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.

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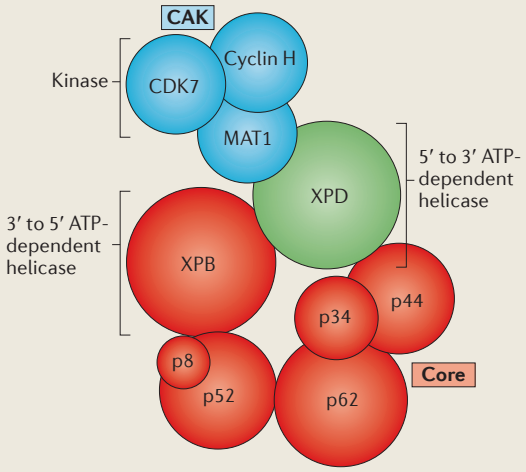
Following gene activation, a host of proteins including RNA polymerase II (Pol II), general transcription factors, cofactors and chromatin-remodelling factors are assembled around the promoter and contribute to the accurate expression of protein-coding genes. In parallel, to maintain genome integrity 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 segregation[29].

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

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 ligase[189], 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 extracts[30] or recombinant proteins[31]; and second, a sophisticated *in vivo* local UV light irradiation technique coupled with immunofluorescence staining[32]. 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 structures[34]; it then promotes bending of the double helix[35], 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 free[36]. 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) ligase[43]. 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 factors[44]. 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 complex[47]. 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 mechanism[48].

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 XPC[48]. 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 DNA[49]. 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 strand[50]. However, although the helicase activity of XPD is clearly required for NER[51–53], 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 chromatin[54]. The crystal structure of *Archaeoglobus fulgidus* XPB was preponderant for understanding the role of the XPB ATPase activity in NER[55]. 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 DNA[56]. 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 XPB[57].

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 verification[61]. As XPB function in NER requires its ATPase activity but not its helicase activity, it has been suggested that XPB might act as a wedge[55] that uses ATP to keep the two strands of DNA around the lesion apart, thereby allowing XPD to unwind the DNA[56]. 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 complexes[33]. 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 activity[64]. 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.

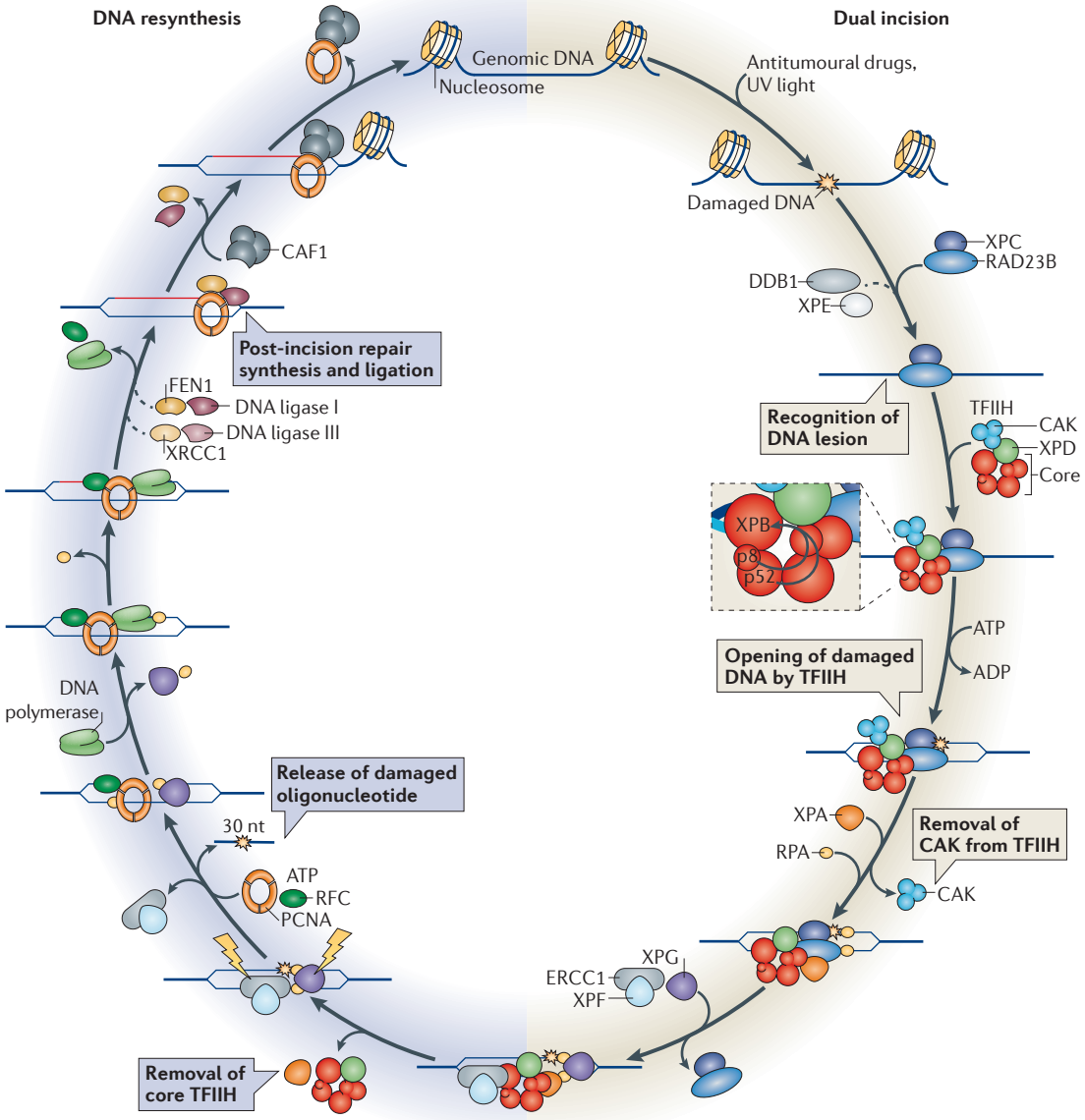


Figure 1 | **TFIIH opens DNA to allow the incision and excision of damaged oligonucleotides.** During global genome repair (GGR), which occurs following exposure to genotoxic agents such as ultraviolet (UV) light or antitumoural drugs, a lesion on the DNA (yellow star) is initially recognized through 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 TFIIH 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 XPC, as well as by the p52 and p8 subunits of TFIIH. 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 TFIIH. 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 (FEN 1) 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 TTD[65] that results from defective TFIIH, researchers were unable to identify the mutations that cause this disorder. However, studies in yeast[66] 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 disorder[67]. 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 XPA[68]. 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 XPD[47]. 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 homodimeric[70] 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 resynthesis[31]. 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 site[76]. 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 site[82]. This suggests that XPD might have an additional role in translocation during the damage recognition process *in vivo*. Although not without shortcomings[83], 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 model[84].

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, respectively[76]. 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 manner[85]. After the recruitment of RFC, PCNA and DNA polymerase, repair synthesis is initiated, which precedes 3′ DNA cleavage by XPG[86]. 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 cells[89]. 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 required[90]. 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 cells[91]. 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, TFIIE, 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 TFIIH[94]. 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 complex[95]. Similarly, XPC mutations delay the recruitment of TFIIH to damaged DNA[48]. 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.

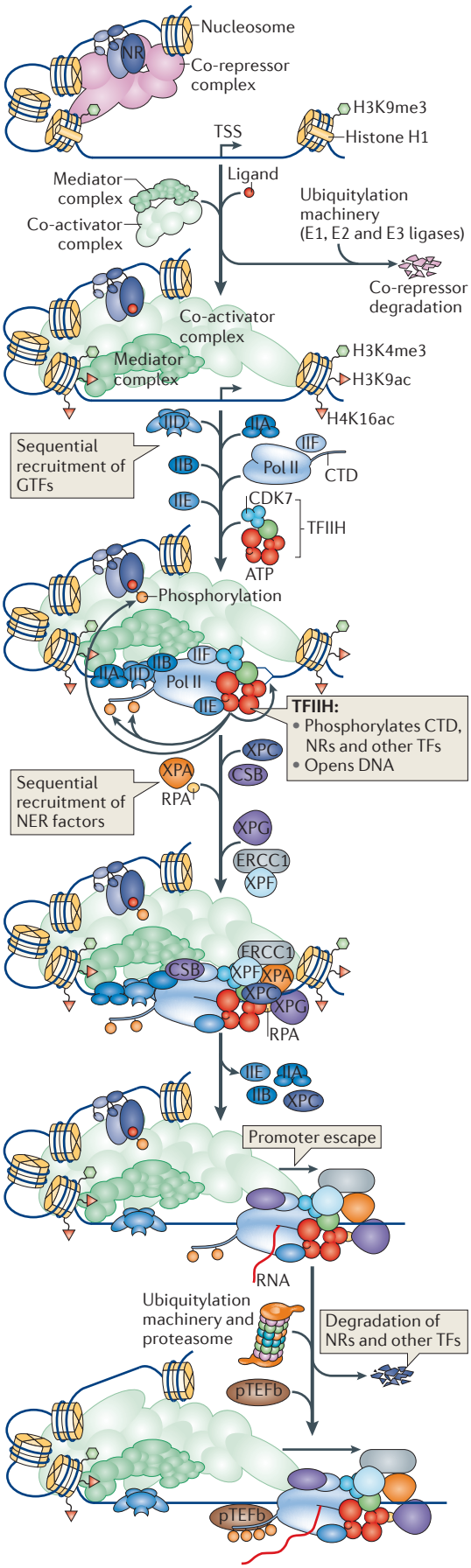
TFIIH in transcription

Initially identified as an essential factor for Pol II-mediated transcription[7–9], TFIIH also participates in the transcription of ribosomal RNA (rRNA) by Pol I[96–98] 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 factors[103–107]. 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 XPB[108] is required for promoter opening[109,110] and promoter escape[111–113]. 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 transcription[114].

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 transcription[120] 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 phosphorylation[123], cyclin H that has been phosphorylated by CDK8 of the Mediator complex can repress CDK7 activity[124]. 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 TFIIH)[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 snRNAs[130]. 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 TFIIH.

TFIIH and nuclear receptors. In addition to its 'basal' functions, TFIIH 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], FIR[149] or its *D. melanogaster* orthologue Half pint (HFP)[150], as well as nuclear receptors. The interaction between TFIIH and each nuclear receptor is specific[151] and either occurs in the absence of ligand — as observed for retinoic acid receptor-α1 (RARα1) and RARγ[152,153], androgen receptor[151,154], peroxisome proliferator activated receptor-α (PPARα), PPARβ (also known as PPARδ), PPARγ1 and PPARγ2 (REF. 155) and thyroid hormone receptor-α1 (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 TFIIH, except vitamin D receptors (VDRs), which lack a functional A/B domain[159]. However, TFIIH 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 TFIIH 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 kinases[164]. 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 TFIIH (as observed for thyroid hormone receptor α1)[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 organization[166], interacts with the non-phosphorylated form of RARγ to repress gene transcription but not with other RAR isoforms[167]. CDK7-mediated phosphorylation of RARγ disrupts the interaction of this receptor with vinexin-β and restores RARγ transactivation.

Furthermore, TFIIH-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 genes[151]. 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 TFIIH and nuclear receptors, an even higher level of complexity emerges if one considers that TFIIH might cooperate with partners of nuclear receptors. This was observed for PPARγ co-activator 1α (PGC1α)[168], which is a metabolic regulator and a transcriptional co-activator for several nuclear receptors[169], and also for the metastasis-associated protein 1 (MTA1), which represses oestrogen receptor-driven transcription[170]. Interestingly, MTA1 might disrupt CAK-induced transactivation control of oestrogen receptors, which suggests that TFIIH activity can, in turn, be modulated by these factors. Such a control of TFIIH function is also well illustrated by

◀ Figure 2 | **TFIIH is an essential factor of transcription initiation.** Gene activation requires a large number of co-regulatory complexes with various functions and enzymatic activities[203]. 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 TFIIH are sequentially recruited. The ATPase-dependent helicase activity of XPB within TFIIH allows promoter opening. The cyclin dependent kinase 7 (CDK7) subunit of TFIIH 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 expression[171] 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 PIC[172] and regulates the kinase activity of TFIIH through its CDK8 kinase subunit[124]. Other factors also participate in nuclear receptor-mediated transactivation by targeting TFIIH, as illustrated by the action of the co-chaperone Ydj1 in yeast[173].

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 TFIIH[176]. 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 instability[177].

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 dwarfism[180]. 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 abnormalities[181]. 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 ataxia[182]. 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 transcription[110]), 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 transcription[185]. 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 genes[185]. 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 stability[186]. 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 tissue[182]. By using an XPD-mutated TTD mouse model that also develops hypoplasia of adipose tissue[187], 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 patients[155]. Patients with TTD also develop neurological features, such as microcephaly and hypomyelination[188]. 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 components[156].

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 damage[189]. 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 repair[190]. 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 cells[191]. 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 complex[6]. 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.

1. Bohr, V. A., Smith, C. A., Okumoto, D. S. & Hanawalt, P. C. DNA repair in an active gene: removal of pyrimidine dimers from the DHFR gene of CHO cells is much more efficient than in the genome overall. *Cell* **40**, 359–369 (1985).
2. Mellon, I., Spivak, G. & Hanawalt, P. C. Selective removal of transcription-blocking DNA damage from the transcribed strand of the mammalian *DHFR* gene. *Cell* **51**, 241–249 (1987).
3. Schaeffer, L. *et al.* DNA repair helicase: a component of BTF2 (TFIIH) basic transcription factor. *Science* **260**, 58–63 (1993).
Demonstrated that the helicase XPB, which is involved in NER, is closely associated with the TFIIH transcription complex, suggesting that DNA repair and transcription are functionally related.
4. Feaver, W. J. *et al.* Dual roles of a multiprotein complex from *S. cerevisiae* in transcription and DNA repair. *Cell* **75**, 1379–1387 (1993).
5. Schmitz, K. M. *et al.* TAF12 recruits Gadd45a and the nucleotide excision repair complex to the promoter of rRNA genes leading to active DNA demethylation. *Mol. Cell* **33**, 344–353 (2009).
Revealed that the DNA repair machinery is recruited to the promoter of active genes, keeping these promoters in a hypomethylated state.
6. Le May, N. *et al.* NER factors are recruited to active promoters and facilitate chromatin modification for transcription in the absence of exogenous genotoxic attack. *Mol. Cell* **38**, 54–66 (2010).
Showed the sequential recruitment of the NER factors XPC, XPA, RPA, XPG and XPF–ERCC1 to the promoters of inducible genes in the absence of exogenous genotoxic attack. These NER factors (except cockayne syndrome B protein (CSB; also known as ERCC6)) are required to allow histone modifications and active DNA demethylation that are necessary for efficient transcription.
7. Conaway, R. C. & Conaway, J. W. An RNA polymerase II transcription factor has an associated DNA-dependent ATPase (dATPase) activity strongly stimulated by TATA region of promoters. *Proc. Natl Acad. Sci. USA* **86**, 7356–7360 (1989).
Reported the purification of a transcription factor from rat liver that was designated transcription factor-δ, which has an associated DNA-dependent ATPase activity.
8. Gerard, M. *et al.* Purification and interaction properties of the human RNA polymerase B(II) general transcription factor BTF2. *J. Biol. Chem.* **266**, 20940–20945 (1991).
Described the purification of the human cell transcription factor BTF2, which is required for the transcription of class II genes.
9. Feaver, W. J., Gileadi, O. & Kornberg, R. Purification and characterization of yeast RNA polymerase II transcription factor b. *J. Biol. Chem.* **266**, 19000–19005 (1991).
Reported the purification of a transcription factor from yeast that was designated Tfb, which is required for Pol II transcription.
10. Flores, O., Lu, H. & Reinberg, D. Factors involved in specific transcription by mammalian RNA polymerase II. Identification and characterization of factor IIH. *J. Biol. Chem.* **267**, 2786–2793 (1992).
11. Schaeffer, L. *et al.* The ERCC2/DNA repair protein is associated with the class II BTF2/TFIIH transcription factor. *EMBO J.* **13**, 2388–2392 (1994).
12. Weber, C. A., Salazar, E. P., Stewart, S. A. & Thompson, L. H. *ERCC2*: cDNA cloning and molecular characterization of human nucleotide excision repair gene with high homology to yeast *RAD3*. *EMBO J.* **9**, 1437–1447 (1990).
13. Weeda, G., Ma, L., van der Ham, R., van der Eb, A. J. & Hoeijmakers, J. H. J. Structure and expression of the human *XPBC/ERCC-3* gene involved in DNA repair disorders xeroderma pigmentosum and Cockayne's syndrome. *Nucleic Acids Res.* **19**, 6301–6308 (1991).
14. Feaver, W. J., Gileadi, O., Li, Y. & Kornberg, R. D. CTD kinase associated with yeast RNA polymerase II initiation factor b. *Cell* **67**, 1223–1230 (1991).
15. Roy, R. *et al.* The MO15 cell cycle kinase is associated with the TFIIH transcription-DNA repair factor. *Cell* **79**, 1093–1101 (1994).
Revealed that MO15 (also known as CDK7) kinase is present in the TFIIH transcription complex.
16. Fisher, R. P. & Morgan, D. O. A novel cyclin associates with MO15/CDK7 to form the CDK-activating kinase. *Cell* **78**, 713–724 (1994).
17. Mäkelä, T. P. *et al.* A cyclin associated with the CDK-associated kinase MO15. *Nature* **371**, 254–257 (1994).
18. Adamczewski, J. P. *et al.* MAT1, cdk7 and cyclin H form a kinase complex which is UV light-sensitive upon association with TFIIH. *EMBO J.* **15**, 1877–1884 (1996).
19. Rossignol, M., Kolb-Cheynel, I. & Egly, J. M. Substrate specificity of the cdk-activating kinase (CAK) is altered upon association with TFIIH. *EMBO J.* **16**, 1628–1637 (1997).
20. Larochelle, S., Pandur, J., Fisher, R. P., Salz, H. K. & Suter, B. Cdk7 is essential for mitosis and for *in vivo* Cdk-activating kinase activity. *Genes Dev.* **12**, 370–381 (1998).
21. Fesquet, D., Morin, N., Doree, M. & Devault, A. Is Cdk7/cyclin H/MAT1 the genuine cdk activating kinase in cycling *Xenopus* egg extracts? *Oncogene* **15**, 1303–1307 (1997).

22. Wu, L. *et al.* RNA antisense abrogation of MAT1 induces G1 phase arrest and triggers apoptosis in aortic smooth muscle cells. *J. Biol. Chem.* **274**, 5564–5572 (1999).
23. Aprelikova, O., Xiong, Y. & Liu, E. T. Both p16 and p21 families of cyclin-dependent kinase (CDK) inhibitors block the phosphorylation of cyclin-dependent kinases by the CDK-activating kinase. *J. Biol. Chem.* **270**, 18195–18197 (1995).
24. Fesquet, D. *et al.* The MO15 gene encodes the catalytic subunit of a protein kinase that activates cdc2 and other cyclin dependent kinases (CDKs) through phosphorylation of Thr161 and its homologues. *EMBO J.* **12**, 3111–3121 (1993).
25. Matsuoka, M., Kato, J. Y., Fisher, R. P., Morgan, D. O. & Sherr, C. J. Activation of cyclin-dependent kinase 4 (cdk4) by mouse MO15-associated kinase. *Mol. Cell. Biol.* **14**, 7265–7275 (1994).
26. Poon, R. Y. C., Yamashita, K., Adamczewski, J. P., Hunt, T. & Shuttleworth, J. The cdc2-related protein p40MO15 is the catalytic subunit of a protein kinase that can activate p33cdk2 and p34cdc2. *EMBO J.* **12**, 3123–3132 (1993).
27. Solomon, M. J., Harper, W. J. & Shuttleworth, J. CAK, the p34cdc2 activating kinase contains a protein kinase identical to or closely related to p40MO15. *EMBO J.* **12**, 3133–3142 (1993).
28. Fisher, R. P. Secrets of a double agent: CDK7 in cell-cycle control and transcription. *J. Cell Sci.* **118**, 5171–5180 (2005).
29. Ito, S. *et al.* MMXD, a TFIIH-independent XPD–MMS19 protein complex involved in chromosome segregation. *Mol. Cell* **39**, 632–640 (2010).
30. Sancar, A. Mechanisms of DNA excision repair. *Science* **266**, 1954–1956 (1994).
31. Aboussekhra, A. *et al.* Mammalian DNA nucleotide excision repair reconstituted with purified protein components. *Cell* **80**, 859–868 (1995).
32. Volker, M. *et al.* Sequential assembly of the nucleotide excision repair factors *in vivo*. *Mol. Cell* **8**, 213–224 (2001).
33. Hanawalt, P. C. & Spivak, G. Transcription-coupled DNA repair: two decades of progress and surprises. *Nature Rev. Mol. Cell Biol.* **9**, 958–970 (2008).
34. Clement, F. C. *et al.* Dynamic two-stage mechanism of versatile DNA damage recognition by xeroderma pigmentosum group C protein. *Mutat. Res.* **685**, 21–28 (2010).
35. Bunick, C. G., Miller, M. R., Fuller, B. E., Fanning, E. & Chazin, W. J. Biochemical and structural domain analysis of xeroderma pigmentosum complementation group C protein. *Biochemistry* **45**, 14965–14979 (2006).
36. Min., J. H. & Pavletich, N. P. Recognition of DNA damage by the Rad4 nucleotide excision repair protein. *Nature* **449**, 570–575 (2007).
37. Sugasawa, K. *et al.* A multistep damage recognition mechanism for global genomic nucleotide excision repair. *Genes Dev.* **15**, 507–521 (2001).
38. Mocquet, V. *et al.* The human DNA repair factor XPC–HR23B distinguishes stereoisomeric benzo[*a*] pyrenyl-DNA lesions. *EMBO J.* **26**, 2923–2932 (2007).
39. Keeney, S., Chang, G. J. & Linn, S. Characterization of a human DNA damage binding protein implicated in xeroderma pigmentosum E. *J. Biol. Chem.* **268**, 21293–21300 (1993).
40. Takao, M. *et al.* A 127 kDa component of a UV-damaged DNA-binding complex which is defective in some xeroderma pigmentosum group E patients is homologous to a slime mold protein. *Nucleic Acids Res.* **21**, 4111–4118 (1993).
41. Fitch, M. E. *et al.* The DDB2 nucleotide excision repair gene product p48 enhances global genomic repair in p53 deficient human fibroblasts. *DNA Repair (Amst.)* **2**, 819–826 (2003).
42. Wang, Q. E., Zhu, Q., Wani, G., Chen, J. & Wani, A. A. UV radiation-induced XPC translocation within chromatin is mediated by damaged-DNA binding protein, DDB2. *Carcinogenesis* **25**, 1033–1043 (2004).
43. Fei, J. *et al.* Regulation of nucleotide excision repair by UV-DDB: prioritization of damage recognition to internucleosomal DNA. *PLoS Biol.* **9**, e1001183 (2011).
44. Gillette, T. G. *et al.* Distinct functions of the ubiquitin–proteasome pathway influence nucleotide excision repair. *EMBO J.* **25**, 2529–2538 (2006).
45. Araki, M. *et al.* Centrosome protein centrin 2/caltractin 1 is part of the xeroderma pigmentosum group C complex that initiates global genome nucleotide excision repair. *J. Biol. Chem.* **276**, 18665–18672 (2001).
46. Xie, Z., Liu, S., Zhang, Y. & Wang, Z. Roles of Rad23 protein in yeast nucleotide excision repair. *Nucleic Acids Res.* **32**, 5981–5990 (2004).
47. Tapias, A. *et al.* Ordered conformational changes in damaged DNA induced by nucleotide excision repair factors. *J. Biol. Chem.* **279**, 19074–19083 (2004).
48. Bernardes de Jesus, B. M., Bjoras, M., Coin, F. & Egly, J. M. Dissection of the molecular defects caused by pathogenic mutations in the DNA repair factor XPC. *Mol. Cell. Biol.* **28**, 7225–7235 (2008).
49. Bootsma, D. & Hoeijmakers, J. H. J. DNA repair. Engagement with transcription. *Nature* **363**, 114–115 (1993).
50. Wood, R. D. DNA damage recognition during nucleotide excision repair in mammalian cells. *Biochimie* **81**, 39–44 (1999).
51. Coin, F. *et al.* Mutations in the XPD helicase gene result in XP and TTD phenotypes, preventing interaction between XPD and the p44 subunit of TFIIH. *Nature Genet.* **20**, 184–188 (1998).
Demonstrated that mutations in the XPD C-terminal domain that are found in most patients with xeroderma pigmentosum and TTD prevent the interaction with p44, thus explaining the observed decrease in XPD helicase activity and the NER defect.
52. Dubaele, S. *et al.* Basal transcription defect discriminates between xeroderma pigmentosum and trichothiodystrophy in XPD patients. *Mol. Cell* **11**, 1635–1646 (2003).
53. Tirode, F., Busso, D., Coin, F. & Egly, J. M. Reconstitution of the transcription factor TFIIH: assignment of functions for the three enzymatic subunits, XPB, XPD, and cdk7. *Mol. Cell* **3**, 87–95 (1999).
54. Oksenych, V., de Jesus, B. B., Zhovmer, A., Egly, J. M. & Coin, F. Molecular insights into the recruitment of TFIIH to sites of DNA damage. *EMBO J.* **28**, 2971–2980 (2009).
55. Fan, L. *et al.* Conserved XPB core structure and motifs for DNA unwinding: implications for pathway selection of transcription or excision repair. *Mol. Cell* **22**, 27–37 (2006).
56. Coin, F., Oksenych, V. & Egly, J. M. Distinct roles for the XPB/p52 and XPD/p44 subcomplexes of TFIIH in damaged DNA opening during nucleotide excision repair. *Mol. Cell* **26**, 245–256 (2007).
Revealed that the helicase activity of XPB is not used for damaged DNA opening, which is instead driven by the ATPase activity of XPB in combination with the helicase activity of XPD. Furthermore, TFIIH from patients with mutated XPB is unable to induce DNA opening around the lesion owing to impaired XPB–p52 interaction and ATPase stimulation.
57. Fregoso, M. *et al.* DNA repair and transcriptional deficiencies caused by mutations in the *Drosophila* p52 subunit of TFIIH generate developmental defects and chromosome fragility. *Mol. Cell. Biol.* **27**, 3640–3650 (2007).
58. Fan, L. *et al.* XPD helicase structures and activities: insights into the cancer and aging phenotypes from XPD mutations. *Cell* **133**, 789–800 (2008).
59. Liu, H. *et al.* Structure of the DNA repair helicase XPD. *Cell* **133**, 801–812 (2008).
60. Wolski, S. C. *et al.* Crystal structure of the FeS cluster-containing nucleotide excision repair helicase XPD. *PLoS Biol.* **6**, e149 (2008).
61. Mathieu, N., Kaczmarek, N. & Naegeli, H. Strand- and site-specific DNA lesion demarcation by the xeroderma pigmentosum group D helicase. *Proc. Natl Acad. Sci. USA* **107**, 17545–17550 (2010).
62. Theis, K., Chen, P. J., Skorvaga, M., Van Houten, B. & Kisker, C. Crystal structure of UvrB, a DNA helicase adapted for nucleotide excision repair. *EMBO J.* **18**, 6899–6907 (1999).
63. Skorvaga, M., Theis, K., Mandavilli, B. S., Kisker, C. & Van Houten, B. The β-hairpin motif of UvrB is essential for DNA binding, damage processing, and UvrC-mediated incisions. *J. Biol. Chem.* **277**, 1553–1559 (2002).
64. Reardon, J. T. & Sancar, A. Recognition and repair of the cyclobutane thymine dimer, a major cause of skin cancers, by the human excision nuclease. *Genes Dev.* **17**, 2539–2551 (2003).
65. Stefanini, M., Botta, E., Lanzafame, M. & Orioli, D. Trichothiodystrophy: from basic mechanisms to clinical implications. *DNA Repair (Amst.)* **9**, 2–10 (2010).
66. Ranish, J. A. *et al.* Identification of TFB5, a new component of general transcription and DNA repair factor IIH. *Nature Genet.* **36**, 707–713 (2004).
67. Giglia-Mari, G. *et al.* A new, tenth subunit of TFIIH is responsible for the DNA repair syndrome trichothiodystrophy group A. *Nature Genet.* **36**, 714–719 (2004).
Demonstrated that p8 is an evolutionarily conserved subunit of TFIIH and identified *GTF2H5* as the gene that causes the NER defect in TTD-A.
68. Coin, F. *et al.* p8/TTD-A as a repair-specific TFIIH subunit. *Mol. Cell* **21**, 215–226 (2006).
69. Vermeulen, W. *et al.* Sublimiting concentration of TFIIH transcription/DNA repair factor causes TTD-A trichothiodystrophy disorder. *Nature Genet.* **26**, 307–313 (2000).
70. Vitorino, M. *et al.* Solution structure and self-association properties of the p8 TFIIH subunit responsible for trichothiodystrophy. *J. Mol. Biol.* **368**, 473–480 (2007).
71. Kainov, D. E., Vitorino, M., Cavarelli, J., Poterszman, A. & Egly, J. M. Structural basis for group A trichothiodystrophy. *Nature Struct. Mol. Biol.* **15**, 980–984 (2008).
72. Park, C. H. & Sancar, A. Formation of a ternary complex by human XPA, ERCC1, and ERCC4(XPF) excision repair proteins. *Proc. Natl Acad. Sci. USA* **91**, 5017–5021 (1994).
73. Krasikova, Y. S., Rechkunova, N. I., Maltseva, E. A., Petruseva, I. O. & Lavrik, O. I. Localization of xeroderma pigmentosum group A protein and replication protein A on damaged DNA in nucleotide excision repair. *Nucleic Acids Res.* **38**, 8083–8094 (2010).
74. Ikegami, T. *et al.* Solution structure of the DNA- and RPA-binding domain of the human repair factor XPA. *Nature Struct. Biol.* **5**, 701–706 (1998).
75. Saijo, M., Kuraoka, I., Masutani, C., Hanaoka, F. & Tanaka, K. Sequential binding of DNA repair proteins RPA and ERCC1 to XPA *in vitro*. *Nucleic Acids Res.* **24**, 4719–4724 (1996).
76. Evans, E., Moggs, J. G., Hwang, J. R., Egly, J. M. & Wood, R. D. Mechanism of open complex and dual incision formation by human nucleotide excision repair factors. *EMBO J.* **16**, 6559–6573 (1997).
77. Coin, F. *et al.* Nucleotide excision repair driven by the dissociation of CAK from TFIIH. *Mol. Cell* **31**, 9–20 (2008).
Showed the release of CAK from the core TFIIH during the engagement of this complex in DNA repair. Following repair, CAK reappears with the core subunit of TFIIH on chromatin, coincident with the resumption of transcription.
78. Svejstrup, J. Q. *et al.* Different forms of TFIIH for transcription and DNA repair: holo-TFIIH and a nucleotide excision repairosome. *Cell* **80**, 21–28 (1995).
79. Araujo, S. J. *et al.* 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 Dev.* **14**, 349–359 (2000).
80. Sandrock, B. & Egly, J. M. A yeast four-hybrid system identifies Cdk-activating kinase as a regulator of the XPD helicase, a subunit of transcription factor IIH. *J. Biol. Chem.* **276**, 35328–35333 (2001).
81. Fan, W. & Luo, J. SIRT1 regulates UV-induced DNA repair through deacetylating XPA. *Mol. Cell* **39**, 247–258 (2010).
82. Sugasawa, K., Akagi, J., Nishi, R., Iwai, S. & Hanaoka, F. Two-step recognition of DNA damage for mammalian nucleotide excision repair: directional binding of the XPC complex and DNA strand scanning. *Mol. Cell* **36**, 642–653 (2009).
83. Naegeli, H. & Sugasawa, K. The xeroderma pigmentosum pathway: decision tree analysis of DNA quality. *DNA Repair (Amst.)* **10**, 673–683 (2011).
84. Kesseler, K. J., Kaufmann, W. K., Reardon, J. T., Elston, T. C. & Sancar, A. A mathematical model for human nucleotide excision repair: damage recognition by random order assembly and kinetic proofreading. *J. Theor. Biol.* **249**, 361–275 (2007).
85. Mocquet, V. *et al.* Sequential recruitment of the repair factors during NER: the role of XPG in initiating the resynthesis step. *EMBO J.* **27**, 155–167 (2008).
86. Staresincic, L. *et al.* Coordination of dual incision and repair synthesis in human nucleotide excision repair. *EMBO J.* **28**, 1111–1120 (2009).

87. Moggs, J. G., Yarema, K. J., Essigmann, J. M. & Wood, R. D. Analysis of incision sites produced by human cell extracts and purified proteins during nucleotide excision repair of a 1,3-intrastrand d(GpTpG)-cisplatin adduct. *J. Biol. Chem.* **271**, 7177–7186 (1996).
88. Gillet, L. C. & Scharer, O. D. Molecular mechanisms of mammalian global genome nucleotide excision repair. *Chem. Rev.* **106**, 253–276 (2006).
89. Lehmann, A. R. DNA polymerases and repair synthesis in NER in human cells. *DNA Repair (Amst.)* **10**, 730–733 (2011).
90. Ogi, T. *et al.* Three DNA polymerases, recruited by different mechanisms, carry out NER repair synthesis in human cells. *Mol. Cell* **37**, 714–727 (2010).
91. Moser, J. *et al.* Sealing of chromosomal DNA nicks during nucleotide excision repair requires XRCC1 and DNA ligase IIIα in a cell-cycle-specific manner. *Mol. Cell* **27**, 311–323 (2007).
92. Gaillard, P. H. L. *et al.* Chromatin assembly coupled to DNA repair: a new role for chromatin assembly factor I. *Cell* **86**, 887–896 (1996).
93. Polo, S. E., Roche, D. & Almouzni, G. New histone incorporation marks sites of UV repair in human cells. *Cell* **127**, 481–493 (2006).
94. Ito, S. *et al.* XPG stabilizes TFIIH, allowing transactivation of nuclear receptors: implications for Cockayne Syndrome in XP-G/CS Patients. *Mol. Cell* **26**, 231–243 (2007).
Showed that XPG forms a stable complex with TFIIH and functions in maintaining the architecture of TFIIH, which underlines the contribution of XPG to transcription.
95. Coin, F. *et al.* Phosphorylation of XPB helicase regulates TFIIH nucleotide excision repair activity. *EMBO J.* **23**, 4835–4846 (2004).
96. Hoogstraten, D. *et al.* Rapid switching of TFIIH between RNA polymerase I and II transcription and DNA repair *in vivo*. *Mol. Cell* **10**, 1163–1174 (2002).
97. Iben, S. *et al.* TFIIH plays an essential role in RNA polymerase I transcription. *Cell* **109**, 297–306 (2002).
Found that TFIIH serves a function in ribosomal gene transcription. TFIIH is required for productive but not abortive ribosomal DNA transcription, which implies a post-initiation role for TFIIH in transcription.
98. Assfalg, R. *et al.* TFIIH is an elongation factor of RNA polymerase I. *Nucleic Acids Res.* **40**, 650–659 (2011).
99. Barski, A. *et al.* Pol II and its associated epigenetic marks are present at Pol III-transcribed noncoding RNA genes. *Nature Struct. Mol. Biol.* **17**, 629–634 (2010).
100. Oler, A. J. *et al.* Human RNA polymerase III transcriptomes and relationships to Pol II promoter chromatin and enhancer-binding factors. *Nature Struct. Mol. Biol.* **17**, 620–628 (2010).
101. Kornberg, R. D. Eukaryotic transcriptional control. *Trends Cell Biol.* **9**, M46–M49 (1999).
102. Sims, R. J. 3rd, Mandal, S. S. & Reinberg, D. Recent highlights of RNA-polymerase-II-mediated transcription. *Curr. Opin. Cell Biol.* **16**, 263–271 (2004).
103. Cairns, B. R. *et al.* RSC, an essential, abundant chromatin-remodeling complex. *Cell* **87**, 1249–1260 (1996).
104. Chao, D. M. *et al.* A mammalian SRB protein associated with an RNA polymerase II holoenzyme. *Nature* **380**, 82–85 (1996).
105. Kim, Y. J., Bjorklund, S., Li, Y., Sayre, M. H. & Kornberg, R. D. A multiprotein mediator of transcriptional activation and its interaction with the C-terminal repeat domain of RNA polymerase II. *Cell* **77**, 599–608 (1994).
106. Ossipow, V., Tassan, J. P., Nigg, E. A. & Schibler, U. A mammalian RNA polymerase II holoenzyme containing all components required for promoter-specific transcription initiation. *Cell* **83**, 137–146 (1995).
107. Zawel, L. & Reinberg, D. Common themes in assembly and function of eukaryotic transcription complexes. *Annu. Rev. Biochem.* **64**, 533–561 (1995).
108. Douziech, M. *et al.* Mechanism of promoter melting by the xeroderma pigmentosum complementation group B helicase of transcription factor IIH revealed by protein-DNA photo-cross-linking. *Mol. Cell. Biol.* **20**, 8168–8177 (2000).
109. Holstege, F. C., van der Vliet, P. C. & Timmers, H. T. Opening of an RNA polymerase II promoter occurs in two distinct steps and requires the basal transcription factors IIE and IIH. *EMBO J.* **15**, 1666–1677 (1996).
Presented a model in which the crucial function of TFIIH-associated DNA helicases is to create an ssDNA region during transcription.
110. Coin, F., Bergmann, E., Tremeau-Bravard, A. & Egly, J. M. Mutations in XPB and XPD helicases found in xeroderma pigmentosum patients impair the transcription function of TFIIH. *EMBO J.* **18**, 1357–1366 (1999).
111. Moreland, R. J. *et al.* A role for the TFIIH XPB DNA helicase in promoter escape by RNA polymerase II. *J. Biol. Chem.* **274**, 22127–22130 (1999).
112. Dvir, A. *et al.* A role for ATP and TFIIH in activation of the RNA polymerase II preinitiation complex prior to transcription initiation. *J. Biol. Chem.* **271**, 7245–7248 (1996).
113. Dvir, A., Conaway, R. C. & Conaway, J. W. A role for TFIIH in controlling the activity of early RNA polymerase II elongation complexes. *Proc. Natl Acad. Sci. USA* **94**, 9006–9010 (1997).
114. Liu, J. *et al.* Defective interplay of activators and repressors with TFIH in xeroderma pigmentosum. *Cell* **104**, 353–363 (2001).
115. Lu, H., Zawel, L., Fisher, L., Egly, J. M. & Reinberg, D. Human general transcription factor IIH phosphorylates the C-terminal domain of RNA polymerase II. *Nature* **358**, 641–645 (1992).
Showed that the phosphorylation of the C-terminal domain of the largest subunit of Pol II by CDK7 contributes to the transition from transcription initiation to elongation.
116. Feaver, W. J., Svejstrup, J. Q., Henry, N. L. & Kornberg, R. D. Relationship of CDK-activating kinase and RNA polymerase II CTD kinase TFIIH/TFIIK. *Cell* **79**, 1103–1109 (1994).
117. Shiekhattar, R. *et al.* Cdk-activating kinase complex is a component of human transcription factor TFIIH. *Nature* **374**, 283–287 (1995).
118. Bensaude, O. *et al.* Regulated phosphorylation of the RNA polymerase II C-terminal domain (CTD). *Biochem. Cell Biol.* **77**, 249–255 (1999).
119. Buratowski, S. Progression through the RNA polymerase II CTD cycle. *Mol. Cell* **36**, 541–546 (2009).
120. Serizawa, H., Conaway, J. W. & Conaway, R. C. Phosphorylation of C-terminal domain of RNA polymerase II is not required in basal transcription. *Nature* **363**, 371–374 (1993).
121. Cho, E., Tagaki, T., Moore, C. R. & Buratowski, S. mRNA capping enzyme is recruted to the transcritption complex by phosphorylation of the RNA polymerase II carboxy-terminal domain. *Genes Dev.* **11**, 3319–3326 (1997).
122. Komarnitsky, P., Cho, E. J. & Buratowski, S. Different phosphorylated forms of RNA polymerase II and associated mRNA processing factors during transcription. *Genes Dev.* **14**, 2452–2460 (2000).
123. Helenius, K. *et al.* Requirement of TFIIH kinase subunit Mat1 for RNA Pol II C-terminal domain Ser5 phosphorylation, transcription and mRNA turnover. *Nucleic Acids Res.* **39**, 5025–5035 (2011).
124. Akoulitchev, S., Chuikov, S. & Reinberg, D. TFIIH is negatively regulated by cdk8-containing mediator complexes. *Nature* **407**, 102–106 (2000).
125. Yakovchuk, P., Goodrich, J. A. & Kugel, J. F. B2 RNA and Alu RNA repress transcription by disrupting contacts between RNA polymerase II and promoter DNA within assembled complexes. *Proc. Natl Acad. Sci. USA* **106**, 5569–5574 (2009).
126. O'Gorman, W., Thomas, B., Kwek, K. Y., Furger, A. & Akoulitchev, A. Analysis of U1 small nuclear RNA interaction with cyclin H. *J. Biol. Chem.* **280**, 36920–36925 (2005).
127. Akhtar, M. S. *et al.* TFIIH kinase places bivalent marks on the carboxy-terminal domain of RNA polymerase II. *Mol. Cell* **34**, 387–393 (2009).
128. Glover-Cutter, K. *et al.* TFIIH-associated Cdk7 kinase functions in phosphorylation of C-terminal domain Ser7 residues, promoter-proximal pausing, and termination by RNA polymerase II. *Mol. Cell. Biol.* **29**, 5455–5464 (2009).
129. Kim, M., Suh, H., Cho, E. J. & Buratowski, S. Phosphorylation of the yeast Rpb1 C-terminal domain at serines 2, 5, and 7. *J. Biol. Chem.* **284**, 26421–26426 (2009).
130. Egloff, S. *et al.* Serine-7 of the RNA polymerase II CTD is specifically required for snRNA gene expression. *Science* **318**, 1777–1779 (2007).
131. Cho, E. J., Kobor, M. S., Kim, M., Greenblatt, J. & Buratowski, S. Opposing effects of Ctk1 kinase and Fcp1 phosphatase at Ser 2 of the RNA polymerase II C-terminal domain. *Genes Dev.* **15**, 3319–3329 (2001).
132. Zhou, M. *et al.* Tat modifies the activity of CDK9 to phosphorylate serine 5 of the RNA polymerase II carboxyl-terminal domain during human immunodeficiency virus type 1 transcription. *Mol. Cell. Biol.* **20**, 5077–5086 (2000).
133. Ahn, S. H., Kim, M. & Buratowski, S. Phosphorylation of serine 2 within the RNA polymerase II C-terminal domain couples transcription and 3′ end processing. *Mol. Cell* **13**, 67–76 (2004).
134. Gebara, M. M., Sayre, M. H. & Corden, J. L. Phosphorylation of the carboxy-terminal repeat domain in RNA polymerase II by cyclin-dependent kinases is sufficient to inhibit transcription. *J. Cell. Biochem.* **64**, 390–402 (1997).
135. Hengartner, C. J. *et al.* Temporal regulation of RNA polymerase II by Srb10 and Kin28 cyclin-dependent kinases. *Mol. Cell* **2**, 43–53 (1998).
136. Bonnet, F., Vigneron, M., Bensaude, O. & Dubois, M. F. Transcription-independent phosphorylation of the RNA polymerase II C-terminal domain (CTD) involves ERK kinases (MEK1/2). *Nucleic Acids Res.* **27**, 4399–4404 (1999).
137. Dvir, A., Peterson, S. R., Knuth, M. W., Lu, H. & Dynan, W. S. Ku autoantigen is the regulatory component of a template-associated protein kinase that phosphorylates RNA polymerase II. *Proc. Natl Acad. Sci. USA* **89**, 11920–11924 (1992).
138. Trigon, S. *et al.* Characterization of the residues phosphorylated *in vitro* by different C-terminal domain kinases. *J. Biol. Chem.* **273**, 6769–6775 (1998).
139. Chambers, R. S. & Kane, C. M. Purification and characterization of an RNA polymerase II phosphatase from yeast. *J. Biol. Chem.* **271**, 24408–24504 (1996).
140. Lin, P. S., Dubois, M. F. & Dahmus, M. E. TFIIF-associating carboxyl-terminal domain phosphatase dephosphorylates phosphoserines 2 and 5 of RNA polymerase II. *J. Biol. Chem.* **277**, 45949–45956 (2002).
141. Mosley, A. L. *et al.* Rtr1 is a CTD phosphatase that regulates RNA polymerase II during the transition from serine 5 to serine 2 phosphorylation. *Mol. Cell* **34**, 168–178 (2009).
142. Phatnani, H. P. & Greenleaf, A. L. Phosphorylation and functions of the RNA polymerase II CTD. *Genes Dev.* **20**, 2922–2936 (2006).
143. Corden, J. L. Transcription. Seven ups the code. *Science* **318**, 1735–1736 (2007).
144. Egloff, S. & Murphy, S. Cracking the RNA polymerase II CTD code. *Trends Genet.* **24**, 280–288 (2008).
145. Lu, H., Fisher, R. P., Bailey, P. & Levine, A. J. The CDK7-cycH-p36 complex of transcription factor IIH phosphorylates p53, enhancing its sequence-specific DNA binding activity *in vitro*. *Mol. Cell. Biol.* **17**, 5923–5934 (1997).
146. Xiao, H. *et al.* Binding of basal transcription factor TFIIH to the acidic activation domains of VP16 and p53. *Mol. Cell. Biol.* **14**, 7013–7024 (1994).
147. Tong, X., Drapkin, R., Reinberg, D. & Kieff, E. The 62- and 80-kDa subunits of transcription factor IIH mediate the interaction with Epstein-Barr virus nuclear protein 2. *Proc. Natl Acad. Sci. USA* **92**, 3259–3263 (1995).
148. Qadri, I., Conaway, J. W., Conaway, R. C., Schaack, J. & Siddiqui, A. Hepatitis B virus transactivator protein, HBx, associates with the components of TFIIH and stimulates the DNA helicase activity of TFIIH. *Proc. Natl Acad. Sci. USA* **93**, 10578–10583 (1996).
149. Liu, J. *et al.* The FBP interacting repressor targets TFIIH to inhibit activated transcription. *Mol. Cell* **5**, 331–341 (2000).
150. Mitchell, N. C. *et al.* Hfp inhibits *Drosophila myc* transcription and cell growth in a TFIIH/Hay-dependent manner. *Development* **137**, 2875–2884 (2010).
151. Chymkowitch, P., Le May, N., Charneau, P., Compe, E. & Egly, J. M. The phosphorylation of the androgen receptor by TFIIH directs the ubiquitin/proteasome process. *EMBO J.* **30**, 468–479 (2011).
152. Bastien, J. *et al.* TFIIH interacts with the retinoic acid receptor-γ and phosphorylates its AF-1-activating domain through cdk7. *J. Biol. Chem.* **275**, 21896–21904 (2000).
153. Rochette-Egly, C., Adam, S., Rossignol, M., Egly, J. M. & Chambon, P. Stimulation of RARα activation function AF-1 through binding to the general transcription factor TFIIH and phosphorylation by CDK7. *Cell* **90**, 97–107 (1997).
Revealed that RARα is targeted by the CDK7 subunit of TFIIH, suggesting that the activity of a transactivator could be modulated through its interaction with a general transcription factor.

154. Lee, D. K., Duan, H. O. & Chang, C. From androgen receptor to the general transcription factor TFIIH. Identification of cdk activating kinase (CAK) as an androgen receptor NH_2-terminal associated coactivator. *J. Biol. Chem.* **275**, 9308–9313 (2000).
155. Compe, E. *et al.* Dysregulation of the peroxisome proliferator-activated receptor target genes by XPD mutations. *Mol. Cell. Biol.* **25**, 6065–6076 (2005).
156. Compe, E. *et al.* Neurological defects in trichothiodystrophy reveal a coactivator function of TFIIH. *Nature Neurosci.* **10**, 1414–1422 (2007).
Reported hypomyelination in the central nervous system of mice with TTD, which is related to the dysregulation of various thyroid hormone target genes. Proposed that such a dysregulation is likely to result from the inability of the mutated TFIIH to fully participate in the recruitment of thyroid hormone receptors to their response elements.
157. Chen, D. *et al.* Activation of estrogen receptor-α by S118 phosphorylation involves a ligand-dependent interaction with TFIIH and participation of CDK7. *Mol. Cell* **6**, 127–137 (2000).
158. Liu, Y. *et al.* p62, a TFIIH subunit, directly interacts with thyroid hormone receptor and enhances T3-mediated transcription. *Mol. Endocrinol.* **19**, 879–884 (2005).
159. Drane, P., Compe, E., Catez, P., Chymkowitch, P. & Egly, J. M. Selective regulation of vitamin D receptor-responsive genes by TFIIH. *Mol. Cell* **16**, 187–197 (2004).
160. Nigg, E. A. Cyclin-dependent kinase 7: at the cross-roads of transcription, DNA repair and cell cycle control? *Curr. Opin. Cell Biol.* **8**, 312–317 (1996).
161. Morgan, D. O. Cyclin-dependent kinases: engines, clocks, and microprocessors. *Annu. Rev. Cell Dev. Biol.* **13**, 261–291 (1997).
162. Schwartz, B. E., Larochelle, S., Suter, B. & Lis, J. T. Cdk7 is required for full activation of *Drosophila* heat shock genes and RNA polymerase II phosphorylation *in vivo*. *Mol. Cell. Biol.* **23**, 6876–6886 (2003).
163. Larochelle, S. *et al.* Requirements for Cdk7 in the assembly of Cdk1/cyclin B and activation of Cdk2 revealed by chemical genetics in human cells. *Mol. Cell* **25**, 839–850 (2007).
164. Rochette-Egly, C. Nuclear receptors: integration of multiple signalling pathways through phosphorylation. *Cell Signal.* **15**, 355–366 (2003).
165. Keriel, A., Stary, A., Sarasin, A., Rochette-Egly, C. & Egly, J. M. XPD mutations prevent TFIIH-dependent transactivation by nuclear receptors and phosphorylation of RARα. *Cell* **109**, 125–135 (2002).
Demonstrated that mutations in *XPD* result in the decreased ability of nuclear receptors to be phosphorylated by TFIIH and to stimulate expression of target genes.
166. Kioka, N. *et al.* Vinexin: a novel vinculin-binding protein with multiple SH3 domains enhances actin cytoskeletal organization. *J. Cell Biol.* **144**, 59–69 (1999).
167. Bour, G., Plassat, J. L., Bauer, A., Lalevee, S. & Rochette-Egly, C. Vinexin-β interacts with the non-phosphorylated AF-1 domain of retinoid receptor-γ (RARγ) and represses RARγ-mediated transcription. *J. Biol. Chem.* **280**, 17027–17037 (2005).
168. Sano, M. *et al.* Menage-a-trois 1 is critical for the transcriptional function of PPARγ coactivator 1. *Cell. Metab.* **5**, 129–142 (2007).
169. Puigserver, P. & Spiegelman, B. M. Peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α): transcriptional coactivator and metabolic regulator. *Endocr. Rev.* **24**, 78–90 (2003).
170. Talukder, A. H. *et al.* MTA1 interacts with MAT1, a cyclin-dependent kinase-activating kinase complex ring finger factor, and regulates estrogen receptor transactivation functions. *J. Biol. Chem.* **278**, 11676–11685 (2003).
171. Conaway, R. C. & Conaway, J. W. Function and regulation of the Mediator complex. *Curr. Opin. Genet. Dev.* **21**, 225–230 (2011).
172. Esnault, C. *et al.* Mediator-dependent recruitment of TFIIH modules in preinitiation complex. *Mol. Cell* **31**, 337–346 (2008).
Reported a direct interaction between a Mediator 'head' subunit and a TFIIH core subunit and concluded that the Mediator 'head' module has a crucial role in TFIIH and TFIIE recruitment to the PIC.
173. Moriel-Carretero, M., Tous, C. & Aguilera, A. Control of the function of the transcription and repair factor TFIIH by the action of the cochaperone Ydj1. *Proc. Natl Acad. Sci. USA* **108**, 15300–15305 (2011).
174. Manuguerra, M. *et al.* XRCC3 and XPD/ERCC2 single nucleotide polymorphisms and the risk of cancer: a HuGE review. *Am. J. Epidemiol.* **164**, 297–302 (2006).
175. Zhang, J., Gu, S. Y., Zhang, P., Jia, Z. & Chang, J. H. ERCC2 Lys751Gln polymorphism is associated with lung cancer among Caucasians. *Eur. J. Cancer* **46**, 2479–2484 (2010).
176. Le May, N. *et al.* TFIIH transcription factor, a target for the Rift Valley hemorrhagic fever virus. *Cell* **116**, 541–550 (2004).
177. Jaitovich-Groisman, I. *et al.* Transcriptional regulation of the TFIIH transcription repair components XPB and XPD by the hepatitis B virus x protein in liver cells and transgenic liver tissue. *J. Biol. Chem.* **276**, 14124–14132 (2001).
178. Kraemer, K. H. *et al.* Xeroderma pigmentosum and related disorders: examining the linkage between defective DNA repair and cancer. *J. Invest. Dermatol.* **103**, 96S–101S (1994).
179. Cleaver, J. E. Cancer in xeroderma pigmentosum and related disorders of DNA repair. *Nature Rev. Cancer* **5**, 564–573 (2005).
180. de Boer, J. & Hoeijmakers, J. H. Nucleotide excision repair and human syndromes. *Carcinogenesis* **21**, 453–460 (2000).
181. Nance, M. A. & Berry, S. A. Cockayne syndrome: review of 140 cases. *Am. J. Med. Genet.* **84**, 42–68 (1992).
182. Itin, P. H., Sarasin, A. & Pittelkow, M. R. Trichothiodystrophy: update on the sulfur-deficient brittle hair syndromes. *J. Am. Acad. Dermatol.* **44**, 891–920 (2001).
183. Hashimoto, S. & Egly, J. M. Trichothiodystrophy view from the molecular basis of DNA repair/transcription factor TFIIH. *Hum. Mol. Genet.* **18**, R224–R230 (2009).
184. Berneburg, M. & Lehmann, A. R. Xeroderma pigmentosum and related disorders: defects in DNA repair and transcription. *Adv. Genet.* **43**, 71–102 (2001).
185. Ueda, T., Compe, E., Catez, P., Kraemer, K. H. & Egly, J. M. Both XPD alleles contribute to the phenotype of compound heterozygote xeroderma pigmentosum patients. *J. Exp. Med.* **206**, 3031–3046 (2009).
186. Botta, E. *et al.* Reduced level of the repair/transcription factor TFIIH in trichothiodystrophy. *Hum. Mol. Genet.* **11**, 2919–2928 (2002).
Showed that alterations in any of the gene products that result in the clinical phenotype of TTD specifically reduce the cellular content of the TFIIH complex.
187. de Boer, J. *et al.* A mouse model for the basal transcription/DNA repair syndrome trichothiodystrophy. *Mol. Cell* **1**, 981–990 (1998).
188. Bergmann, E. & Egly, J. M. Trichothiodystrophy, a transcription syndrome. *Trends Genet.* **17**, 279–286 (2001).
189. Takagi, Y. *et al.* Ubiquitin ligase activity of TFIIH and the transcriptional response to DNA damage. *Mol. Cell* **18**, 237–243 (2005).
190. Frit, P. *et al.* Transcriptional activators stimulate DNA repair. *Mol. Cell* **10**, 1391–1401 (2002).
191. Fong, Y. W. *et al.* A DNA repair complex functions as an oct4/sox2 coactivator in embryonic stem cells. *Cell* **147**, 120–131 (2011).
Revealed a selective co-activator role of an NER complex in transcription in the context of embryonic stem cells.
192. Gibbons, B. J. *et al.* Subunit architecture of general transcription factor TFIIH. *Proc. Natl Acad. Sci. USA* **109**, 1949–1954 (2012).
193. Chang, W. H. & Kornberg, R. D. Electron crystal structure of the transcription factor and DNA repair complex, core TFIIH. *Cell* **102**, 609–613 (2000).
194. Schultz, P. *et al.* Molecular structure of human TFIIH. *Cell* **102**, 599–607 (2000).
References 193 and 194 showed the electron crystal structure of the yeast core TFIIH and the human TFIIH complex, respectively.
195. Rabut, G. *et al.* The TFIIH subunit Tfb3 regulates cullin neddylation. *Mol. Cell* **43**, 488–495 (2011).
196. Guzder, S. N., Sung, P., Prakash, L. & Prakash, S. Nucleotide excision repair in yeast is mediated by sequential assembly of repair factors and not by a pre-assembled repairosome. *J. Biol. Chem.* **271**, 8903–8910 (1996).
197. Matsui, T., Segall, J., Weil, P. & Roeder, R. Multiple factors required for accurate initiation of transcription by purified RNA polymerase II. *J. Biol. Chem.* **255**, 11992–11996 (1980).
198. Samuels, M., Fire, A. & Sharp, P. A. Separation and characterization of factors mediating accurate transcription by RNA polymerase II. *J. Biol. Chem.* **257**, 14419–14427 (1982).
199. Sawadogo, M. & Roeder, R. Interaction of a gene-specific transcription factor with the adenovirus major late promoter upstream of the TATA box region. *Cell* **43**, 165–175 (1985).
200. Reinberg, D. & Roeder, R. G. Factors involved in specific transcription by mammalian RNA polymerase II. Purification and functional analysis of initiation factors IIB and IIE. *J. Biol. Chem.* **262**, 3310–3321 (1987).
201. Buratowski, S., Hahn, S., Guarente, L. & Sharp, P. A. Five intermediate complexes in transcription initiation by RNA polymerase II. *Cell* **56**, 549–561 (1989).
202. Conaway, J. W., Hanley, J. P., Garrett, K. P. & Conaway, R. C. Transcription initiated by RNA polymerase II and transcription factors from liver. Structure and action of transcription factors epsilon and tau. *J. Biol. Chem.* **266**, 7804–7811 (1991).
203. Perissi, V. & Rosenfeld, M. G. Controlling nuclear receptors: the circular logic of cofactor cycles. *Nature Rev. Mol. Cell Biol.* **6**, 542–554 (2005).

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Competing interests statement
The authors declare no competing financial interests.

FURTHER INFORMATION
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ERRATUM

TFIIH: when transcription met DNA repair

Emmanuel Compe and Jean-Marc Egly

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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.