

TFIIH: when transcription met DNA repair

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Abstract | The transcription initiation factor TFIIH is a remarkable protein complex that has a fundamental role in the transcription of protein-coding genes as well as during the DNA nucleotide excision repair pathway. The detailed understanding of how TFIIH functions to coordinate these two processes is also providing an explanation for the phenotypes observed in patients who bear mutations in some of the TFIIH subunits. In this way, studies of TFIIH have revealed tight molecular connections between transcription and DNA repair and have helped to define the concept of ‘transcription diseases’.

Nucleotide excision repair (NER). The repair pathway that is used to remove the vast majority of lesions that are located on a DNA single strand, including lesions caused by ultraviolet (UV) light and cisplatin damage.

Helicases

Enzymes that move directionally along a nucleic acid phosphodiester backbone and separate two annealed nucleic acid strands by using energy derived from ATP hydrolysis.

Following gene activation, a host of proteins including RNA polymerase II (Pol II), general transcription factors, cofactors and chromatin-remodelling factors are assembled around the promoter and contribute to the accurate expression of protein-coding genes. In parallel, to maintain genome integrity and to ensure the continuation of transcription, DNA lesions that are caused by genotoxic agents have to be eliminated. This implies that there must be connections between the seemingly disparate events of transcription and DNA repair. A link between DNA repair and transcription was first suspected when it was found that the repair of DNA damage (in particular, ultraviolet (UV) light-induced cyclobutane pyrimidine dimers) is much faster and more efficient on the coding strand of active genes than on the other parts of the genome^{1,2}. Several years later, the multi-protein complex transcription initiation factor TFIIH (BOX1) was found to be indispensable during basal transcription and during nucleotide excision repair (NER) of DNA damage, thus revealing the functional link between these two processes^{3,4}. The more recent demonstration that NER factors localize to the promoters of activated genes^{5,6} strengthens the idea of an interplay between NER and transcription and raises questions about how these factors might act in proximity to ongoing transcription in the absence of exogenous genotoxic attack.

The story of TFIIH started in 1989, when a factor named general transcription factor- δ (purified from rat liver)⁷ or basic transcription factor 2 (BTF2, purified from HeLa cells)⁸ was characterized as an indispensable transcription factor *in vitro*. This factor was also isolated from yeast (termed yeast Pol II transcription factor b)⁹ and was finally designated TFIIH in 1992 (REF. 10). Peptide microsequencing revealed that TFIIH contains ERCC3 (excision repair cross complementing 3; also known as XPB)

and ERCC2 (also known as XPD)^{3,11}, which are two potential helicases involved in DNA repair^{12,13}. Its fundamental role during NER has since been established, and TFIIH (or some of its subunits) has also been shown to affect other cellular processes. For example, the CAK (cyclin-dependent kinase (CDK)-activating kinase) subcomplex of TFIIH^{14–19} has been implicated in cell cycle control during the transition from G2 to M phase^{20–22}. Indeed, this subcomplex is responsible for the activating phosphorylation of several kinases, including CDK1, CDK2, CDK4 and CDK6 (REFS 23–27), and these phosphorylation events are required for cell cycle progression (reviewed in REF. 28). Furthermore, the XPD subunit, which associates with the TFIIH core complex, also interacts with MMS19 in the MMXD complex, which is required for chromosome segregation²⁹.

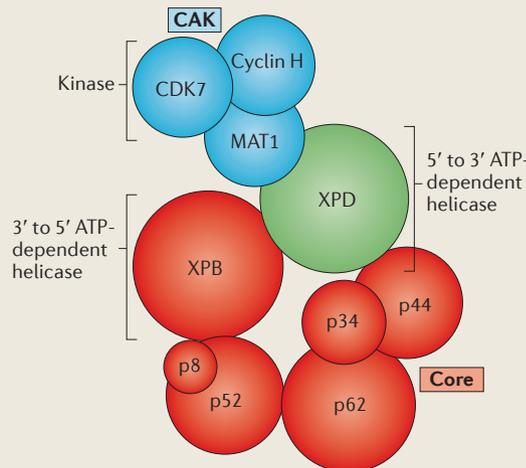
The demonstration that TFIIH has various cellular functions was greatly facilitated by the fact that mutations in its XPB, XPD and p8 (also known as TF2H5 and TTDA) subunits cause autosomal recessive disorders, including trichothiodystrophy (TTD), xeroderma pigmentosum and, in rare cases, the combined symptoms of xeroderma pigmentosum and Cockayne syndrome (TABLE 1). Whereas these diseases were initially defined as DNA repair syndromes, it seems that some of their clinical features cannot be explained by DNA repair defects alone and might be due to deficiencies in transcription. With this in mind, it has been hypothesized that such mutations in TFIIH might disturb the molecular architecture of this complex and consequently might affect its positioning within intermediate complexes that alter transcription and/or NER.

In this Review, we focus on the molecular roles of TFIIH and its functional partners in both DNA repair and transcription. We also discuss the insights that have

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doi:10.1038/nrm3350
Published online 10 May 2012
Corrected online 1 June 2012

Box 1 | The structure of TFIIH

Mammalian TFIIH is a multiprotein complex with ten subunits that consists of two main functional subcomplexes: the core complex, which is composed of six subunits (xeroderma pigmentosum group B complementing protein (XPB), p62, p52, p44, p34 and p8); and the CAK (cyclin-dependent kinase (CDK)-activating kinase) complex, which is composed of CDK7, cyclin H and MAT1 (REFS 15,18,19,192) (see the figure). The core and CAK subcomplexes are bridged by the XPD subunit, which interacts with p44 and MAT1 of the core or the CAK subcomplex, respectively^{51,80}. Electron microscopy and image processing of the TFIIH complex revealed that it forms a ring-like structure with a central cavity that possibly interacts with DNA^{193,194}. TFIIH has several intrinsic enzymatic activities: CDK7 is a cyclin-dependent kinase and XPB and XPD are thought to act as ATP-dependent helicases of opposite polarities. Interestingly, in yeast, the subunit Ssl1 (suppressor of stem-loop protein 1, which is the homologue of p44) is an E3 ubiquitin ligase¹⁸⁹, and TFIIH regulates cullin neddylation via its RNA polymerase II transcription factor b (Tfb3) subunit (which is the homologue of mammalian MAT1)¹⁹⁵.



been gained into how different mutations in TFIIH might disrupt NER and transcription and thereby give rise to the phenotypes observed in different disorders.

TFIIH in repair

The main role of TFIIH in NER (BOX 2) is to open the DNA around the lesion and thereby allow the excision of the damaged oligonucleotide and its replacement by a new DNA fragment. The advances in our understanding of how TFIIH affects NER have been driven by: first, *in vitro* reconstitution assays that use damaged DNA (which contains either a *cis*-platin adduct or a thymine dimer) as a substrate together with crude cellular extracts³⁰ or recombinant proteins³¹; and second, a sophisticated *in vivo* local UV light irradiation technique coupled with immunofluorescence staining³². These technical advances have indeed helped to define how TFIIH functions after a DNA lesion has been recognized by either the global genome repair (GGR) pathway or the transcription-coupled repair (TCR) pathway of NER; we discuss the GGR pathway here and refer readers to a review of the TCR pathway (REF. 33).

XPC-mediated recognition of DNA lesions. In the GGR pathway (FIG. 1), XPC (xeroderma pigmentosum group C complementing protein) initially recognizes the damaged site and prepares this site for TFIIH recruitment. XPC can rapidly detect various DNA lesions that do not share any common chemical structures³⁴; it then promotes bending of the double helix³⁵, thus forming a transient recognition intermediate before a more stable

repair-initiating complex is established. Structural studies of Rad4, which is the yeast homologue of XPC, have revealed that XPC covers only the 3' side of a DNA lesion and leaves the 5' side almost completely free³⁶. XPC (or Rad4 in yeast) thermodynamically destabilizes and distorts the DNA double helix, and this distortion is crucial for XPC recognition and the recruitment of additional NER factors^{37,38}. In some cases, UV light-damaged DNA-binding protein (UV-DDB), which consists of DDB1 and DDB2 (REFS 39,40), promotes the recognition of lesions^{41,42}. Interestingly, it has been proposed that preferential UV-DDB accumulation on internucleosomal DNA leads to the ubiquitylation of XPC by cullin 4A (CUL4A) ligase⁴³. In this model, DDB2 (also known as XPE) would bind damaged DNA, and CUL4A ligase, associated with DDB1, would target XPC, DDB2 and/or nearby histones for ubiquitylation. This process is thought to reposition XPC and to result in the recruitment of further NER factors⁴⁴. Once XPC is bound to the lesion, other XPC-binding partners such as centrin 2 (REF. 45) and/or RAD23 homologue B (RAD23B)⁴⁶ might stabilize XPC. The correct positioning of XPC is thought to be important for the subsequent recruitment of TFIIH and the excision of damaged DNA. However, removal of the damaged oligonucleotide can occur *in vitro* in the absence of RAD23B, centrin 2 and the UV-DDB complex⁴⁷. This does not exclude the possibility that these factors might contribute to the optimal positioning of XPC in a cellular context. And, when the XPC-damaged DNA intermediate complex is not accurately positioned (as is observed with mutated forms of XPC), XPC is rapidly degraded by a proteasome-independent mechanism⁴⁸.

TFIIH opens damaged DNA for excision. When correctly bound to damaged DNA, the carboxy-terminal domain of XPC might adopt a three-dimensional structure that enables the recruitment of TFIIH through the interaction of XPC with at least two subunits of TFIIH: p62, which interacts with both the C-terminal and the amino-terminal regions of XPC; and XPB, which associates with the C-terminal region of XPC⁴⁸. TFIIH then mediates the excision of the damaged DNA, and several studies have aimed to elucidate how the different subunits of TFIIH mediate NER. For example, the concomitant presence of XPB and XPD helicases within TFIIH raises the question of how these subunits regulate NER. A model was initially proposed in which each helicase acts on both sides of the lesion to unwind the damaged DNA⁴⁹. In an alternative model, the two helicases were proposed to bind at the lesion and move on individual DNA strands, so that blockage of either helicase could discriminate between the damaged strand and the undamaged strand⁵⁰. However, although the helicase activity of XPD is clearly required for NER⁵¹⁻⁵³, the helicase activity of XPB turned out to be dispensable, which suggests that only one of the TFIIH helicase activities is required during NER. Nonetheless, the ATPase activity of XPB participates in the NER pathway by anchoring TFIIH to the damaged chromatin⁵⁴. The crystal structure of *Archaeoglobus fulgidus* XPB was preponderant for understanding the role of the XPB ATPase activity in NER⁵⁵. In addition to

Table 1 | **Composition of the human TFIIH complex**

TFIIH subcomplex	Human	Yeast	Function	Human genetic disorders
Core	XPB	Ssl2	3' to 5' ATP-dependent helicase	Trichothiodystrophy and combined xeroderma pigmentosum and Cockayne syndrome
	p62	Tfb1	Structural function and interacts with transcription factors and NER factors	
	p52	Tfb2	Regulates the XBP ATPase activity	
	p44	Ssl1	E3 ubiquitin ligase (in yeast)	
	p34	Tfb4	Structural function and strong interaction with p44	
	p8	Tfb5	Regulates the XBP ATPase activity	Trichothiodystrophy
XPD	XPD	Rad3	5' to 3' ATP-dependent helicase and forms a bridge between the CAK and the core	Trichothiodystrophy, xeroderma pigmentosum and combined xeroderma pigmentosum and Cockayne syndrome
CAK	CDK7	Kin28	Kinase	
	Cyclin H	Ccl1	Modulates the CDK7 kinase activity	
	MAT1	Tfb3	CAK stabilization and regulates cullin neddylation (in yeast)	

CAK, cyclin-dependent kinase-activating kinase subcomplex; Ccl1, cyclin C like 1; CDK7, cyclin-dependent kinase 7; MAT1, ménage à trois 1; NER, nucleotide excision repair; Ssl, suppressor of stem-loop protein; Tfb, RNA polymerase II transcription factor b; XPB, xeroderma pigmentosum group B complementing protein.

an ATP-binding site (which is located within the helicase motif Ia), there are two other structural motifs in XPB, which are termed RED and Thumb, the latter of which binds to DNA in a sequence-independent manner. It has been suggested that a large conformational change, which is driven by ATP hydrolysis, brings the RED and Thumb domains of XPB in close proximity to each other, and that this conformation favours the anchoring of TFIIH to DNA⁵⁶. The XPB ATPase activity is regulated by XPC, as well as by the p8 and p52 subunits of TFIIH. The contribution of p52 was revealed by studies of the marionette (*mrn*) gene (which encodes p52) in *Drosophila melanogaster*, as in these studies mutations that destabilize the interaction between p52 and XPB consequently reduced the ATPase activity of XPB⁵⁷.

The study of XPD helicase function during NER was facilitated by the numerous XPD mutations that are found in patients with xeroderma pigmentosum and

TTD and that diminish NER activity. Mutations in the helicase motifs of XPD (which abrogate the unwinding activity of XPD) or in its C-terminal end (which weaken the interaction with the p44 subunit) result in a decreased ability of TFIIH to open damaged DNA, which is a crucial step in NER^{51,52}. Crystal structure data of XPD homologues from *Sulfolobus acidocaldarius*, *Sulfolobus tokodaii* and *Thermoplasma acidophilum*^{58–60} revealed the presence of an 'arch domain' and a 4FeS cluster in the helicase domain HD1. These structural results suggest that the channel under the arch, which is formed by HD1, the arch domain and the 4FeS domain, forms a passageway for the translocation of single-stranded DNA (ssDNA) during XPD-mediated unwinding of the damaged DNA.

Interestingly, in addition to its role in DNA opening, it has been proposed that XPD participates in DNA damage recognition and verification⁶¹. As XPB function in NER requires its ATPase activity but not its helicase activity, it has been suggested that XPB might act as a wedge⁵⁵ that uses ATP to keep the two strands of DNA around the lesion apart, thereby allowing XPD to unwind the DNA⁵⁶. The putative role of XPD in damage sensing has been supported by the characterization of a β -hairpin structural motif in UvrB (the prokaryotic homologue of XPD), and this motif is essential for DNA binding and damage processing^{62,63}. In the current model, XPB-mediated opening of the damaged DNA would allow correct binding of XPD to the DNA, and XPD would then utilize its helicase activity to verify the DNA damage and ensure that the backbone distortion is not the result of an unusual DNA sequence. This process has been termed 'enzymatic proofreading' and supports a bipartite damage recognition model in

Box 2 | **The nucleotide excision repair pathway**

The nucleotide excision repair (NER) pathway removes bulky DNA adducts that are caused by ultraviolet (UV) light irradiation, genotoxic chemicals and reactive metabolic by-products, each of which induce a strong distortion of the DNA double helix through covalent modification of one DNA strand. NER occurs by the sequential assembly of repair proteins at the site of DNA damage^{32,196}. There are two NER subpathways: the global genome repair (GGR) pathway, which is initiated by xeroderma pigmentosum group C complementing protein (XPC) and removes DNA lesions from anywhere in the genome; and the transcription-coupled repair (TCR) pathway, whereby DNA damage that is located in the transcribed strand of active genes is recognized by elongating RNA polymerase II complexes³³. After a lesion has been recognized, the subsequent steps in NER are identical for GGR and TCR. The ability of both pathways to detect DNA damage is crucial for reducing the risk of mutations that can result from incorrect or incomplete replication.

which the function of XPC–RAD23B is limited to the recognition of a DNA backbone distortion, whereas XPD is required to verify the presence of DNA damage through its helicase activity⁶⁴. Further structural

analysis of the complex that is formed between XPD and damaged DNA should be undertaken to clearly demonstrate that human XPD participates in damage recognition.

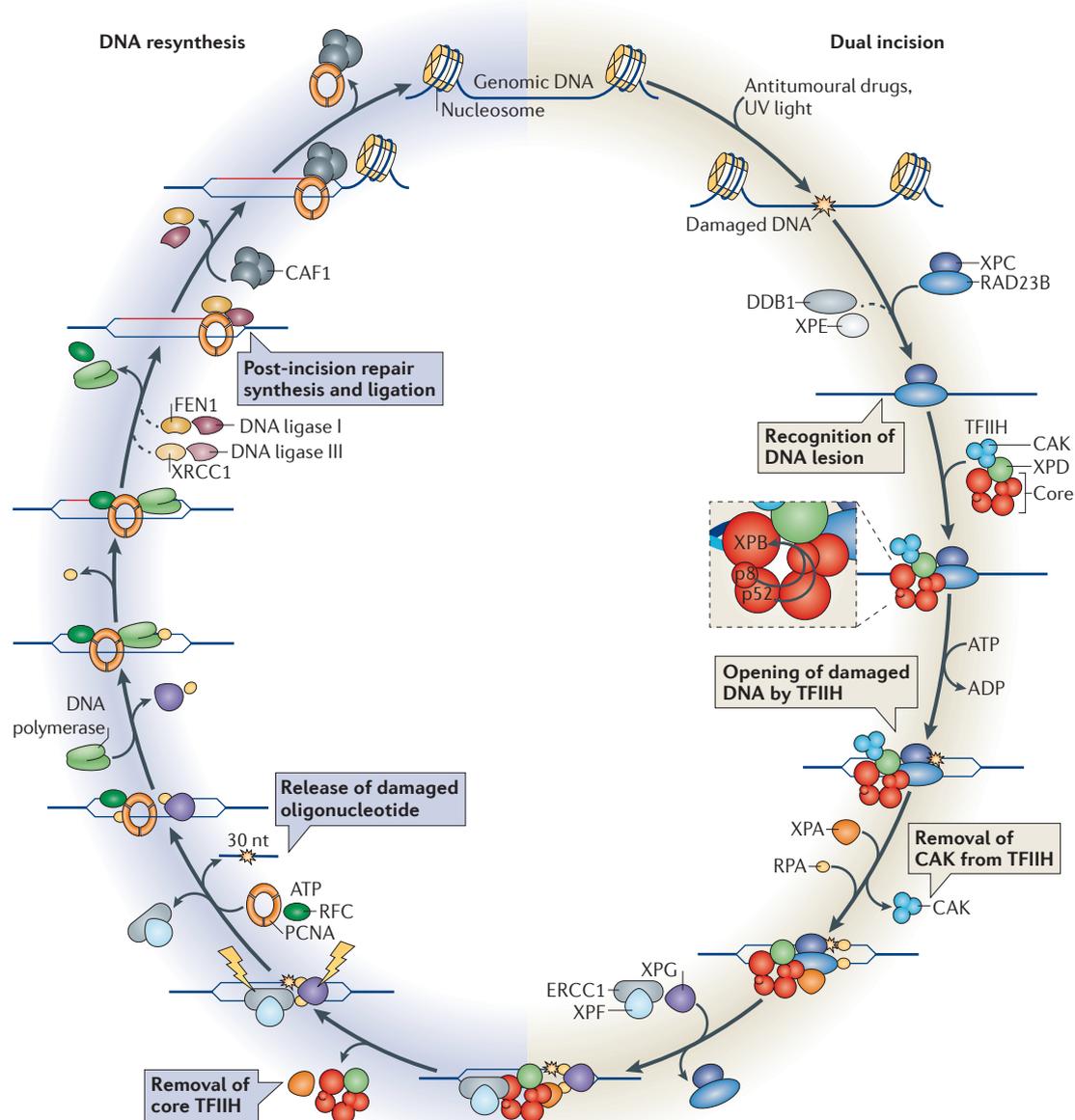


Figure 1 | TFIIF opens DNA to allow the incision and excision of damaged oligonucleotides. During global genome repair (GGR), which occurs following exposure to genotoxic agents such as ultraviolet (UV) light or antitumoural drugs, a lesion on the DNA (yellow star) is initially recognized through the binding of xeroderma pigmentosum group C complementing protein (XPC)–RAD23B and/or the lesion sensor UV light-damaged DNA-binding protein (UV-DDB) complex (which contains DDB1 and XPE). The XPC–RAD23B complex mediates the recruitment of the transcription initiation factor TFIIF to the damaged DNA, and this promotes opening of the DNA in an ATP-dependent manner. The unwinding of the DNA requires the helicase activity of XPD and the ATPase activity of XPB, the latter of which is regulated by the p52 and p8 subunits of TFIIF. The next step involves the recruitment of XPA, which promotes the release of the CAK (cyclin-dependent kinase (CDK)-activating kinase) subcomplex, and the association of replication protein A (RPA) with the single-stranded damaged DNA. The dissociation of CAK is a prerequisite for the enlargement of the DNA opening that is required to promote the recruitment of the XPF–excision repair cross complementing 1 (ERCC1) complex and XPG and the release of XPC–RAD23B. XPF–ERCC1 makes an incision in the damaged DNA strand at the 5' side of the bubble. This allows the concomitant incision at the 3' side by XPG and the release of the core TFIIF. DNA resynthesis begins when replication factor C (RFC) loads proliferating cell nuclear antigen (PCNA) onto the damaged DNA to accommodate DNA polymerase δ (Pol δ), Pol ϵ and/or Pol κ . The final ligation step can be carried out by the DNA ligase I-flap endonuclease 1 (FEN1) complex or by the DNA ligase III–X-ray repair cross-complementing protein 1 (XRCC1) complex, depending on the cell cycle stage. Finally, chromatin assembly factor 1 (CAF1) mediates the arrival of histones H3 and H4 to allow nucleosome reassembly on the repaired DNA. nt, nucleotide.

Transfer RNAs

(tRNAs). The ribonucleic acids that transport specific amino acids to the ribosome for incorporation into the growing polypeptide chain.

In addition to the function of XPB and XPD in NER, special attention has recently focused on the p8 subunit of TFIIH. After 10 years of investigations into the human TTD-A disorder, which is a particular form of TTD⁶⁵ that results from defective TFIIH, researchers were unable to identify the mutations that cause this disorder. However, studies in yeast⁶⁶ helped to characterize the tenth subunit of TFIIH, termed Tfb5, which is the homologue of p8. Mutations in this subunit turned out to result in the TTD-A disorder⁶⁷. Strikingly, although p8 is dispensable for transcription (at least *in vitro*), the role of this subunit is crucial in NER, during which p8 stimulates the ATPase activity of XPB in a DNA-dependent manner and promotes the recruitment of XPA⁶⁸. XPB, with the help of p8, is thereby thought to act as an ATP-driven motor that supplies the energy that is required to reorganize the intermediate DNA repair complex and thereby supports the repositioning of XPC–RAD23B and the unwinding of DNA by XPD⁴⁷. It seems that p8 also acts as a stabilizer of TFIIH, as the cellular concentration of TFIIH decreases considerably when p8 is mutated^{67–69}. Live-cell imaging studies have indicated that there are two distinct kinetic pools of p8: one with slow mobility that is bound to TFIIH and a free fraction that is homodimeric⁷⁰ and shuttles between the nucleus and the cytoplasm. Following UV light irradiation, the free dimeric p8 fraction might shift towards a more stable complex with TFIIH through interaction with the C-terminal end of p52, which shares a common fold with p8 (REF. 71).

When TFIIH is correctly bound to the XPC–damaged DNA complex, replication protein A (RPA) is recruited, which protects the ssDNA from enzymatic hydrolysis and prepares it for DNA resynthesis³¹. RPA arrives together with XPA, which seems to stabilize the TFIIH–XPC–damaged DNA ternary complex^{72–75} through an unclear mechanism. XPA associates with the N-terminal moiety of XPC that has been repositioned by TFIIH; this results in the expansion of the DNA ‘bubble’ around the damaged site⁷⁶. In addition to the potential function of XPA in maintaining this open DNA structure, the C-terminal region of XPA mediates the release of CAK from the TFIIH core subcomplex and the arrival of other NER-specific factors such as XPG (also known

as ERCC5) and XPF–ERCC1 (REF. 77). Experiments have indicated that CAK is not required for DNA repair and even identified CAK as an inhibitor of NER activity^{77–80}. Whether post-translational modifications of XPA (such as its deacetylation by sirtuin 1 (SIRT1))⁸¹ are involved in CAK removal and/or in other NER steps remains to be established.

An alternative and/or complementary step of this model proposes that XPC would be positioned at a region with disrupted base pairing upstream from the lesion and would be further translocated together with XPA by XPD helicase at the damaged site⁸². This suggests that XPD might have an additional role in translocation during the damage recognition process *in vivo*. Although not without shortcomings⁸³, a mathematical model has validated that these roles of XPC and XPD are possible by comparing a model of random order assembly and kinetic proofreading with a sequential assembly model⁸⁴.

The release of the damaged oligonucleotide. The generation of an open structure on the damaged DNA complex provides a platform for the arrival of the structure-specific endonucleases XPF–ERCC1 and XPG that are responsible for carrying out incisions 5′ and 3′ of the damaged site, respectively⁷⁶. Concomitantly to an incision being made 5′ of the damaged site, XPC, followed by XPA and TFIIH, are released from the DNA template and are recycled. XPG and XPF–ERCC1 endonucleases remain on the gapped DNA intermediate together with RPA, which coats the ssDNA region. Next, proliferating cell nuclear antigen (PCNA) and replication factor C (RFC) are positioned at the 3′ primer template, and this forces the release of XPF endonuclease in an ATP-dependent manner⁸⁵. After the recruitment of RFC, PCNA and DNA polymerase, repair synthesis is initiated, which precedes 3′ DNA cleavage by XPG⁸⁶. Following the release of XPG, RPA and the excised fragment of approximately 30 nucleotides^{87,88}, the post-incision stage of NER consists of gap-filling DNA synthesis, ligation and the restoration of chromatin structure. Recent findings have revealed the complexity of the repair synthesis and ligation, which seem to depend at least partly on the growth state of cells⁸⁹. Indeed, it seems that in non-proliferating cells, the preference is for DNA polymerase δ (Pol δ) and Pol κ to synthesize the new DNA, whereas in cycling cells Pol ϵ is also required⁹⁰. The nick that is formed when DNA has been resynthesized is sealed by either DNA ligase III–X-ray repair cross-complementing protein 1 (XRCC1) in quiescent cells or by both DNA ligase III–XRCC1 and DNA ligase I–flap endonuclease 1 (FEN1)^{79,85} in dividing cells⁹¹. After ligation has occurred, chromatin assembly factor 1 (CAF1) mediates the arrival of histones H3 and H4 (REFS 92,93). This suggests that factors such as CAF1 ensure that nucleosome reassembly and/or repositioning on the naked DNA starts only after DNA repair has ended.

Importantly, there are several close connections between TFIIH and the different partners that are required to eliminate DNA damage. As an example, XPG strengthens the interaction between core TFIIH and the CAK subcomplexes, and XPG forms a stable

Box 3 | The transcription of eukaryotic protein-coding genes

Transcription is the molecular process by which a complementary RNA copy of a DNA sequence is made. In eukaryotes, three different types of RNA polymerases activate the transcription of a distinct class of RNAs: RNA polymerase I (Pol I) transcribes ribosomal RNAs (rRNAs); Pol II transcribes small regulatory RNAs and RNAs that will become mRNAs; and Pol III transcribes small RNAs such as transfer RNAs (tRNAs).

Transcription by Pol II proceeds through sequential steps, which include chromatin remodelling, assembly of the pre-initiation complex (PIC), opening of the promoter, formation of the first phosphodiester bond, promoter clearance, elongation and termination. Transcription initiation requires at least six general transcription factors (TFIIA, TFIIB, TFIID, TFIIIE, TFIIF and TFIIH) that allow RNA synthesis and can be further regulated by activators and repressors. Although emerging evidence indicates that the composition of PIC is not universal but promoter-dependent, *in vitro* experiments have led to a model in which basal transcription factors are sequentially assembled with Pol II to generate the PIC^{8,197–202}.

complex with TFIIH⁹⁴. Furthermore, it was found that mutation of the C-terminal end of XPB prevents the 5' incision that is triggered by the XPF-ERCC1 endonuclease complex⁹⁵. Similarly, XPC mutations delay the recruitment of TFIIH to damaged DNA⁴⁸. Thus, there seems to be an intimate relationship among the sensing of damaged DNA, the recruitment of TFIIH and the preparation of DNA for repair before the enzymes that mediate resynthesis are recruited.

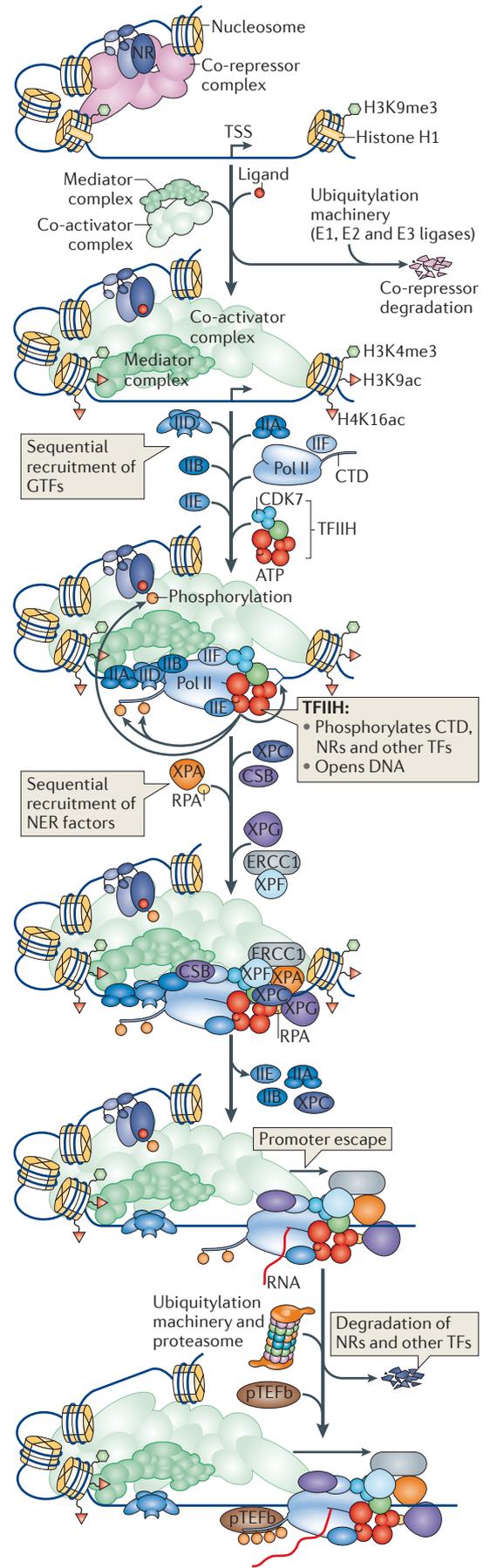
TFIIH in transcription

Initially identified as an essential factor for Pol II-mediated transcription⁷⁻⁹, TFIIH also participates in the transcription of ribosomal RNA (rRNA) by Pol I⁹⁶⁻⁹⁸ and probably also in the synthesis of 5S rRNA, tRNA and other small RNAs that are transcribed by Pol III^{99,100}.

Most of the transcription studies have focused on Pol II (BOX 3), which transcribes protein-encoding genes, most small nuclear RNAs (snRNAs) and microRNAs (miRNAs)^{101,102}. Although it was suggested that a pre-assembled holoenzyme complex that contains all the transcription components might be recruited to promoters, the initiation of transcription by Pol II actually seems to result from the sequential recruitment of general transcription factors¹⁰³⁻¹⁰⁷. Typically, TFIID binds to the promoter, followed by TFIIA and TFIIB, which stabilize promoter-bound TFIID. After the recruitment of Pol II and TFIIF, a stable complex forms at the promoter together with TFIID-TFIIA-TFIIB, and this drives the association of TFIIE and the subsequent entry of TFIIH (FIG. 2).

Cooperation between XPB and CDK7 in basal transcription. When the pre-initiation complex (PIC) has been established, the ATP-dependent helicase activity of XPB¹⁰⁸ is required for promoter opening^{109,110} and promoter escape¹¹¹⁻¹¹³. This role of XPB can be regulated by transcription factors, as illustrated by the actions of FBP (FUSE-binding protein) and FIR (FBP-interacting repressor; also known as PUF60), which stimulate or inhibit, respectively, XPB helicase activity during the regulation of *c-MYC* gene transcription¹¹⁴.

After the establishment of this open complex, transcription is initiated; this intimately depends on the phosphorylation status of the C-terminal domain (CTD) of the largest subunit of Pol II^{15,115-119}. The human Pol II CTD contains 52 heptad repeats that can be phosphorylated on Ser2, Ser5 and Ser7. Phosphorylation of Ser5 by the CDK7 kinase subunit of TFIIH controls the initiation of transcription¹²⁰ and enhances the association of the Pol II CTD with the 7-methylguanosine (m7G) RNA capping machinery^{121,122}. This TFIIH kinase activity towards the CTD of Pol II can be modulated by different factors, including MAT1 (ménage à trois 1) and cyclin H, which are two binding partners of CDK7 within the CAK subcomplex^{18,19}. In particular, it has been shown that although MAT1 deletion reduces Pol II Ser5 phosphorylation¹²³, cyclin H that has been phosphorylated by CDK8 of the Mediator complex can repress CDK7 activity¹²⁴. Pol II CTD phosphorylation by TFIIH also requires the contribution of



Ribosomal RNA (rRNA). The ribonucleic acid element of the ribosome, which orchestrates protein synthesis.

Small nuclear RNAs (snRNAs). Small ribonucleic acids, which are located in the nucleus and are involved in different molecular processes such as transcriptional regulation and RNA splicing.

MicroRNAs (miRNAs). Short ribonucleic acids that are post-transcriptional regulators able to recognize complementary sequences on target mRNA transcripts.

Spliceosomal snRNAs

Small ribonucleic acids that participate in the removal of introns from pre-mRNA.

Nuclear receptors

Ligand-dependent and -independent transcription factors that are highly conserved evolutionarily from invertebrates to higher organisms. The nuclear receptor superfamily includes receptors for thyroid and steroid hormones, retinoids and vitamin D, as well as 'orphan' receptors of unknown ligands.

Ubiquitin–proteasome machinery

A selective system of protein degradation. This first requires the ubiquitin conjugation of the target protein via three types of enzymes: E1 (ubiquitin-activation enzyme), E2 (ubiquitin-conjugation enzyme) and E3 (ubiquitin ligase). Polyubiquitylated substrates are then recognized and degraded by the 26S proteasome in an ATP-dependent manner.

non-coding RNAs, such as B2 RNA (which specifically represses Pol II CTD phosphorylation by TFIID)¹²⁵ and the U1 snRNA (which is a core splicing component that stimulates the Pol II CTD kinase activity of CDK7)¹²⁶. CDK7 also phosphorylates Ser7 of the Pol II CTD^{127–129}, and this seems to be functionally important for the processing of spliceosomal snRNAs¹³⁰. Phosphorylation of Ser2 by CDK9 (REFS 131,132), which is a cyclin-dependent kinase associated with positive transcription elongation factor b (pTEFb), results in transcription-coupled recruitment of 3'-end processing factors^{122,133}. In addition to these Pol II CTD kinases and others (such as CDK2 (REF. 134), CDK8 (REF. 135), extracellular signal-regulated kinase 1 (ERK1) and ERK2 (REF. 136) or DNA-dependent protein kinase^{137,138}), the Pol II CTD phosphorylation status requires the action of CTD phosphatases, such as TFIIF-associated CTD phosphatase 1 (FCP1; also known as CTDp1) which targets Ser2 (REFS 131,139,140) and Pol II-associated protein 2 (RPAP2), which targets Ser5 (REF. 141). These different Pol II CTD-modification states, which include bivalent marks, are postulated to define a spatiotemporal code that instructs ordered engagement of Pol II with functional complexes at various stages of the transcription cycle^{119,142–144} and are probably initiated by TFIID.

TFIID and nuclear receptors. In addition to its 'basal' functions, TFIID can modulate the activity of several transcriptional regulators, including p53 (REF. 145), herpes simplex virion protein VP16 (REF. 146), Epstein–Barr nuclear antigen 2 (EBNA2)¹⁴⁷, hepatitis B virus (HBV) X protein (HBX)¹⁴⁸, FIR¹⁴⁹ or its *D. melanogaster* orthologue Half pint (HFP)¹⁵⁰, as well as nuclear receptors. The interaction between TFIID and each nuclear receptor is specific¹⁵¹ and either occurs in the absence of ligand — as observed for retinoic acid receptor- α 1 (RAR α 1) and RAR γ ^{152,153}, androgen receptor^{151,154},

peroxisome proliferator activated receptor- α (PPAR α), PPAR β (also known as PPAR δ), PPAR γ 1 and PPAR γ 2 (REF. 155) and thyroid hormone receptor- α 1 (REF. 156) — or the interaction occurs in response to hormone — as found for oestrogen receptor- α ¹⁵⁷ and thyroid hormone receptor- β ¹⁵⁸. All nuclear receptors so far studied are phosphorylated within their A/B domain by the CDK7 subunit of TFIID, except vitamin D receptors (VDRs), which lack a functional A/B domain¹⁵⁹. However, TFIID can still regulate some VDR-responsive genes such as cytochrome P450 family 24 (CYP24) by phosphorylating the VDR DNA-binding partner ETS1, which might fulfil the role of an A/B domain.

Understanding the effects of nuclear receptor phosphorylation by TFIID has been complicated by the fact that CDK7 influences diverse molecular processes^{160–163} and that nuclear receptors are subjected to several post-translational modifications, including phosphorylation by other kinases¹⁶⁴. Nonetheless, phosphorylation by CDK7 is necessary for optimal nuclear receptor-mediated transactivation^{153,155,157,165}. Whereas the stabilization of nuclear receptor binding to their response elements might require a phosphorylation-independent effect of TFIID (as observed for thyroid hormone receptor α 1)¹⁵⁶, phosphorylation might specifically influence the interaction of nuclear receptors with other factors. As an example, vinexin- β , which is a nuclear protein that participates in actin cytoskeletal organization¹⁶⁶, interacts with the non-phosphorylated form of RAR γ to repress gene transcription but not with other RAR isoforms¹⁶⁷. CDK7-mediated phosphorylation of RAR γ disrupts the interaction of this receptor with vinexin- β and restores RAR γ transactivation.

Furthermore, TFIID-mediated phosphorylation can regulate the turnover of nuclear receptors by triggering their ubiquitin-mediated degradation by the proteasome (that is, the ubiquitin–proteasome machinery). Indeed, it has been shown that phosphorylation of androgen receptor by CDK7 directs the specific recruitment of the mouse homologue of the E3 ubiquitin ligase MDM2 and the proteasome to the promoter of androgen receptor-specific target genes¹⁵¹. However, impairing CDK7-mediated androgen receptor phosphorylation can also preferentially promote the recruitment of CHIP (C terminus of heat shock protein 70 (HSP70)-interacting protein), which is another E3 ligase, and this results in dysregulated androgen receptor turnover and thereby the disrupted transactivation of target genes.

In addition to a direct relationship between TFIID and nuclear receptors, an even higher level of complexity emerges if one considers that TFIID might cooperate with partners of nuclear receptors. This was observed for PPAR γ co-activator 1 α (PGC1 α)¹⁶⁸, which is a metabolic regulator and a transcriptional co-activator for several nuclear receptors¹⁶⁹, and also for the metastasis-associated protein 1 (MTA1), which represses oestrogen receptor-driven transcription¹⁷⁰. Interestingly, MTA1 might disrupt CAK-induced transactivation control of oestrogen receptors, which suggests that TFIID activity can, in turn, be modulated by these factors. Such a control of TFIID function is also well illustrated by

◀ **Figure 2 | TFIID is an essential factor of transcription initiation.** Gene activation requires a large number of co-regulatory complexes with various functions and enzymatic activities²⁰³. Typically, genes are maintained in a latent or silenced state by co-repressor complexes that promote chromatin condensation, by histone H1 and histone post-translational modifications such as trimethylation of histone H3 at Lys9 (H3K9me3) and histone acetylation (H3K9ac) and methylation of the CpG islands near to the potential transcription start site (TSS). In the case of nuclear receptor (NR) responsive genes, gene activation is initiated following ligand induction and this promotes the removal and degradation of co-repressor complexes and the recruitment of co-activator complexes, including factors with chromatin remodelling activity, the Mediator complex and factors that are involved in RNA processing. The general transcription factors (GTFs) TFIID (which contains TATA box-binding protein), TFIIA, TFIIB (which stabilizes TFIID), RNA polymerase II (Pol II), TFIIF (which anchors Pol II to the pre-initiation complex (PIC)), TFIIE and finally TFIID are sequentially recruited. The ATPase-dependent helicase activity of XPB within TFIID allows promoter opening. The cyclin dependent kinase 7 (CDK7) subunit of TFIID phosphorylates the carboxy-terminal domain (CTD) of the largest subunit of Pol II, nuclear receptors and possibly other transcription factors. The nucleotide excision repair (NER) factors (pigmentosum group C complementing protein (XPC), cockayne syndrome B protein (CSB), XPA, XPG and XPF–excision repair cross complementing 1 (ERCC1)) are then sequentially recruited to the promoter. This is followed by the promoter escape of Pol II in absence of TFIIA, TFIIB, TFIIE and XPC. Productive elongation starts after phosphorylation of the CTD of Pol II by positive transcription elongation factor b (pTEFb) and the ubiquitin–proteasome machinery contributes to the turnover of nuclear receptors and other co-activators.

the influence of the transcriptional Mediator complex. This complex is a key regulator of gene expression¹⁷¹ that functions as an adaptor and conveys essential information from transcription factors that are bound at upstream responsive elements to the basal Pol II transcription machinery. The Mediator complex promotes the positioning of TFIIH into the PIC¹⁷² and regulates the kinase activity of TFIIH through its CDK8 kinase subunit¹²⁴. Other factors also participate in nuclear receptor-mediated transactivation by targeting TFIIH, as illustrated by the action of the co-chaperone Ydj1 in yeast¹⁷³.

The TFIIH disorders

TFIIH is directly involved in the aetiology of various diseases. Genetic polymorphisms of genes that encode subunits of TFIIH (such as *XPD* and *XPB*) seem to be associated with increased cancer susceptibility in many tissues, including skin tissue, breast tissue and lung tissue^{174,175}. In addition to genetic variations, virus-encoded proteins also target TFIIH. For example, the non-structural proteins of the Rift Valley haemorrhagic fever (RVHF) virus outcompete XPD for p44 binding in the core complex, sequester p44 along with XPB in filamentous structures and prevent the formation of TFIIH¹⁷⁶. This leads to a rapid and drastic suppression of host cellular RNA synthesis that parallels a decrease in TFIIH cellular concentration. HBV, which is a risk factor for hepatocellular carcinoma, also acts by disrupting the expression of TFIIH components and might decrease NER activity, thus increasing genomic instability¹⁷⁷.

Mutations in *GTF2H5* (which encodes p8), *XPB* and *XPD* cause the human autosomal recessive disorders xeroderma pigmentosum, TTD and the combined symptoms of xeroderma pigmentosum and Cockayne syndrome. Patients with xeroderma pigmentosum have a 1,000-fold increased frequency of skin cancer^{178,179}. In addition, patients with xeroderma pigmentosum can develop progressive neurological degeneration, immature sexual development and dwarfism¹⁸⁰. Several mutations in the XPD and XPB helicases of TFIIH can cause xeroderma pigmentosum, sometimes combined with Cockayne syndrome, which associates with severe cachectic dwarfism, mental retardation, microcephaly and retinal and skeletal abnormalities¹⁸¹. Patients with TTD typically have dry and easily brittle hair and develop sterility, short stature and various neurological defects, including mental retardation, spasticity, tremors and ataxia¹⁸². TTD is caused by mutations in XPB, XPD and p8 (REF. 183).

For many years, these diseases were attributed to impaired NER, as this process is reduced or even absent in cells that have been isolated from patients. However, the clinical complexity of these syndromes cannot be solely explained on the basis of a DNA repair defect and may also involve transcription deficiencies. For instance, the skin photosensitivity observed in some patients can be correlated with an NER defect, whereas other clinical features, such as sterility or lipodystrophy, could be explained by dysfunctions in hormone-dependent transcriptional regulation^{49,184}.

Many have tried to provide explanations for the broad range of clinical features that are observed in patients with xeroderma pigmentosum and TTD. Such studies have considered the various cellular functions of TFIIH and the position of the mutations found in the different subunits of TFIIH. Although few patients have been described with XPB mutations (and this reflects the essential role of this subunit in transcription¹¹⁰), XPD mutations have been associated with xeroderma pigmentosum and TTD. The heterogeneity of the phenotypes that arise from these XPD mutations suggests that each mutation differently affects the biochemical properties of TFIIH and consequently that each mutation might disrupt distinct steps of transcription¹⁸⁵. Depending on the cellular context, TFIIH might establish distinct interactions with various transcription factors. Therefore, each TFIIH mutation would specifically affect some factors and not others and thus influence the expression of distinct genes¹⁸⁵. Interestingly, the TTD mutations that are found in *XPB*, *XPD* and *GTF2H5* reduce the cellular concentration of TFIIH^{69,186}. These findings support the hypothesis that reduced levels of TFIIH in individuals with TTD might have a significant effect on genes that are highly expressed in differentiated tissues. Nevertheless, the reduced levels of TFIIH that were observed in patients do not correlate with the heterogeneity of the phenotypes, suggesting that the clinical features in TTD are not just a result of altered TFIIH stability¹⁸⁶. Such heterogeneity might be due to the combined effects of reduced TFIIH levels and the specific effects that each mutation has on components of the transcription machinery.

Most of the XPD mutations found in patients suffering from either xeroderma pigmentosum, TTD or xeroderma pigmentosum and Cockayne syndrome weaken the binding between XPD and p44, which consequently reduces XPD helicase activity during NER^{52,58}. These mutations also disturb the architecture of TFIIH and its ability to accurately interfere with nuclear receptors. Studies have thus tried to determine whether dysfunctions in hormone-dependent transcription might contribute to the phenotypes observed in patients that bear these mutations. As an example, patients with TTD have facial features that appear prematurely aged owing to the lack of subcutaneous fatty tissue, and female patients lack breast tissue¹⁸². By using an XPD-mutated TTD mouse model that also develops hypoplasia of adipose tissue¹⁸⁷, it was demonstrated that this mutation disrupts CDK7-mediated phosphorylation of PPARs (which are implicated in lipid metabolism and adipogenesis) and that this mutation consequently impairs the expression of PPAR target genes. This explains, at least partially, the adipose defect that is observed in patients¹⁵⁵. Patients with TTD also develop neurological features, such as microcephaly and hypomyelination¹⁸⁸. In this case, as TFIIH stabilizes the binding of thyroid hormone receptors to their DNA-responsive elements, the limiting amount of TFIIH in TTD cells contributes to the dysregulation of thyroid hormone receptor-responsive genes that encode particular major myelin structural components¹⁵⁶.

Crosstalk between transcription and repair

Given that TFIIH has various cellular functions, it has been arduous to define which phenotypes are exclusively related to deficiencies in transcription and which are caused by defects in other cellular processes such as DNA repair. This is made more difficult by the fact that other molecular connections exist between transcription and DNA repair. For a while, the relationship between these processes was discerned only by the common TFIIH subunits that are involved, which could result from a distinct requirement for XPB and XPD in each process. However, it was then shown in yeast that a ubiquitin ligase activity of TFIIH, via its p44 subunit, mediates the transcriptional response to DNA damage¹⁸⁹. We now know that other factors that are involved in transcription are also implicated in DNA repair, and vice versa. For example, transcriptional activators (such as Gal4–VP16 and RAR) can stimulate DNA repair¹⁹⁰. Conversely, a DNA repair complex (that contains XPC) seems to also function as a co-activator for octamer-binding protein 4 (OCT4; also known as POU5F1) and SOX2 in embryonic stem cells¹⁹¹. Finally, NER factors are recruited to active promoters and facilitate chromatin modification to regulate transcription in the absence of exogenous genotoxic attack^{5,6}. Indeed, NER factors seem to be associated with the transcription machinery at the promoters of several activated nuclear receptor-dependent genes. The recruitment occurs in a sequential order following PIC assembly and is distinct from the order that is required for a repair complex⁶. Although NER factors are not essential for PIC formation, it is likely that NER components optimize the efficiency of transcription, as patient cell lines that are mutated in different NER factors (such as XPC, XPA or XPG) dysregulate nuclear receptor-dependent

genes owing to impaired association of NER factors with the transcription machinery. Such observations raise the question of the potential role or roles of the NER factors at the promoters of active genes. Although poorly understood, it seems that NER factors might influence chromatin remodelling^{5,6}. Nonetheless, this involvement of repair factors during transcription is forcing a reconsideration of the broad clinical features that are described for the so-called xeroderma pigmentosum, TTD and Cockayne syndrome repair syndromes.

Conclusions and perspectives

Studies of TFIIH have demonstrated the tight connections between factors that ensure accurate initiation of RNA synthesis, including the basal transcription machinery, transcription cofactors, the Mediator complex and NER factors. In retrospect, one can appreciate how the methodical and sophisticated dissection of TFIIH functions during transcription and NER has also shed light on the biological machines that regulate these two processes and the medical consequences of errors in these processes. Last but not least, studies of TFIIH have demonstrated the close links between transcription and DNA repair and have also given rise to a new concept of 'transcription diseases'. Further characterization of TFIIH binding partners will improve our understanding of the complexity of the mechanisms that specifically regulate the expression of protein coding genes at the right time and in the right amount in each cell. More importantly, such studies should provide explanations for the phenotypes that are observed in patients with mutations in the components of the transcription machinery and might allow therapeutic strategies to be designed that can modulate gene expression patterns.

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Acknowledgements

The authors thank all of their past and present associates who have participated to the TFIID adventure. The authors especially would like to thank R. Conaway and H. Naegeli for critical reading of the manuscript and F. Coin for helpful discussions. The authors apologize to all their colleagues whose important findings could not be included in this Review because of space limitations. This study was supported by a European Research Council advanced grant, the Agence Nationale de la Recherche (N#ANR-08MIEN-022-03), the Association pour la Recherche sur le Cancer and the Institut National du Cancer (INCA-2008-041). E.C. and J.M.E. are supported by the Institut National de la Santé et de la Recherche Médicale.

Competing interests statement

The authors declare no competing financial interests.

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ERRATUM

TFIIH: when transcription met DNA repair

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Nature Reviews Molecular Cell Biology **13**, 343–354 (2012)

There was an error in table 1 on page 345 of this article: XPD is a 5' to 3' ATP-dependent helicase and not a 3' to 5' ATP-dependent helicase. This has been corrected online. We apologize for any confusion caused to readers.