Review TRENDS in Genetics Vol.22 No.8 August 2006

When transcription and repair meet: a complex system

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Transcription-coupled repair (TCR) is a mechanism that removes DNA lesions so that genes can be transcribed correctly. However, the sequence of events that results in a DNA lesion being repaired remains elusive. In this review, we illustrate the potential chain of events leading to the elimination of the damaged DNA and the proper resumption of transcription. We focus on the roles of CSA and CSB proteins, which, when mutated, impair TCR. Defective TCR is one of the features of Cockayne syndrome, a DNA-repair disorder.

Disturbing transcription

DNA damage occurs constantly from various sources, either endogenous (generated by cellular metabolism) or exogenous (e.g. genotoxic chemicals, ionizing radiation and UV irradiation). Guaranteeing the stability of the genetic information and maintaining the gene sequence intact is one of the priorities of the cell, which has developed a variety of DNA-repair mechanisms enabling proper transcription and replication.

DNA lesions can disturb transcription in different ways, in addition to blocking the elongating RNA polymerase. As a consequence of DNA-damage, caused by UV irradiation, and crosslinking agents, such as cisplatin, the cell can shut down the transcription process completely [1], probably to enable repair of damaged DNA. Therefore, accurate transcription relies on the efficiency of DNA repair, because the RNA polymerase cannot bypass the lesion. Nevertheless, a decrease in the level of transcription might directly or indirectly result in a deficiency of some components of the basal transcriptional machinery. For example, the crosslinking agent cisplatin might disturb the wrapping of the DNA around the nucleosome, influencing in part the arrival of some chromatin remodelling factors that are necessary for transcription. As another example, TBP, a TATA-box-binding factor, exhibits a strong affinity for the 'kink' induced by the DNA lesion [2,3]. It is found sequestered at sites of DNA damage, and is therefore unavailable for transcription by RNA polymerase II (RNA Pol II) [4]. Similarly, cisplatin adducts inhibit rRNA synthesis by RNA Pol I, by hijacking the human upstream binding transcription factor (hUBF) [5] and reducing the amount of hUBF available to bind to the promoter. Furthermore, there are some variations in the cellular concentration of the hypo-phosphorylated RNA Pol II (RNA Pol IIA) that decrease after UV irradiation [6], probably reflecting either an accumulation of hyperphosphorylated RNA Pol II (RNA Pol IIO) [7] at the site of the UV-induced lesion and/or a defect in recycling RNA Pol IIO, which affects resumption of transcription. We also observed a decrease in both forms (i.e. hypo- and hyperphosphorylated RNA Pol II), which is associated with a defect in transcription initiation [8], in group B cells from patients with Cockayne syndrome (a DNA-repair disorder).

Overall, downregulating transcription would prevent new rounds of transcription on damaged genes, so that new elongating RNA Pol II would not interfere with the RNA Pol II that is stalled in front of the damage and engaged in the repair process. The fate of the stalled RNA Pol IIO remains one of the major enigmas in how the cell reacts to damaged DNA.

An overview of transcription-coupled repair

Although lesions can interfere with transcription and therefore allow time for DNA repair, there are situations where transcription might be necessary for DNA repair. For example, it was first shown that the DNA sequence corresponding to the dihydrofolate reductase (*DHFR*) gene was repaired much faster than DNA sequences elsewhere in the genome [9]. It was later observed that there was a dramatic difference in the efficiency of removal of UV-induced pyrimidine dimers (CPD) between the transcribed and non-transcribed strands of *DHFR* [10]. These observations led to the characterization of the transcription-coupled repair (TC-NER) mechanism in which repair of damage on the transcribed strand relies on ongoing transcription. In mammalian cells, the inhibition of RNA Pol II transcription elongation by α-amanitin inhibits TC-NER [11], whereas in yeast, a temperature-sensitive allele of the catalytic subunit of RNA Pol II inhibits transcription and thus TC-NER [12]. However, further investigations of repair rates along the promoter and transcribed sequences of the human *JUN* gene after UV irradiation revealed rapid repair of both transcribed and non-transcribed DNA strands near the transcription initiation site [13]. Such an increased rate of repair in the promoter area could be attributed to the binding of transcriptional activators that induce a local ATP-dependent chromatin remodelling, which facilitates not only the positioning of the transcription pre-initiation complex but also (when required) the accessibility of the

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Available online 23 June 2006

 0168-9525/$ - see front matter doi:10.1016/j.tig.2006.06.006

DNA-repair machinery to the lesion [14]. It thus seems that the rapid repair of lesions in a transcribed gene relies on at least two mechanisms: (i) the first involving a local rearrangement of the chromatin that would permit the access of repair factors in the vicinity of promoter sequences and then facilitate the arrival of the transcription machinery; and (ii) the second mechanism occurs only in the presence of a stalled elongating RNA Pol II. The first leads to faster repair of both strands, whereas the second leads to the faster repair of lesions only in the transcribed strand.

The chromatin remodelling activities associated with the pre-initiation stage of transcription is a mechanism that we define as transcription-associated repair and does not rely on the elongation process. This mechanism will not be discussed in this review. However, TC-NER implies a specific process dealing with the stalled elongating RNA Pol II that requires accessory factors. There is likely to be a link between TC-NER and chromatin remodelling. However, a relationship between DNA damage and histone phosphorylation has been demonstrated. Histone modification, or the damage itself, is responsible for the association of chromatin-modifying complexes near the damage site that can change the chromatin structure to enable the repair machinery to gain access to the damaged lesion [15,16]. Proteins that remodel chromatin include ATP-dependent modifiers such as SWI/SNF histone acetyl transferases and/or p300/CBP.

TC-NER partners and mediators

Biochemical defects in the specific repair of transcribed gene sequences are found in cells from patients with rare inherited syndromes, such as Cockayne syndrome (CS), xeroderma pigmentosum (XP), combined xeroderma pigmentosum and Cockayne syndrome (XP/CS), and trichothiodystrophy (TTD). Phenotypes associated with XP, XP/CS and TTD arise from mutations in different genes involved in two NER pathways: global genome nucleotide excision repair (GG-NER) [17] and TC-NER. However, cells from CS patients are characterized by mutations in *CSA* and *CSB* genes, which are involved in TC-NER.

In GG-NER, a DNA lesion is recognized by the XPC–HR23B (the human rad23 homologue) complex, probably helped *in vivo* by XPE (also called UV-DDB2 [18]). The association of XPC with HR23B enables the recruitment of TFIIH, the subunits of which (XPB, XPD, p8/TTD-A) promote an opening around the DNA lesion in an ATP-dependent manner [17,19]. The complex is further stabilized by XPA [19], and the single strand (ss) DNA regions created are then bound and protected by RPA. Next, the two endonucleases XPG and XPF-ERCC1 are recruited onto the damaged open structure leading to a cut on both 3′ and 5′ sides of the lesion. The resulting damaged-incised patch is then removed and the gap filled by a DNA resynthesis reaction involving proliferating cell nuclear antigen (PCNA), replication protein C (RFC) and DNA polymerase δ and ε [17,20–23]. Five of the seven proteins involved in GG-NER are also part of the TC-NER pathway (Table 1): TFIIH, XPA, replication protein A (RPA), XPG and XPF-ERCC1. XPE [24] and XPC–hHR23B [25] are not involved in TC-NER because cells derived from patients harbouring mutations in XPC and XPE can still perform TC-NER, whereas GG-NER is either reduced or completely absent [21,18].

In TC-NER, a model is proposed in which the elongating RNA Pol II would initiate TC-NER by triggering the recruitment of NER factors necessary for the removal of the damage, a role devoted to XPC in GG-NER (Figure 1). However, how and when the DNA-repair factors are recruited to enable the elongating RNA Pol II to read the gene accurately is not clearly understood. Indeed, the repair reaction has to deal not only with the lesion but also with the stalled RNA Pol II, which could interfere with the repair machinery. Therefore, in addition to the common chromatin remodelling and DNA-repair factors, TC-NER will need other specific factors to deal with complex containing RNA Pol II and the blocking lesion.

Investigations in cells derived from CS patients or from XP patients that have a partial CS phenotype led to the identification of the specific TC-NER factors, CSA and CSB [26,27] and also underlined the role of the XPB and XPD subunits of TFIIH in addition to XPG in TC-NER [28]. Other factors such as mms19 [29–32] and XAB2 [33] were also found to be associated with a molecular defect in the TC-NER pathway.

Does CSB have a specific role in TC-NER?

In *Escherichia coli*, the coupling mechanism between transcription and repair is mediated by *mfd*, the mutation frequency decline protein which, in addition to recruiting the repair factors, can release the stalled RNA Pol II [34]. The duality of the role of *mfd* is important, because simply displacing RNA Pol II from the template without recruiting the repair factors would also lead to a defect

Table 1. The main nucleotide excision repair proteins[a]

Gene	Repair mechanism	Associated disorder	Function
XPC	GG–NER	XP	DNA binding
XPE(*DDB2*)	GG–NER	XP	DNA binding–E3–ubiquitin ligase
XPB	GG–NER and TC–NER	TTD, XP/CS	Helicase 3′–5′
XPD	GG–NER and TC–NER	XP, TTD, XP/CS	Helicase 5′–3′
XPA	GG–NER and TC–NER	XP	Damage verification
RPA	GG–NER and TC–NER		ssDNA binding
XPG	GG–NER and TC–NER	XP, XP/CS	3′ exonuclease
XPF	GG–NER and TC–NER	XP	5′ exonuclease
CSB (also known as *ERCC6*)	TC–NER	CS	DNA–dependent ATPase and chromatin remodelling
CSA (also known as *ERCC8*)	TC–NER	CS	E3 ubiquitin ligase

Abbreviations: GG–NER, global genome nucleotide excision repair; TC–NER, transcription–coupled nucleotide excision repair; XP, xeroderma pigmentosum; TTD, trichothiodystrophy; CS, Cockayne syndrome; XP/CS, combined xeroderma pigmentosum and Cockayne syndrome.

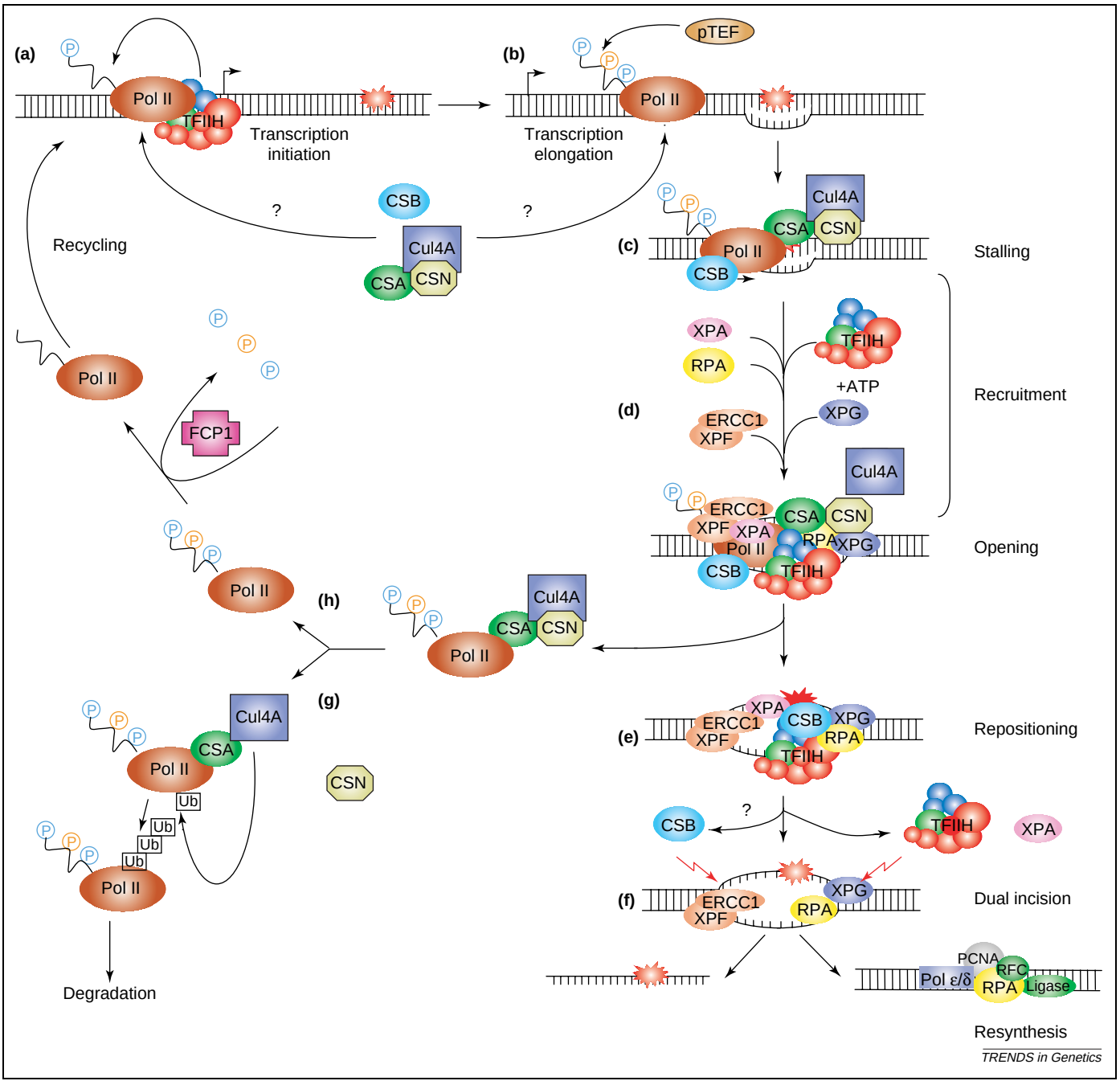

Figure 1. A TCR model. Once the pre-initiation complex is formed, **(a)** the addition of ATP initiates the synthesis of the first phosphodiester bond and the phosphorylation of RNA Pol IIA by TFIIH signals transcription elongation (promoter escape). **(b)** Next RNA Pol IIO phosphorylation and activity is regulated by the combined action of other kinases, such as pTEFb and FCP1 phosphatase. CSB and the CSA complex (containing the Cul4A ubiquitin ligase) can both interact with the two forms of the RNA Pol II and might therefore be recruited either during the initiation step or during the elongation step of transcription. **(c)** After UV irradiation, the elongating RNA Pol IIO is arrested in front of a damage lesion on the transcribed DNA strand. CSN is recruited to the CSA complex and inhibits the ubiquitin activity of the CSA complex so that it does not prematurely degrade the stalled RNA Pol IIO. **(d)** In the meantime, CSB might push RNA Pol IIO forward, providing it with sufficient time to recruit the repair factors in a sequential manner. **(e)** Once the repair complex has assembled around the lesion, RNA Pol IIO might be released, whereas CSB probably helps reposition the repair complex. **(f)** The removal of the lesion is carried out the same way as GG-NER because they share common factors for this step. Once released, RNA Pol IIO can either **(g)** be degraded by the CSA complex, which has lost its inhibitory partner CSN, or **(h)** be recycled after dephosphorylation by FCP1.

in TC-NER. It was shown that *mfd* promotes forward translocation of RNA Pol II when a block in the template is encountered [35]. This translocation is likely to transform the RNA Pol II complex into a more open state that facilitates the access of downstream DNA to the repair factors.

In recent years, human CSB and the yeast rad26, the homologue of CSB, which were thought to be the eucaryotic counterparts of *mfd* have been the focus of much research. CSB is a member of the SWI/SNF2 family of DNA-dependent ATPases, and contains seven conserved helicase motifs. Members of SWI/SNF chromatin remodelling factors have a role in DNA repair by increasing the accessibility of the lesion in the mononucleosome core particle [36]. Photobleaching studies have shown that CSB, as part of a large complex, transiently interacts with the transcription machinery to verify that RNA synthesis occurs properly. This

interaction is prolonged following transcription arrest induced by DNA damage, probably reflecting the engagement of CSB in TC-NER [37]. This supports a hypothesis in which CSB would travel along with the RNA Pol II starting from the initiation site and/or transiently binds to the elongating RNA Pol II when needed. Indeed, CSB was shown to interact with proteins that function in transcription and/or DNA repair, such as histones [38], XPG [39], transcription activator p53 [39–42], hypo-and hyper-phosphorylated RNA pol II, together with TFIIE and TFIIH transcription factors [40,43,44].

As a function of the DNA damage-induced distortion, the elongating RNA Pol II is either forced forward to bypass the lesion so that it can continue transcription or is blocked. Therefore, it seems that, depending on the type of lesion, CSB can contribute to the behaviour of RNA Pol II. CSB can help RNA Pol II to bypass oxidative DNA damage [45,46], but with some miss-incorporations (S. Feuerhahn, unpublished data). For example, in a UV- induced blocking lesion, CSB might induce the addition of one nucleotide to the nascent transcript by the stalled RNA Pol II, underlining its possible role as an elongation factor [47–49].

Moreover, the ability of CSB to push the RNA Pol II forward might reflect a mechanism that provides sufficient energy to RNA Pol II to bypass the lesion. If the bypass does not occur it might provide enough time for the stalled RNA Pol II to recruit NER and/or TC-NER-specific factors. It is unclear how the DNA-repair factors bind to the stalled RNA Pol IIO: on the one hand, CSB has been shown to be absolutely required to recruit TFIIH onto the RNA Pol II [50]; on the other hand, we have observed a CSB-independent recruitment of the NER factors onto the RNA Pol IIO [51]. Although this issue requires further investigation, we cannot exclude the possibility that CSB could also participate in the remodeling of RNA Pol II-repair factors-DNA damage interface to position the repair complex correctly around the lesion [51]. Although no helicase activity was found in a classical DNA strand-displacement assay [43], the 'CSB helicase and/or ATPase' could effectively displace the bound proteins from their nucleic acid tracks during remodelling of the chromatin structure [38,52], leading to a repositioning and/or a (partial) release of some TC-NER components.

CSB might not be restricted to TC-NER in human cells. It is possible that CSB acts as a 'general auxiliary repair (and perhaps a transcription) factor'. CS cells are sensitive to other DNA-damaging agents than UV light, such as 4-nitroquinoline-1-oxide (4-NQO) [53–55], ionizing radiation and γ-irradiation [54], which induce oxidative damage and ssDNA breaks. In addition, OGG1 DNA glycosylase [56] and PARP-1 [57], two factors involved in base excision repair (BER) were also found in complexes containing CSB, suggesting the involvement of CSB in other DNA-repair mechanisms. Although the repair for 6–4PPs photoproducts (from UV-radiation) and the N-(deoxyguanosin-8-yl)-2-acetylaminofluorene (dG-C8-AAF) adduct [from N-acetoxy-2-acetylaminofluorene (NA-AAF) treatment] occurs without strand bias, the overall repair rate of these lesions by GG-NER is delayed in CS cells compared with that observed in wild-type cells [58,59]. In these conditions, CSB might affect the chromatin conformation of both active genes and those throughout the genome, enabling the efficient repair of different types of lesions.

The fate of the stalled RNA Pol II

The fate of the stalled RNA Pol II, which needs to be discriminated from the paused RNA Pol II, which can either resume transcription by itself or with the help of specific transcription elongation factors is of considerable interest (see Ref. [60]). Which of the following reactions condition and initiate the repair process: backtracking, ubiquitylation, phospho/dephosphorylation or release and recycling? An RNA Pol II that stalled at a UV-induced CPD was shown *in vitro* to block the access of photolyase (a bacterial repair protein) to the lesion [49]. Therefore, the stalled RNA Pol II, which has recruited DNA-repair factors, also needs to be displaced; this enables the repair factors to be positioned correctly to remove the damage, thus allowing transcription to resume. However, CSB is not capable of disrupting the ternary complex RNA Pol IIO–RNA–DNA [43]. This role could be partially fulfilled by a rearrangement of the NER complex once it has assembled around the RNA Pol II, along with CSB (and perhaps CSA) and additional unknown factor(s) [51]. Although the human transcription factor release II (HuF2) has been shown to dissociate RNA Pol II that is stalled at CPDs, its involvement in TC-NER has not been thoroughly investigated [61].

One fact is certain: after exposure to UV irradiation or treatment by cisplatin, a fraction of RNA Pol IIO is ubiquitylated [62]. The UV-induced ubiquitylation and subsequent degradation of RNA Pol IIO could prevent it from being recycled, and might explain the cellular decrease of RNA Pol II [63], and the decrease in transcription. However, we cannot rule out the possibility that the stalled RNA Pol II is recycled by specific phosphatases, such as FCP1 [64,65]. Interestingly, in CS cells, although the UV-induced ubiquitylation of RNA Pol II does not occur properly [66], the UV-induced degradation rates of RNA Pol II were not significantly altered compared with those of wild-type cells [7], suggesting that ubiquitylation and the subsequent degradation of RNA Pol II are two separate mechanisms. Together, these data have led to the hypothesis that degradation is not necessary to remove RNA Pol II from the damaged site or to trigger TC-NER. Recent data have shed light on the mechanism of ubiquitylation of RNA Pol II. Only phosphorylation at serine 2 of the carboxyl terminal domain (CTD) of largest subunit of RNA Pol II, a hallmark of the elongating RNA Pol IIO, can lead to ubiquitylation of RNA Pol II, which increases in arrested or stalled RNA Pol II [67]. This suggests that ubiquitylation has a potential role in regulating the events following transcriptional arrest, perhaps by promoting the recruitment of co-factors (DNA-repair- or elongation factors). Interestingly, the 19S regulatory subunit of the proteasome, which has a proteolysis-independent function, has been shown to have a role in transcription [68].

A putative role of CSA in TCR

CSA is found in different protein complexes that contain RNA Pol II [69,70]; it interacts with CSB (at least *in vitro* [26]), XAB2 and TFIIH [26,33]. Although CSA and CSB do not co-localize *in vivo*, they might transiently interact with each other. CSA can be part of a complex containing the cullin-based ubiquitin E3 ligase (in addition to DDB1, Cul4A and Roc1), which is regulated by the COP9 signalosome complex (CSN), a multiprotein complex of the ubiquitin-proteasome pathway (for a review, see Ref. [71]). A CSA complex containing CSN does not have ubiquitin ligase activity. Hypophosphorylated RNA Pol II was also found in the CSA complex, suggesting that it is incorporated into the transcription pre-initiation complex and travels along the DNA strand with RNA Pol II during elongation. Nevertheless, after UV irradiation, the CSA complex could accumulate on RNA Pol IIO stalled at the UV-induced lesion and subsequently recruit CSN, leading to downregulation of ubiquitin ligase E3.

Therefore, the CSA–CSN complex would prevent early degradation of the stalled RNA Pol IIO and preserve the integrity of factors necessary for TC-NER. It is likely that TC-NER occurs independently of the RNA Pol II proteolysis pathway [72]. This is consistent with a model in which CSB pushes a blocked RNA Pol IIO forward in the vicinity of the lesion, enabling the recruitment of the repair factors (Figure 1). In yeast, rad26 can be found in a complex together with Def1 [73]. Although Def1 is not required for TC-NER *per se*, both proteins could act in concert as a back-up rescue mechanism. Rad26 might protect RNA Pol II from degradation after UV irradiation, whereas Def1 might be required for ubiquitylation and the subsequent degradation of RNA Pol II, presumably when the damage cannot be rapidly repaired by the rad26-dependent TCR pathway.

Concluding remarks

The coupling between transcription and repair directed by several TC-NER-specific factors requires a set of actions that probably involve chromatin remodelling, recruitment of a repair complex, recycling and/or ubiquitylation of RNA Pol II. CSB and CSA seem to be the key players in TC-NER, although their exact functions have not been identified. The broad range in type and severity of CS phenotypes and the lack of clear genotype–phenotype relationships [74–76] imply that CSB also has a role in other pathways. Indeed, although mutations in CS proteins prevent TC-NER from functioning correctly, mutations in XP genes (with the exception of XPC and XPE) cause a defect in both the TC-NER and GG-NER of UV-induced lesions without exhibiting the severe developmental and neurological defects associated with CS. Although CSB truncated polypeptides generated by some mutations could interfere with the different processes in which wild-type CSB is involved, a complete absence of the CSB protein, found in one CS patient, leads to UV-sensitive syndrome (UVsS). The clinical manifestations of UVsS are acute sunburn, photosensitivity, skin dryness, freckles in some cases, pigment anomalies and telangiectasia but no abnormalities in physical and neurological development [77].

However, it is clear that unravelling what lays beneath the CS phenotypes would require the complete understanding of the biochemical function of the CS proteins and their key roles in other mechanisms.

Acknowledgements

We thank our colleagues, especially Vincent Mocquet, for sharing their results and for useful discussions. This study was supported by funds from La Ligue contre le Cancer (equipe labelisée, contract N°EL2004), the Ministere de l'Education National et de la Recherche for ACI grants (BCMS N°03 2 535) and the GIS-Maladies Rares. J.P.L. is supported by grants from the Association pour la Recherche contre le Cancer (ARC) and the Fondation pour La Recherche Medicale (FRM).

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Genetics conferences in autumn 2006

British society for human genetics: annual conference
18-20 September 2006
York, UK
http://www.bshg.org.uk/york2006.htm

Dynamic organization of nuclear function
27 September - 1 October 2006
Cold Spring Harbor Laboratory, NY, USA
http://meetings.cshl.edu/meetings/nucleus06.shtml

Molecular genetics of aging
4-8 October 2006
Cold Spring Harbor Laboratory, NY, USA
http://meetings.cshl.edu/meetings/aging06.shtml

American society of human genetics: annual meeting
9-13 October 2006
New Orleans, LA, USA
http://www.ashg.org/genetics/ashg/menu-annmeet.shtml

Genes, brain/mind and behaviour
3-4 November 2006
EMBL Heidelberg, Germany
http://www.embl.org/aboutus/sciencesociety/conferences/2006/scope06.html

Pharmacogenomics
15-18 November 2006
Cold Spring Harbor Laboratory, NY, USA
http://meetings.cshl.edu/meetings/pharm06.shtml