3 ubiquitin ligase complex (Groisman et al., 2003). CSA can ubiquitylate CSB as well as the stalled Pol II (Groisman et al., 2006; Nakazawa et al., 2020). CSA also physically interacts with UV-stimulated scaffold protein A (UVSSA) (van der Weegen et al., 2020), another important TC-NER protein.

One mechanism for TFIIH recruitment in TC-NER is through its physical interaction with UVSSA (Okuda et al., 2017; van der Weegen et al., 2020; Figure 3). In this regard, it has been shown that UVSSA also interacts with the PH domain of TFIIH subunit p62 (Okuda et al., 2017), in a way similar to the interaction between XPC and TFIIH in GG-NER. Another mechanism for TFIIH recruitment is via Pol II ubiquitylation. Recruitment of CSA to the stalled Pol II leads to mono-ubiquitylation of the largest Pol II subunit, Rpb1, at Lys1268 (Nakazawa et al., 2020; Tufegdžić Vidaković et al., 2020). Interestingly, Rpb1-Lys1268 ubiquitylation enhances the association of the TFIIH core complex with the stalled Pol II, and this mechanism appears to involve ubiquitylated UVSSA at Lys414 (Nakazawa et al., 2020). An additional TC-NER factor that may participate in TFIIH recruitment to stalled Pol II is ELOF1. It was suggested that ELOF1, a conserved elongation factor, interacts with both Pol II and the $CRL4^{CSA}$ E3 ligase, and positions $CRL4^{CSA}$ for Pol II ubiquitylation at the Rpb1-Lys1268 residue (van der Weegen et al., 2021). As Pol II ubiquitylation increases Pol II-TFIIH interaction (Nakazawa et al., 2020), ELOF1 likely facilitates this process by enhancing Pol II ubiquitylation. For more details of the molecular mechanism of TC-NER in humans as well as other species, readers are referred to two recent reviews (Nieto Moreno et al., 2023; Selby et al., 2023).

Despite TFIIH's roles in DNA unwinding and damage verification in GG-NER, how TFIIH stimulates TC-NER is much less understood. It is generally assumed that TFIIH plays identical roles in the two NER sub-pathways and there is some evidence supporting this hypothesis. For example, it has been shown that a helicase-dead XPD mutant abolishes both subpathways in yeast (Duan et al., 2020). However, it is also important to note that TC-NER significantly differs from GG-NER in that the two DNA strands are pre-melted in a transcription bubble by RNA Pol II (Figure 3). When RNA Pol II is stalled by the damage, it is conceivable that TFIIH may not need to unwind the two strands from scratch. Instead, it is possible that TFIIH may just need to extend the transcription bubble to ~30

nt for the formation of NER pre-incision complex. Consistent with this notion, clinical data have shown that mutations in XPD, the major helicase responsible for DNA unwinding, are mainly associated with the skin cancer-prone disease, xeroderma pigmentosum (XP), which is generally considered to be caused by GG-NER defects (Coin et al., 1998; Lehann, 2001). Only a small number of XPD mutations are associated with the severe symptom of XP in combination with the TC-NER disease, Cockayne syndrome (CS) (Lehann, 2001; Rapin et al., 2000).

One possible explanation for the clinical observations is that the XPD mutations in most patients may retain partial helicase activity that is strong enough to increase the bubble size using the pre-melted DNA in TC-NER. However, the attenuated helicase activity may not be enough for generating a repair bubble in GG-NER on an almost fully annealed DNA double helix. More detailed DNA repair studies in different XPD mutant cells (e.g., XP-only or XP plus CS) may help us understand the underlying mechanism for different XPD symptoms and delineate the exact roles of TFIIH in the two subpathways. Furthermore, to what extent XPD's damage verification function is required for TC-NER is also up for debate; because RNA Pol II stalling should already be a stringent mechanism to verify the presence of DNA damage. Whether TC-NER needs both Pol II stalling and TFIIH to verify damage presence needs more experimental analysis.

It is also still not fully understood if RNA Pol II is evicted from the DNA to make way for the TFIIH repair complex, along with other NER factors, or if it simply backtracks along the DNA in the transcription bubble. There are a number of theories about what could be happening (Chiou et al., 2018; Selvam et al., 2019), but each raises its own questions. If RNA Pol II dissociates from the DNA, how is it recruited back? Does it retain the transcript in progress, or does it need to start at the promoter region again? If RNA Pol II is backtracked, what is the mechanism promoting Pol II backtracking along the DNA? Considering TFIIH's DNA helicase function, future studies should also test a potential role for TFIIH in aiding Pol II dissociation from DNA or backtracking in TC-NER.

2.4 | TFIIH functions as a ubiquitin ligase in DNA damage repair

The TFIIH complex contains E3 ubiquitin (Ub) ligase activity, which primarily resides within the p44 subunit (Ssl1 in yeast) in the ring finger domain (RNF) (Takagi et al., 2005). The p44 subunit is known for its role in the enhancement of XPD helicase activity in the NER pathway, but this E3 Ub ligase activity is interesting in the context of TFIIH's role in both NER and transcription. It is noted that RNA Pol II is ubiquitinated during transcription and during repair; however, the evidence suggests that this is not the role for p44's E3 Ub Ligase. It is suggested that Ssl1-mediated ubiquitin ligase function targets unknown transcription activator proteins to mediate the DNA damage response, as mutations introduced in this RNF domain in Ssl1 leads to a reduction in transcription of DNA repair genes in response to exposure to DNA damage (Takagi et al., 2005). Whether the ubiquitylation-mediated transcription response directly affects DNA repair has not been analyzed.

3 | TFIIH MUTATIONS, DISEASES/DISORDERS, AND POTENTIAL THERAPEUTIC OPPORTUNITIES

Due to the crucial role of TFIIH in NER, germline mutations in TFIIH subunits have been linked with human disorders, including XP, XP in combination with CS (XP/CS), and Trichothiodystrophy (TTD; Coin et al., 1998; Lehann, 2001; Rapin et al., 2000). Most of the pathogenic TFIIH germline mutations occur in the XPD subunit. Of note, many of the mutations within the XPD protein that lead to the XP, XP/CS, and TTD disease states are found toward the end of the protein (Table 1), in the final helicase residues and the p44 binding domain (Lehann, 2001). Furthermore, somatic mutations in TFIIH, particularly mutations in the XPD subunit, have been widely observed in human cancers (Kim et al., 2016). Somatic mutations in XPD can presumably increase genome instability and promote tumorigenesis. On the other hand, mutations in XPD represent potential vulnerability of tumor cells that can be targeted by treatment with DNA damaging agents, such as platinum-based chemotherapy, thus providing an important opportunity to treat these tumors (Li et al., 2019).

3.1 | TFIIH and XP

XP is an autosomal recessive disorder, characterized by photosensitivity and the predisposition to skin cancer. There are many other factors, such as thinning hair and skin, freckles, effects on the eye, and even when sunscreen is used, the likelihood of cancer is still very high from a young age. Of the affected individuals with XP, approximately 25% could develop neurological affects, such as acquired microcephaly, hearing loss, cognitive impairment, impacted central nervous system, and neurode-generation (Kraemer et al., 2022). This has come to be to known as XP neurological disease (Krasikova et al., 2021). XP can arise from mutations occurring in several factors in the NER pathway, with varying clinical outcomes. These complementation groups vary in severity and rate of occurrence within the population; however, mutations within XPA, XPC, and XPD are most common and account for more than 70% of all XP cases (Cleaver, 2008; Martens et al., 2021).

Most XP-associated mutations in TFIIH are found in the XPD subunit, particularly at arginine 683 (R683) in the C-terminal domain of XPD (Taylor et al., 1997). This residue is close to one of XPD's DNA helicase motifs and its mutation attenuates the helicase activity in vitro (Coin et al., 2007). A number of other XP-associated mutations have also been found, mainly in the C-terminal domain of XPD (Table 1). It is generally believed that XP symptoms are correlated with defects in the GG-NER subpathway (de Laat et al., 1999; Fousteri & Mullenders, 2008; Martens et al., 2021). The global repair deficiency increases UV mutations and higher risk of carcinogenesis in exposed skins cells. Hence, the clinical observations imply that the XP-associated mutations in the XPD gene may selectively block the GG-NER subpathway, but have less severe effect on TC-NER.

Mutations in other TFIIH subunits can also lead to XP. For example, mutations in XPB and p8 subunits have been shown to cause XP symptoms (Rimel & Taatjes, 2018; Singh et al., 2015).

3.2 | TFIIH and XP/CS symptoms

CS is also an autosomal recessive disorder, characterized by neurodegeneration and premature aging. Other CS phenotypes include cerebellar atrophy and demyelination. There are multiple proteins within the NER pathway that lead to CS, particularly for the two initiation factors in TC-NER, CSB, and CSA. Several mutations in CSB or CSA have been shown to cause CS, but they do not lead to XP, suggesting CS is specifically related to defective TC-NER activity (Fousteri & Mullenders, 2008; Rapin et al., 2000). The mechanism of CS is especially interesting and puzzling, because UV damage does not directly occur in the brain and it is unknown to what extent failure to repair bulky lesions in active genes in neuronal cells contributes to the onset of CS. Alternatively, previous studies suggest that CS may be caused by defective repair of oxidative damage and/or improper expression of genes related to neuron development (Wang et al., 2014). Interestingly, a small number of mutations in the XPD gene are associated with XP combined with CS (XP/CS) (Lehann, 2001; Rapin et al., 2000). If TC-NER deficiency plays a causative role in CS, these XP/CS mutations in XPD may cause deficiency in both subpathways in NER. The identified XP/CS mutations are located either within the conserved helicase motif, or in the p44-interacting domain (Lehann, 2001). Why these mutations cause both XP and CS symptoms whereas the majority of other XPD mutations lead to XP disease, but not CS, remains unclear.

3.3 | TFIIH and trichothiodystrophy

TTD is another autosomal recessive disorder, caused by mutations within the NER proteins, including TFIIH. TTD is characterized by sulfur-deficient brittle hair, dry and scaly skin (ichthyosis), congenital cataracts, poor coordination, and skeletal abnormalities (Lehann, 2001; Stefanini, 2013; Taylor et al., 1997). Despite sensitivity to sunlight, there are no reports of skin cancer or any similarities to the XP group. TTD is considered to be a transcription syndrome. However, it has been noted that TTD does have some repair deficiencies at certain mutation sites, but they are very heterogenous between patients in the severity of repair deficiency (Lehann, 2001).

There is evidence to support the theory that mutations occurring in different proteins can destabilize the TFIIH complex, inhibiting parts of the function that occur during transcription (Botta et al., 2002; Stefanini, 2013). This inhibition will then cause deficiency in pre-initiation complex (PIC) assembly and the ability for the DNA to be opened for transcription initiation. Different mutations may have the potential to behave differently, depending on where the mutation is located within the protein, which protein in TFIIH is affected, and how this mutation affects the interactions between the individual subunits of the TFIIH complex (Coin et al., 1998; Singh et al., 2015; Taylor et al., 1997). As shown in Table 1, mutations in XPD, XPB, and p8 subunits have been implicated in TTD.

3.4 | Effects of defective TFIIH on carcinogenesis and cancer treatment

As TFIIH plays a critical role in maintaining genome stability, cells with defective TFIIH are more likely to have high genome instability, which may further elevate cancer risk. Indeed, somatic mutations in the XPD gene, which is also named ERCC2, have been widely observed in tumors, such as bladder and urothelial cancers (Kim et al., 2016). Tumors of

the urothelial tract and bladder are associated with exposure to tobacco and other DNA damaging chemicals that induce bulky lesions (Freedman et al., 2011; Ploeg et al., 2009). Lack of TFIIH may render the exposed cells more vulnerable to these damaging agents, thereby promoting genome instability and tumor growth. Additionally, it has been shown that somatic mutations in XPD are associated with a distinct genomic signature in urothelial tumors, signature 5*, which closely resembles COSMIC signature 5 (Kim et al., 2016). There is also an evidence indicating a correlation between signature 5* and smoking (Kim et al., 2016), which suggests that low repair of tobacco-induced DNA damage in XPD-mutated cancer cells may drive this unique mutation signature. On the other hand, somatic mutations in XPD also represent an intrinsic vulnerability of the tumor cells to various therapies. This idea has been tested in bladder cancer, in which XPD somatic mutations are frequently found. The published data show that many clinically observed XPD mutations enhance sensitivity to cisplatin in cancer cell lines and mouse xenograft models (Li et al., 2019).

Another common mutation site is in the CDK7 subunit of the CAK complex of TFIIH. Mutations in this subunit are associated with triple negative breast cancer, peripheral T-cell lymphomas, and ovarian cancer. Preclinical models have shown that the use of CDK7 inhibitors reduces drug resistance in human cells and mouse models (Rimel & Taatjes, 2018).

4 | CONCLUSIONS

DNA damage can occur throughout life; therefore, it is fundamental for DNA repair to occur to preserve the genetic material encoded. NER is one of the repair pathways, and it is responsible for the removal and repair of bulky lesions within the DNA. NER has two sub-pathways, GG-NER and TC-NER, both of which play an important role and require the recruitment and activity of the TFIIH complex. TFIIH is important for damage verification, unwinding of the DNA, and holding open the excision bubble for the other NER proteins to function. When defects occur in the proteins in TFIIH and the proteins throughout the rest of the pathway, genetic disorders will occur with varying clinical phenotypes and severity. Proteins within the TFIIH complex also provide therapeutic targets in cancer chemotherapeutic treatments to different cancers and understanding mechanisms of resistance within them as well.

However, despite the extensive research and knowledge on the NER pathway and the TFIIH complex, there are still many knowledge gaps regarding the detailed functions of TFIIH in NER. For example, how do XPB and XPD coordinate to open the two DNA strands? What exact roles does TFIIH play in TC-NER? Why germline mutations in XPD, some of them occur in residues close to each other (e.g., Arg601 and Gly602; Lehann, 2001), exhibit significantly different clinical phenotypes? More research is needed to further elucidate the mechanisms and the role of each of the individual subunits of the TFIIH complex in both transcription and the NER pathway.

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REFERENCES

Araújo SJ, Tirode F, Coin F, Pospiech H, Syväoja JE, Stucki M et al. (2000) Nucleotide excision repair of DNA with recombinant human proteins: definition of the minimal set of factors, active forms of TFIIH, and modulation by CAK. Genes & Development, 14(3), 349–359. [PubMed: 10673506]

Botta E, Nardo T, Lehmann AR, Egly J-M, Pedrini AM & Stefanini M (2002) Reduced level of the repair/transcription factor TFIIH in trichothiodystrophy. Human Molecular Genetics, 11(23), 2919–2928. Available from: 10.1093/hmg/11.23.2919 [PubMed: 12393803]

Chatterjee N & Walker GC (2017) Mechanisms of DNA damage, repair and mutagenesis. Environmental and Molecular Mutagenesis, 58(5), 235–263. Available from: 10.1002/em.22087 [PubMed: 28485537]

Chen X, Velmurugu Y, Zheng G, Park B, Shim Y, Kim Y et al. (2015) Kinetic gating mechanism of DNA damage recognition by Rad4/XPC. Nature Communications, 6(1), 5849. Available from: 10.1038/ncomms6849

Chiou Y-Y, Hu J, Sancar A & Selby CP (2018) RNA polymerase II is released from the DNA template during transcription-coupled repair in mammalian cells. Journal of Biological Chemistry, 293(7), 2476–2486. Available from: 10.1074/jbc.RA117.000971 [PubMed: 29282293]

Ciccia A & Elledge SJ (2010) The DNA damage response: making it safe to play with knives. Molecular Cell, 40(2), 179–204. Available from: 10.1016/j.molcel.2010.09.019 [PubMed: 20965415]

Cleaver JE (2008) Diagnosis of Xeroderma pigmentosum and related DNA repair-deficient cutaneous diseases. Current Medical Literature. Dermatology, 13(2), 41–48. [PubMed: 22025901]

Coin F, Marinoni JC, Rodolfo C, Fribourg S, Pedrini AM & Egly JM (1998) Mutations in the XPD helicase gene result in XP and TTD phenotypes, preventing interaction between XPD and the p44 subunit of TFIIH. Nature Genetics, 20(2), 184–188. Available from: 10.1038/2491 [PubMed: 9771713]

Coin F, Oksenych V & Egly J-M (2007) Distinct roles for the XPB/p52 and XPD/p44 subcomplexes of TFIIH in damaged DNA opening during nucleotide excision repair. Molecular Cell, 26(2), 245–256. Available from: 10.1016/j.molcel.2007.03.009 [PubMed: 17466626]

Coin F, Oksenych V, Mocquet V, Groh S, Blattner C & Egly JM (2008) Nucleotide excision repair driven by the dissociation of CAK from TFIIH. Molecular Cell, 31(1), 9–20. Available from: 10.1016/j.molcel.2008.04.024 [PubMed: 18614043]

Compe E & Egly J-M (2012) TFIIH: when transcription met DNA repair. Nature Reviews. Molecular Cell Biology, 13(6), 343–354. Available from: 10.1038/nrm3350 [PubMed: 22572993]

Cooke MS, Evans MD, Dizdaroglu M & Lunec J (2003) Oxidative DNA damage: mechanisms, mutation, and disease. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology, 17(10), 1195–1214. Available from: 10.1096/fj.02-0752rev [PubMed: 12832285]

Duan M, Selvam K, Wyrick JJ & Mao P (2020) Genome-wide role of Rad26 in promoting transcription-coupled nucleotide excision repair in yeast chromatin. Proceedings of the National Academy of Sciences, 117(31), 18608–18616. Available from: 10.1073/pnas.2003868117

Duan M, Speer RM, Ulibarri J, Liu KJ & Mao P (2021) Transcription-coupled nucleotide excision repair: new insights revealed by genomic approaches. DNA Repair, 103, 103126. Available from: 10.1016/j.dnarep.2021.103126 [PubMed: 33894524]

Dubaele S, Proietti De Santis L, Bienstock RJ, Keriel A, Stefanini M, Van Houten B et al. (2003) Basal transcription defect discriminates between xeroderma pigmentosum and trichothiodystrophy in XPD patients. Molecular Cell, 11(6), 1635–1646. Available from: 10.1016/s1097-2765(03)00182-5 [PubMed: 12820975]

Fousteri M & Mullenders LH (2008) Transcription-coupled nucleotide excision repair in mammalian cells: molecular mechanisms and biological effects. Cell Research, 18(1), 73–84. Available from: 10.1038/cr.2008.6 [PubMed: 18166977]

Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A & Abnet CC (2011) Association between smoking and risk of bladder cancer among men and women. JAMA, 306(7), 737–745. Available from: 10.1001/jama.2011.1142 [PubMed: 21846855]

Fuss JO & Tainer JA (2011) XPB and XPD helicases in TFIIH orchestrate DNA duplex opening and damage verification to coordinate repair with transcription and cell cycle via CAK kinase. DNA Repair, 10(7), 697–713. Available from: 10.1016/j.dnarep.2011.04.028 [PubMed: 21571596]

Giglia-Mari G, Zotter A & Vermeulen W (2011) DNA damage response. Cold Spring Harbor Perspectives in Biology, 3(1), a000745. Available from: 10.1101/cshperspect.a000745 [PubMed: 20980439]

Giglia-Mari G, Coin F, Ranish JA, Hoogstraten D, Theil A, Wijgers N, et al. (2004) A new, tenth subunit of TFIIH is responsible for the DNA repair syndrome trichothiodystrophy group A. Nature Genetics, 36(7), 714–719. 10.1038/ng1387 [PubMed: 15220921]

Groisman R, Kuraoka I, Chevallier O, Gaye N, Magnaldo T, Tanaka K et al. (2006) CSA-dependent degradation of CSB by the ubiquitin–proteasome pathway establishes a link between complementation factors of the Cockayne syndrome. Genes & Development, 20(11), 1429–1434. Available from: 10.1101/gad.378206 [PubMed: 16751180]

Groisman R, Polanowska J, Kuraoka I, Sawada J, Saijo M, Drapkin R et al. (2003) The ubiquitin ligase activity in the DDB2 and CSA complexes is differentially regulated by the COP9 signalosome in response to DNA damage. Cell, 113(3), 357–367. Available from: 10.1016/s0092-8674(03)00316-7 [PubMed: 12732143]

Hu J, Adar S, Selby CP, Lieb JD & Sancar A (2015) Genome-wide analysis of human global and transcription-coupled excision repair of UV damage at single-nucleotide resolution. Genes & Development, 29(9), 948–960. Available from: 10.1101/gad.261271.115 [PubMed: 25934506]

Huang JC, Svoboda DL, Reardon JT & Sancar A (1992) Human nucleotide excision nuclease removes thymine dimers from DNA by incising the 22nd phosphodiester bond 5’ and the 6th phosphodiester bond 3’ to the photodimer. Proceedings of the National Academy of Sciences, 89(8), 3664–3668. Available from: 10.1073/pnas.89.8.3664

Kim J, Li C-L, Chen X, Cui Y, Golebiowski FM, Wang H et al. (2023) Lesion recognition by XPC, TFIIH and XPA in DNA excision repair. Nature, 1–6, 170–175. Available from: 10.1038/s41586-023-05959-z

Kim J, Mouw KW, Polak P, Braunstein LZ, Kamburov A, Kwiatkowski DJ et al. (2016) Somatic ERCC2 mutations are associated with a distinct genomic signature in urothelial tumors. Nature Genetics, 48(6), 600–606. Available from: 10.1038/ng.3557 [PubMed: 27111033]

Kokic G, Chernev A, Tegunov D, Dienemann C, Urlaub H & Cramer P (2019) Structural basis of TFIIH activation for nucleotide excision repair. Nature Communications, 10, 2885. Available from: 10.1038/s41467-019-10745-5

Kokic G, Wagner FR, Chernev A, Urlaub H & Cramer P (2021) Structural basis of human transcription–DNA repair coupling. Nature, 598(7880), 368–372. Available from: 10.1038/s41586-021-03906-4 [PubMed: 34526721]

Kraemer KH, DiGiovanna JJ & Tamura D (2022) Xeroderma pigmentosum. In: GeneReviews® [Internet]. Seattle: University of Washington. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1397/

Krasikova Y, Rechkunova N & Lavrik O (2021) Nucleotide excision repair: from molecular defects to neurological abnormalities. International Journal of Molecular Sciences, 22(12), 6220. Available from: 10.3390/ijms22126220 [PubMed: 34207557]

Krasikova YS, Rechkunova NI, Maltseva EA, Anarbaev RO, Pestryakov PE, Sugasawa K et al. (2013) Human and yeast DNA damage recognition complexes bind with high affinity DNA structures mimicking in size transcription bubble. Journal of Molecular Recognition: JMR, 26(12), 653–661. Available from: 10.1002/jmr.2308 [PubMed: 24277610]

Krokan HE & Bjørås M (2013) Base excision repair. Cold Spring Harbor Perspectives in Biology, 5(4), a012583. Available from: 10.1101/cshperspect.a012583 [PubMed: 23545420]

Kuper J, Braun C, Elias A, Michels G, Sauer F, Schmitt DR et al. (2014) In TFIIH, XPD helicase is exclusively devoted to DNA repair. PLoS Biology, 12(9), e1001954. Available from: 10.1371/journal.pbio.1001954 [PubMed: 25268380]

Kusakabe M, Onishi Y, Tada H, Kurihara F, Kusao K, Furukawa M et al. (2019) Mechanism and regulation of DNA damage recognition in nucleotide excision repair. Genes and Environment, 41(1), 2. Available from: 10.1186/s41021-019-0119-6 [PubMed: 30700997]

de Laat WL, Jaspers NGJ & Hoeijmakers JHJ (1999) Molecular mechanism of nucleotide excision repair. Genes & Development, 13(7), 768–785. [PubMed: 10197977]

Lainé J-P & Egly J-M (2006) Initiation of DNA repair mediated by a stalled RNA polymerase IIO. The EMBO Journal, 25(2), 387–397. Available from: 10.1038/sj.emboj.7600933 [PubMed: 16407975]

Lehann AR (2001) The xeroderma pigmentosum group D (XPD) gene: one gene, two functions, three diseases. Genes & Development, 15(1), 15–23. Available from: 10.1101/gad.859501 [PubMed: 11156600]

Li G-M (2008) Mechanisms and functions of DNA mismatch repair. Cell Research, 18(1), 85–98. Available from: 10.1038/cr.2007.115 [PubMed: 18157157]

Li Q, Damish AW, Frazier Z, Liu D, Reznichenko E, Kamburov A et al. (2019) ERCC2 helicase domain mutations confer nucleotide excision repair deficiency and drive cisplatin sensitivity in muscle-invasive bladder cancer. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research, 25(3), 977–988. Available from: 10.1158/1078-0432.CCR-18-1001 [PubMed: 29980530]

Li W, Adebali O, Yang Y, Selby CP & Sancar A (2018) Single-nucleotide resolution dynamic repair maps of UV damage in Saccharomyces cerevisiae genome. Proceedings of the National Academy of Sciences, 115(15), E3408–E3415. Available from: 10.1073/pnas.1801687115

Lieber MR (2010) The mechanism of double-Strand DNA break repair by the nonhomologous DNA end joining pathway. Annual Review of Biochemistry, 79, 181–211. Available from: 10.1146/annurev.biochem.052308.093131

Marteijn JA, Lans H, Vermeulen W & Hoeijmakers JHJ (2014) Understanding nucleotide excision repair and its roles in cancer and ageing. Nature Reviews. Molecular Cell Biology, 15(7), 465–481. Available from: 10.1038/nrm3822 [PubMed: 24954209]

Martens MC, Emmert S & Boeckmann L (2021) Xeroderma pigmentosum: gene variants and splice variants. Genes, 12(8), 1173. Available from: 10.3390/genes12081173 [PubMed: 34440347]

Martin LJ (2008) DNA damage and repair: relevance to mechanisms of neurodegeneration. Journal of Neuropathology and Experimental Neurology, 67(5), 377–387. Available from: 10.1097/NEN.0b013e31816ff780 [PubMed: 18431258]

Mathieu N, Kaczmarek N, Rüthemann P, Luch A & Naegeli H (2013) DNA quality control by a lesion sensor pocket of the xeroderma pigmentosum group D helicase subunit of TFIIH. Current Biology: CB, 23(3), 204–212. Available from: 10.1016/j.cub.2012.12.032 [PubMed: 23352696]

Min J-H & Pavletich NP (2007) Recognition of DNA damage by the Rad4 nucleotide excision repair protein. Nature, 449(7162), 570–575. Available from: 10.1038/nature06155 [PubMed: 17882165]

Mu H, Geacintov NE, Broyde S, Yeo J-E & Schärer OD (2018) Molecular basis for damage recognition and verification by XPC-RAD23B and TFIIH in nucleotide excision repair. DNA Repair, 71, 33–42. Available from: 10.1016/j.dnarep.2018.08.005 [PubMed: 30174301]

Nakazawa Y, Hara Y, Oka Y, Komine O, van den Heuvel D, Guo C et al. (2020) Ubiquitination of DNA damage-stalled RNAPII promotes transcription-coupled repair. Cell, 180(6), 1228–1244.e24. Available from: 10.1016/j.cell.2020.02.010 [PubMed: 32142649]

Nieto Moreno N, Olthof AM & Svejstrup JQ (2023) Transcription-coupled nucleotide excision repair and the transcriptional response to UV-induced DNA damage. Annual Review of Biochemistry, 92(1), 81–113. Available from: 10.1146/annurev-biochem-052621-091205

Oh K-S, Khan SG, Jaspers NGJ, Raams A, Ueda T, Lehmann A et al. (2006) Phenotypic heterogeneity in the XPB DNA helicase gene (ERCC3): xeroderma pigmentosum without and with Cockayne syndrome. Human Mutation, 27(11), 1092–1103. 10.1002/humu.20392 [PubMed: 16947863]

Okuda M, Nakazawa Y, Guo C, Ogi T & Nishimura Y (2017) Common TFIIH recruitment mechanism in global genome and transcription-coupled repair subpathways. Nucleic Acids Research, 45(22), 13043–13055. Available from: 10.1093/nar/gkx970 [PubMed: 29069470]

Ploeg M, Aben KKH & Kiemeney LA (2009) The present and future burden of urinary bladder cancer in the world. World Journal of Urology, 27(3), 289–293. Available from: 10.1007/s00345-009-0383-3 [PubMed: 19219610]

Prakash S & Prakash L (2000) Nucleotide excision repair in yeast. Mutation Research, 451(1–2), 13–24. Available from: 10.1016/s0027-5107(00)00037-3 [PubMed: 10915862]

Rapin I, Lindenbaum Y, Dickson DW, Kraemer KH & Robbins JH (2000) Cockayne syndrome and xeroderma pigmentosum. Neurology, 55(10), 1442–1449. [PubMed: 11185579]

Ray Chaudhuri A & Nussenzweig A (2017) The multifaceted roles of PARP1 in DNA repair and chromatin remodelling. Nature Reviews Molecular Cell Biology, 18(10), 610–621. Available from: 10.1038/nrm.2017.53 [PubMed: 28676700]

Rimel JK & Taatjes DJ (2018) The essential and multifunctional TFIIH complex. Protein Science: A Publication of the Protein Society, 27(6), 1018–1037. Available from: 10.1002/pro.3424 [PubMed: 29664212]

Sancar A, Lindsey-Boltz LA, Unsal-Kaçmaz K & Linn S (2004) Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints. Annual Review of Biochemistry, 73, 39–85. Available from: 10.1146/annurev.biochem.73.011303.073723

Schärer OD (2013) Nucleotide excision repair in eukaryotes. Cold Spring Harbor Perspectives in Biology, 5(10), a012609. Available from: 10.1101/cshperspect.a012609 [PubMed: 24086042]

Schilbach S, Hantsche M, Tegunov D, Dienemann C, Wigge C, Urlaub H et al. (2017) Structures of transcription pre-initiation complex with TFIIH and mediator. Nature, 551(7679), 204–209. Available from: 10.1038/nature24282 [PubMed: 29088706]

Scully R, Panday A, Elango R & Willis NA (2019) DNA double-strand break repair-pathway choice in somatic mammalian cells. Nature Reviews Molecular Cell Biology, 20(11), 698–714. Available from: 10.1038/s41580-019-0152-0 [PubMed: 31263220]

Selby CP, Lindsey-Boltz LA, Li W & Sancar A (2023) Molecular mechanisms of transcription-coupled repair. Annual Review of Biochemistry, 92(1), 115–144. Available from: 10.1146/annurevbiochem-041522-034232

Selby CP & Sancar A (1997) Human transcription-repair coupling factor CSB/ERCC6 is a DNA-stimulated ATPase but is not a helicase and does not disrupt the ternary transcription complex of stalled RNA polymerase II *. Journal of Biological Chemistry, 272(3), 1885–1890. Available from: 10.1074/jbc.272.3.1885 [PubMed: 8999876]

Selvam K, Ding B, Sharma R & Li S (2019) Evidence that moderate eviction of Spt5 and promotion of error-free transcriptional bypass by Rad26 facilitates transcription coupled nucleotide excision repair. Journal of Molecular Biology, 431(7), 1322–1338. Available from: 10.1016/j.jmb.2019.02.010 [PubMed: 30790631]

Singh A, Compe E, Le May N & Egly J-M (2015) TFIIH subunit alterations causing xeroderma pigmentosum and trichothiodystrophy specifically disturb several steps during transcription. American Journal of Human Genetics, 96(2), 194–207. Available from: 10.1016/j.ajhg.2014.12.012 [PubMed: 25620205]

Spivak G (2015) Nucleotide excision repair in humans. DNA Repair, 36, 13–18. Available from: 10.1016/j.dnarep.2015.09.003 [PubMed: 26388429]

Stefanini M (2013) Trichothiodystrophy: a disorder highlighting the cross-talk between DNA repair and transcription. In: Madame curie bioscience database [Internet]. Landes: Bioscience. Available from: https://www.ncbi.nlm.nih.gov/books/NBK6285/

Sugasawa K, Okuda Y, Saijo M, Nishi R, Matsuda N, Chu G et al. (2005) UV-induced ubiquitylation of XPC protein mediated by UV-DDB-ubiquitin ligase complex. Cell, 121(3), 387–400. Available from: 10.1016/j.cell.2005.02.035 [PubMed: 15882621]

Sugitani N, Sivley RM, Perry KE, Capra JA & Chazin WJ (2016) XPA: a key scaffold for human nucleotide excision repair. DNA Repair, 44, 123–135. Available from: 10.1016/j.dnarep.2016.05.018 [PubMed: 27247238]

Takagi Y, Masuda CA, Chang W-H, Komori H, Wang D, Hunter T et al. (2005) Ubiquitin ligase activity of TFIIH and the transcriptional response to DNA damage. Molecular Cell, 18(2), 237–243. Available from: 10.1016/j.molcel.2005.03.007 [PubMed: 15837426]

Taylor EM, Broughton BC, Botta E, Stefanini M, Sarasin A, Jaspers NG et al. (1997) Xeroderma pigmentosum and trichothiodystrophy are associated with different mutations in the XPD (ERCC2) repair/transcription gene. Proceedings of the National Academy of Sciences of the United States of America, 94(16), 8658–8663. Available from: 10.1073/pnas.94.16.8658 [PubMed: 9238033]

Tirode F, Busso D, Coin F & Egly JM (1999) Reconstitution of the transcription factor TFIIH: assignment of functions for the three enzymatic subunits, XPB, XPD, and cdk7. Molecular Cell, 3(1), 87–95. Available from: 10.1016/s1097-2765(00)80177-x [PubMed: 10024882]

Topolska-Woś AM, Sugitani N, Cordoba JJ, Le Meur KV, Le Meur RA, Kim HS et al. (2020) A key interaction with RPA orients XPA in NER complexes. Nucleic Acids Research, 48(4), 2173–2188. Available from: 10.1093/nar/gkz1231 [PubMed: 31925419]

Tsutakawa SE, Tsai C-L, Yan C, Bralić A, Chazin WJ, Hamdan SM et al. (2020) Envisioning how the prototypic molecular machine TFIIH functions in transcription initiation and DNA repair. DNA Repair, 96, 102972. Available from: 10.1016/j.dnarep.2020.102972 [PubMed: 33007515]

Tufegdžić Vidaković A, Mitter R, Kelly GP, Neumann M, Harreman M, Rodríguez-Martínez M et al. (2020) Regulation of the RNAPII pool is integral to the DNA damage response. Cell, 180(6), 1245–1261.e21. Available from: 10.1016/j.cell.2020.02.009 [PubMed: 32142654]

Uchida A, Sugasawa K, Masutani C, Dohmae N, Araki M, Yokoi M et al. (2002) The carboxy-terminal domain of the XPC protein plays a crucial role in nucleotide excision repair through interactions with transcription factor IIH. DNA Repair, 1(6), 449–461. Available from: 10.1016/s1568-7864(02)00031-9 [PubMed: 12509233]

van der Weegen Y, de Lint K, van den Heuvel D, Nakazawa Y, Mevissen TET, van Schie JJM et al. (2021) ELOF1 is a transcription-coupled DNA repair factor that directs RNA polymerase II ubiquitylation. Nature Cell Biology, 23(6), 595–607. Available from: 10.1038/s41556-021-00688-9 [PubMed: 34108663]

van der Weegen Y, Golan-Berman H, Mevissen TET, Apelt K, González-Prieto R, Goedhart J et al. (2020) The cooperative action of CSB, CSA, and UVSSA target TFIIH to DNA damage-stalled RNA polymerase II. Nature Communications, 11(1), 2104. Available from: 10.1038/s41467-020-15903-8

van Eeuwen T, Shim Y, Kim HJ, Zhao T, Basu S, Garcia BA et al. (2021) Cryo-EM structure of TFIIH/Rad4-Rad23-Rad33 in damaged DNA opening in nucleotide excision repair. Nature Communications, 12(1), 3338. Available from: 10.1038/s41467-021-23684-x

van Toorn M, Turkyilmaz Y, Han S, Zhou D, Kim H-S, Salas-Armenteros I et al. (2022) Active DNA damage eviction by HLTF stimulates nucleotide excision repair. Molecular Cell, 82(7), 1343–1358.e8. Available from: 10.1016/j.molcel.2022.02.020 [PubMed: 35271816]

Wang JY (1998) Cellular responses to DNA damage. Current Opinion in Cell Biology, 10(2), 240–247. Available from: 10.1016/s0955-0674(98)80146-4 [PubMed: 9561848]

Wang JYJ (2001) DNA damage and apoptosis. Cell Death and Differentiation, 8(11), 1047–1048. Available from: 10.1038/sj.cdd.4400938 [PubMed: 11687882]

Wang Y, Chakravarty P, Ranes M, Kelly G, Brooks PJ, Neilan E et al. (2014) Dysregulation of gene expression as a cause of Cockayne syndrome neurological disease. Proceedings of the National Academy of Sciences of the United States of America, 111(40), 14454–14459. Available from: 10.1073/pnas.1412569111 [PubMed: 25249633]

Weeda G, Donker I, de Wit J, Morreau H, Janssens R, Vissers CJ, et al. (1997) Disruption of mouse ERCC1 results in a novel repair syndrome with growth failure, nuclear abnormalities and senescence. Current Biology, 7(6), 427–439. 10.1016/s0960-9822(06)00190-4 [PubMed: 9197240]

Winkler GS, Sugasawa K, Eker APM, de Laat WL & Hoeijmakers JHJ (2001) Novel functional interactions between nucleotide excision DNA repair proteins influencing the enzymatic activities of TFIIH, XPG, and ERCC1-XPF. Biochemistry, 40(1), 160–165. Available from: 10.1021/bi002021b [PubMed: 11141066]

Xu J, Lahiri I, Wang W, Wier A, Cianfrocco MA, Chong J et al. (2017) Structural basis for the initiation of eukaryotic transcription-coupled DNA repair. Nature, 551(7682), 653–657. Available from: 10.1038/nature24658 [PubMed: 29168508]

Yi C & He C (2013) DNA repair by reversal of DNA damage. Cold Spring Harbor Perspectives in Biology, 5(1), a012575. Available from: 10.1101/cshperspect.a012575 [PubMed: 23284047]

Yokoi M, Masutani C, Maekawa T, Sugasawa K, Ohkuma Y & Hanaoka F (2000) The xeroderma pigmentosum group C protein complex XPCHR23B plays an important role in the recruitment of transcription factor IIH to damaged DNA. The Journal of Biological Chemistry, 275(13), 9870–9875. Available from: 10.1074/jbc.275.13.9870 [PubMed: 10734143]

Zurita M & Cruz-Becerra G (2016) TFIIH: new discoveries regarding its mechanisms and impact on cancer treatment. Journal of Cancer, 7(15), 2258–2265. Available from: 10.7150/jca.16966 [PubMed: 27994662]

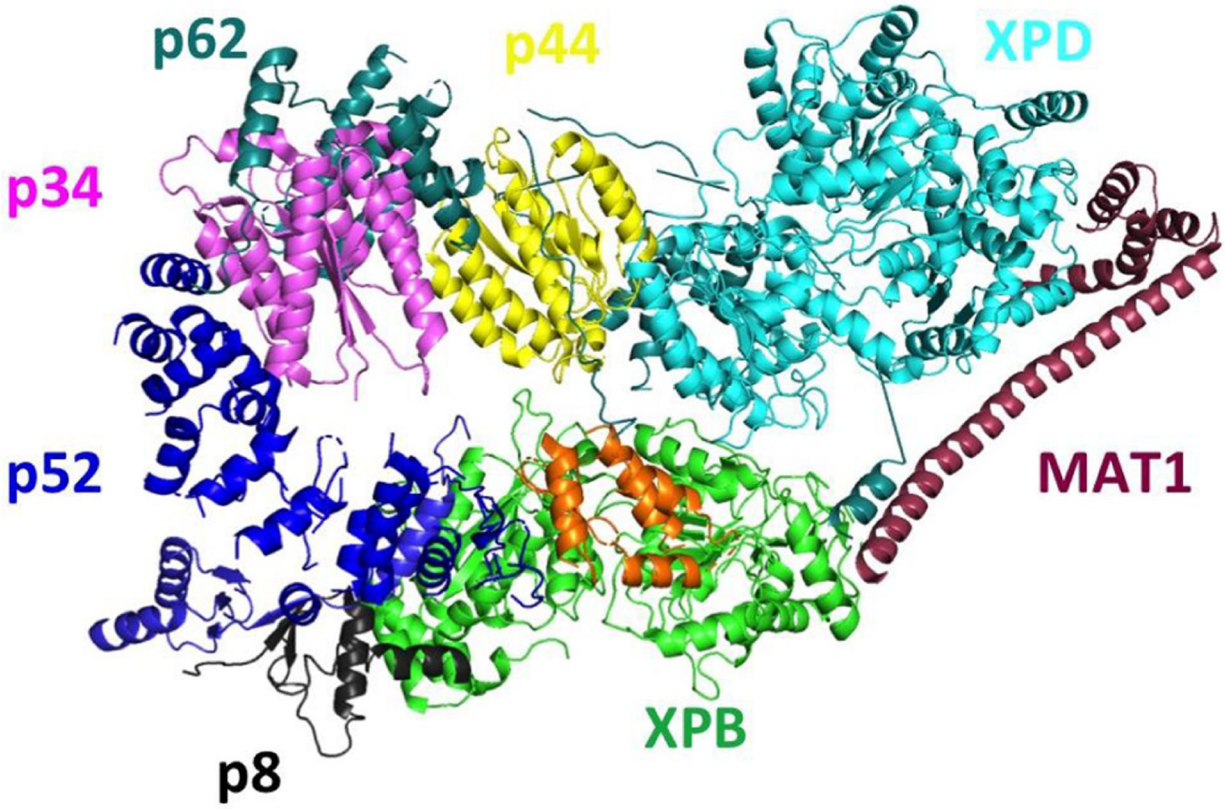

FIGURE 1.

The human TFIIH complex. Eight of the ten TFIIH subunits are recognizable in this structure. The structural model was made with PyMOL using the published data (PDB accession number: 5OF4). TFIIH, transcription factor IIH.

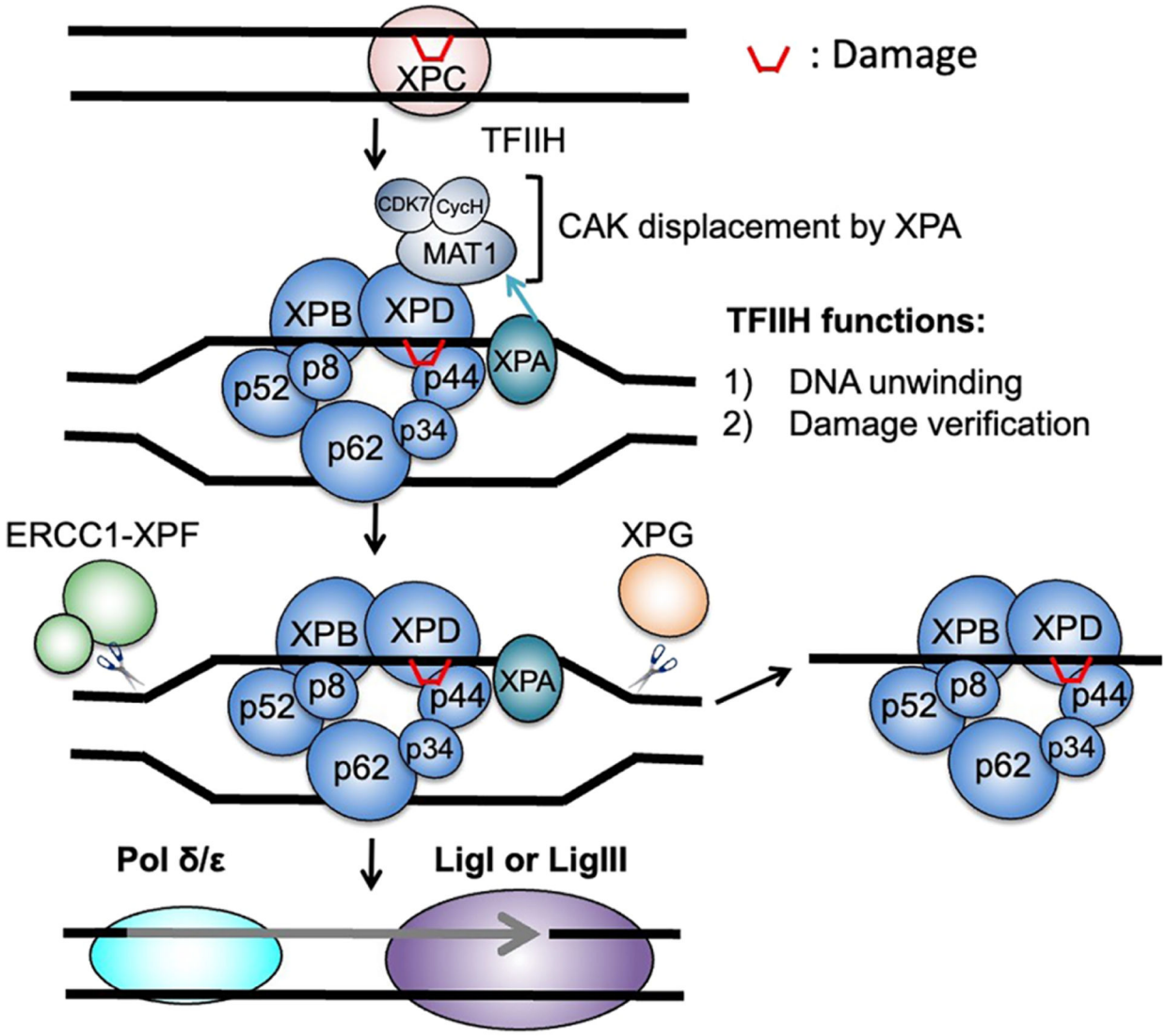

FIGURE 2.

Recruitment and functions of TFIIH in GG-NER. XPC binds to the damage site first. The interaction between XPC and TFIIH subunits p62 and XPB leads to the recruitment of TFIIH. XPA removes the CAK kinase module, which activates the helicase function of the TFIIH core complex to conduct DNA unwinding and damage verification. GG-NER, global genome NER; TFIIH, transcription factor IIH.

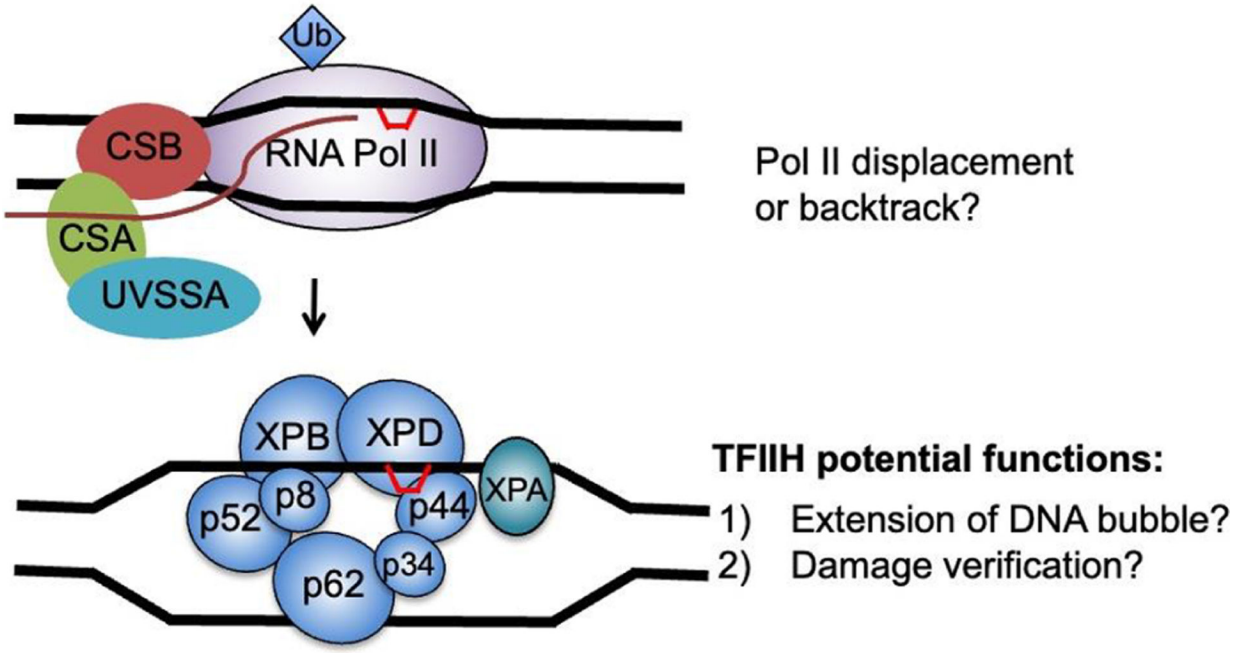

FIGURE 3.

Recruitment and potential functions of TFIIH in TC-NER. The p62 subunit of TFIIH physically interacts with UVSSA and the interaction facilitates TFIIH recruitment to the damage-stalled RNA Pol II. Pol II ubiquitylation at Lys1268 enhances binding of TFIIH to Pol II. As DNA around the lesion is melted by RNA Pol II, the recruited TFIIH potentially extends the transcription bubble to generate a full-sized repair bubble. Similar to GG-NER, TFIIH may also verify the presence of a bulky lesion. However, it is unclear to what extent TC-NER requires TFIIH's damage verification function, because RNA Pol II stalling may play a redundant role. Another potential role for TFIIH is to help Pol II backtracking or displacement. TC-NER, transcription-coupled NER; TFIIH, transcription factor IIH.

TABLE 1

TFIIH mutations and human disorders.

Genes	Mutations	Symptoms
XPD	G47R	XP (Lehann, 2001)
XPD	T76A	XP
XPD	D234N	XP
XPD	R511Q	XP
XPD	S541R	XP
XPD	Y542C	XP
XPD	R601L	XP
XPD	R601W	XP
XPD	R666W	XP
XPD	D683W	XP
XPD	R683Q	XP
XPD	Q726 Stop	XP
XPD	G602D	XP/CS
XPD	G675R	XP/CS
XPD	R112H	TTD
XPD	C259Y	TTD
XPD	R487G	TTD
XPD	R592P	TTD
XPD	A594P	TTD
XPD	R658H	TTD
XPD	R658C	TTD
XPD	C663R	TTD
XPD	D673G	TTD
XPD	G713R	TTD
XPD	R722W	TTD
XPD	A725P	TTD
XPD	Frameshift 730	TTD
XPB	T119P	TTD (Weeda et al., 1997)
XPB	F99S	XP (Oh et al., 2006) XP/CS (Singh et al., 2015)
XPB	Q739insX42 (alteration of the C-terminal 41 amino acids)	XP/CS (Oh et al., 2006)
p8	L21P	TTD (Giglia-Mari et al., 2004)
p8	R56 Stop	TTD
p8	M1T (no start)	TTD

Abbreviation: TFIIH, transcription factor IIH.