The Cellular Response to Transcription-Blocking DNA Damage

Lea H. Gregersen¹ and Jesper Q. Svejstrup¹,*

In response to transcription-blocking DNA lesions such as those generated by UV irradiation, cells activate a multipronged DNA damage response. This response encompasses repair of the lesions that stall RNA polymerase (RNAP) but also a poorly understood, genome-wide shutdown of transcription, even of genes that are not damaged. Over the past few years, a number of new results have shed light on this intriguing DNA damage response at the structural, biochemical, cell biological, and systems biology level. In this review we summarize the most important findings.

The Transcription-Related DNA Damage Response
Cells respond to DNA damage in a variety of ways, including stalling of the cell cycle, initiation of DNA repair, and regulation of transcription, translation, and the ubiquitin–proteasome system to contend with the challenge. However, depending on the nature of the DNA lesion, cells react differently at the level of transcription. For example, double-stranded DNA (dsDNA) breaks appear to mostly result in localized interruption of transcription around the site of DNA breakage [1] while most base damage appears to be largely ignored, resulting mainly in temporary pausing of elongating RNAP (see, e.g. [2]). By contrast, DNA lesions such as those generated by UV irradiation or by chemical modification such as a platinum adduct not only form a blockade of ‘local’ RNAP progression when they occur in the transcribed strand, but also elicit global shutdown of transcription. Understanding how cells respond to such transcription-blocking lesions comprises one of the last important frontiers in DNA repair research.

Transcription-Syndrome Group B Proteins Play Critical Roles in TC-NER
Transcription-coupled nucleotide excision repair (TC-NER) is unique in that it is initiated via the recognition of RNAP rather than by DNA lesions (see Table 1 for an overview of repair factors). Indeed, UV-induced and bulky lesions in the transcribed strand constitute a strong barrier to forward RNAP translocation and result in polymerase stalling/arrest [3–6]. The bulk of RNAP effectively shields the DNA lesion from recognition by DNA damage-binding factors [4,7], explaining why RNAP, rather than the DNA lesion, is the focal point of TC-NER. Interestingly, the initial discovery of TC-NER was made in mammalian cells [8,9] and only later extended to bacteria [10] and yeast [11]. While the molecular details of TC-NER are likely to vary somewhat between the different domains of life, there are also surely many similarities, and a description of the process in bacteria, yeast, and mammalian cells is therefore relevant to the building of working models for the process.

TC-NER in Escherichia coli
In bacterial NER, the UvrA (see Glossary) subunit of the UvrAB complex recognizes the DNA lesion. This is followed by subunit exchange, with UvrC replacing UvrA. UvrC then cleaves the DNA on each side of the lesion, generating an excision product that is removed by UvrD helicase, followed by gap filling and ligation [12]. Transcription intrinsically inhibits repair [13].

¹Mechanisms of Transcription Laboratory, The Francis Crick Institute, 1 Midland Road, London NW1 1AT, UK

*Correspondence: jesper.svejstrup@crick.ac.uk (J.Q. Svejstrup)
but bacteria use Mfd (also known as TRCF) to perform TC-NER. Mfd is a DNA translocase that recognizes RNAP and translocates it forward, resulting in polymerase dissociation when its path is blocked by DNA damage [14]. Mfd then recruits the basic NER machinery through direct interaction with UvrA and repair of the damage proceeds as outlined above [15]. This was until recently believed to be the main or only way in which transcription-blocking lesions are removed in E. coli. Interestingly, a recent report by Nudler and colleagues indicates that UvrD can bind RNAP and use its ATPase activity to translocate the polymerase backward on DNA, exposing the DNA lesion and allowing the general NER machinery to gain access [16]. So, besides removing the incised DNA oligonucleotide after NER, UvrD may also contribute to an early step of TC-NER [17]. It may be relevant to mention that Selby and Sancar have questioned the importance of this new role of UvrD in bacterial TC-NER [18,19].

In a broad sense, Mfd is the functional analog of human CSB and budding yeast Rad26, while the role of UvrD—at least in terms of removing the incised, lesion-containing oligonucleotide—is performed by TFIIH in eukaryotes. These eukaryotic proteins are described in more detail below.

**TC-NER in the Yeast Saccharomyces cerevisiae**

Much of the progress in understanding TC-NER has been based on cellular assays, several of them developed in budding yeast. In these approaches, lesion removal in the transcribed strand (TS) is compared with that in the non-transcribed strand (NTS) at nucleotide resolution across a gene region [20]. Using such methods it has been shown that mutation of the gene encoding the TC-NER factor Rad26 specifically decreases the repair rate in the TS [21]. Interestingly, deletion of RPB3, encoding an RNAPII subunit, also affects TC-NER, and cells lacking both *RAD26* and *RPB3* are much more TC-NER defective and also UV sensitive (while the single mutants are not) [22], suggesting functional redundancy between RNAPII and Rad26 in TC-NER.

Somewhat surprisingly, *RAD26* is dispensable for TC-NER in certain contexts. In the absence of the gene encoding the conserved elongation factor Spt4, or with certain mutations in Spt5 (Spt4’s essential partner), TC-NER is restored in rad26 cells [23,24]. Mutations in other genes encoding RNAPII subunits or elongation factors also restore TC-NER in *rad26* cells [22,25]. These data are important as they suggest that Rad26 is not required for the TC-NER reaction *per se* and underscore the important role played by the RNAPII elongation complex itself in determining repair efficiency.

A number of different models, which are not necessarily mutually exclusive, may explain the role of Rad26 in TC-NER. One possibility is that another protein can substitute for Rad26. In this respect it is interesting that yeast Sen1 has recently been shown to play a role in TC-NER that is distinct from that of Rad26 [26]. Alternatively, efficient and processive transcriptional elongation may represent a particular threat to genome stability in the presence of transcription-blocking DNA damage, and Rad26 would in this model help prevent RNAPII elongation complexes reaching, or becoming irreversibly arrested at, such lesions. In this scenario transcription elongation efficiency is reduced when Spt4/Spt5 or certain other elongation factors are absent, thus eliminating the need for Rad26.

Interestingly, Xu *et al.* recently used a biochemical approach combined with cryoelectron microscopy to investigate Rad26 function [5]. Their structure reveals that Rad26 binds to DNA upstream of RNAPII, dramatically altering the DNA path. It also suggests that Rad26’s translocase activity promotes forward movement of RNAPII by pulling DNA toward itself while...
positioned on the upstream side of the polymerase. This does not result in appreciable dissociation of RNAPII, or read-through, at DNA damage. However, Rad26 can push RNAPII through other obstructions, such as a poly-A tract or a polyamide bound to DNA [5]. These findings confirm and greatly expand on earlier studies showing that the human Rad26 counterpart CSB also fails to dissociate RNAPII from DNA damage but can push the polymerase forward, toward the DNA lesion [6].

Somewhat frustratingly, these new data do little to explain how forward RNAPII movement might be helpful for TC-NER. Interestingly, however, inspection of recent structures of the RNAPII-DSIF (Spt4/Spt5) complexes [27,28] suggests that the Rad26–RNAPII interaction (and thus presumably the CSB–RNAPII interaction) is incompatible with concomitant RNAPII–Spt4/Spt5 interaction. It is thus an intriguing possibility that Rad26 (CSB) may use its DNA translocase activity to move close to RNAPII, dislodging Spt4/Spt5 from the immovable, damage-stalled polymerase (Figure 1). As Spt4/Spt5 normally stabilizes the elongation complex to favor forward translocation, such displacement (and subsequent Rad26/CSB dissociation) might allow the RNAPII elongation complex to backtrack away from the lesion to allow subsequent repair factor recruitment and DNA repair, potentially helping explain why Rad26 is dispensable for TC-NER in cells lacking Spt4/Spt5 function.

TC-NER in Mammalian Cells

Although the basic principles of TC-NER are likely to be conserved from yeast (and bacteria) to mammalian cells, it is clear from the factor requirements that there are notable differences (Table 1). For example, Cockayne syndrome A (CSA) and UVSSA are required for the process in human cells [29–33] but do not have obvious functional homologs in yeast or bacteria. Likewise, CSB has a functionally important ubiquitin-binding domain (UBD) that appears to be absent in Rad26 [34]. Moreover, as outlined above, and in contrast to prokaryotic Mfd, eukaryotic CSB and Rad26 are unable to dislodge damage-stalled RNAPII from DNA [5,6], suggesting that the polymerase is either removed from DNA by other means or backtracked a significant distance away from the damage so that DNA repair and subsequent gap filling can occur. Interestingly in this context, TC-NER reconstitution experiments showed that an RNAPII-covered DNA lesion can be repaired in a CSA-stimulated manner and that RNAPII may be displaced from the DNA in an ATP-dependent but CSA-independent manner, likely by TFIH [35]. TC-NER in these reconstitution assays occurred in the absence of CSA and UVSSA and thus they do not precisely reflect the factor requirements in vivo, but they nevertheless expose important, basic properties of the reaction. These results also potentially take on a new significance in light of the abovementioned data indicating that bacterial TC-NER analogously requires ATP- and UvrD-stimulated removal of RNAPII from the site of the DNA lesion so that the damage can be accessed [16]. An outline model for mammalian TC-NER is presented in Figure 1.

Although the importance of CSA for TC-NER has been known for decades, insight into its precise function is limited. CSA is the substrate-recognition component of an E3 ubiquitin ligase complex, named CRL4, that can also use DDB2 or other proteins as separate substrate-recognition subunits [36]. One function of the CRL4DDB2 complex is to ubiquitylate XPC upon UV-irradiation. XPC is important for general genome repair (GG-NER) but not for TC-NER (Box 1). It is recruited to DNA damage by the DDB1–DDB2 complex, and XPC function and turnover at such sites is regulated at least partly via CRL4DDB2-mediated ubiquitylation [37]. It is potentially telling that, while DDB2 affects GG-NER only, its counterpart CSA is specifically required for TC-NER and is functionally tightly connected to CSA. Indeed, CSA is ubiquitylated in a CRL4CSA-dependent manner [38]. CUL4DDB2–XPC and CUL4CSA–CSB may thus represent miRNA (microRNA): small noncoding RNA molecules (around 22 nucleotides) found in plants, animals, and some viruses that function in RNA silencing and post-transcriptional regulation of gene expression.

PRC1 (polycomb repressive complex 1): transcriptional repressor complex containing subunits such as BMI1.

R loop: a three-stranded nucleic acid structure in genes comprising a DNA:RNA hybrid and the associated non-template single-stranded DNA (ssDNA).

Sent (splicing endonuclease 1): an ATPase-helicase; homolog of the human senataxin protein.

snRNPs (small nuclear ribonucleoprotein): RNA–protein complexes of at least five different kinds (U1, U2, U4, U5, and U6) that combine with RNA and other proteins to form a spliceosome, responsible for splicing of pre-mRNA.

Spt4/Spt5 (transcription elongation factor): conserved transcription elongation factor, named DSIF (DBR sensitivity inducing factor) in human cells.

SWI/SNF (switch/sucrose non-fermentable): a chromatin remodeling complex and founding member of a large group of DNA translocases.

SYT9 (synaptotagmin 9): member of a large group of proteins that regulate membrane trafficking.

TBP (TATA-binding protein): general transcription factor that binds specifically to the TATA box found about 30 base pairs upstream of the transcription start site in some eukaryotic promoters.

TFIH (general RNAPII transcription factor H): general transcription and repair factor required for both transcription and NER.

UBR5 (ubiquitin protein ligase E3 component n-recogin3): ubiquitin ligase of the HECT family.

USP7 (ubiquitin-specific protease 7): deubiquitylating enzyme with many substrates.

Uvr (ultraviolet repair): several Uvr genes exist in Escherichia coli.

UVSSA (UV-stimulated scaffold protein A): mutated in UV-sensitivity syndrome.

Xeroderma pigmentosum (XP): human repair disorder caused by mutations in XP-A, –G, and –V.
### Table 1. NER and Transcription-Repair Coupling Factors

| Mammals          | Yeast | Bacteria (analogous) | Catalytic activity |
|------------------|-------|----------------------|--------------------|
| **NER factors**  |       |                      |                    |
| XPA              |       |                      |                    |
| DNA damage verificaion and scaffold for recruitment of other NER factors |       |                      |                    |
| **TFIIH**        |       |                      |                    |
| Comprises two subcomplexes, a ‘core’ comprising six subunits (XPB, P62, P52, P44, P34, and P8) and a three-subunit kinase comprising CDK7, cyclin H, and MAT1; the core and kinase subcomplexes are bridged by the XPD subunit |       |                      |                    |
| XPD (ERCC2)      |       |                      |                    |
| Promotes opening of DNA around the lesion; DNA damage verification | Rad3  | UvrD                 | 5’–3’ helicase/ATPase/translocase |
|                  |       |                      |                    |
| XPB (ERCC3)      |       |                      |                    |
| Promotes opening of DNA around the lesion | Rad25 (Ssl2) | UvrD                 | 3’–5’ helicase/ATPase |
|                  |       |                      |                    |
| TTDA, P8 (GTF2H5) |       |                      |                    |
| Stimulates the ATPase activity of XPB | Ttd5  |                      |                    |
|                  |       |                      |                    |
| P62 (GTF2H1)     |       |                      |                    |
|                  | Ttd1  |                      |                    |
| P52 (GTF2H4)     |       |                      |                    |
|                  | Ttd2  |                      |                    |
| P44 (GTF2H2)     |       |                      |                    |
|                  | SSL1  |                      |                    |
| P34 (GTF2H3)     |       |                      |                    |
|                  | Ttd4  |                      |                    |
| CDK7             |       |                      |                    |
|                  | Kin28 |                      |                    |
| Cyclin H         |       |                      |                    |
|                  | Cct1  |                      |                    |
| MAT1             |       |                      |                    |
|                  | Tfd3  |                      |                    |
| RPA              |       |                      |                    |
| Binds ssDNA revealed after unwinding | Rpa   |                      |                    |
| XPG              |       |                      |                    |
| Cleaves damaged strand downstream of lesion | Rad2  | UvrC                 | Endonuclease        |
|                  |       |                      |                    |
| XPF–ERCC1        |       |                      |                    |
| Cleaves damaged strand upstream of lesion | Rad10–Rad1 | UvrC                | Endonuclease        |
| **TC-NER factors** |       |                      |                    |
| CSB (ERCC6)      |       |                      |                    |
| Recognizes damage-stalled RNAP II on upstream side; promotes forward movement of RNAP II | Rad26 | TRCF/Mfd             | Translocase         |
|                  |       |                      |                    |
| CSA (ERCC8)      |       |                      |                    |
| Part of the E3 ubiquitin ligase complex CLR4 | Not found | Not found |                    |
| Required for recruitment of UVSSA to CSB |       |                      |                    |
| UVSSA            |       |                      |                    |
| Promotes stabilization of CSB | Not found | Not found |                    |
| USP7             |       |                      |                    |
| Deubiquitylates CSB | Not found | Not found | Ubiquitin protease |
| **GG-NER factors** |       |                      |                    |
| XPC              |       |                      |                    |
| Recognizes helix-distorting lesions | Rad4  | UvrA?                |                    |
|                  |       |                      | Recognizes DNA damage together with UvrB |

**References:**

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functionally related enzyme–substrate constellations required for GG-NER and TC-NER, respectively. Both XPC and CSB also appear to be deubiquitylated by USP7 [30,39,40] (see below) and regulated by SUMOylation [37,41], further underscoring the analogies (Figure 2).

CSB contains a UBD. Without this UBD, CSB can still be recruited to DNA damage and is capable of assembling a TC-NER complex, but no DNA incision/repair occurs [34]. The precise molecular function of CSB’s UBD remains unclear, but one possibility is that it recognizes a ubiquitin moiety added by CRL4<sup>CSA</sup> in either CSB or another protein. Interestingly, CSB is normally very dynamically associated with DNA damage sites but CSB lacking the UBD is slow to dissociate from such lesions [34]. So, it is possible that CRL4<sup>CSA</sup>-mediated ubiquitylation, and recognition thereof by CSB’s UBD, serves to somehow regulate activity and turn over CSB molecules around sites of RNAPII damage stalling, in a fashion analogous to that suggested for XPC [37,42].

Interestingly in this connection, CSA is required for the recruitment of UVSSA to CSB after DNA damage [40] and UVSSA appears to be required for CSB stability [29–31,40]. In the absence of UVSSA, or its interaction partner USP7 [30,40], CSB becomes markedly degraded upon UV-irradiation. The loss of CSB seems unlikely to underlie the failure of UVSSA-deficient cells to perform TC-NER, as CSB overexpression cannot suppress the effect [30]. Importantly, the ubiquitin protease USP7 might work with UVSSA to deubiquitylate CSB and suppress its degradation. It is tempting to speculate that CSB ubiquitylation has not evolved to bring about its proteolysis but rather to regulate its function. In this scenario, dynamic, spatiotemporal (mono)ubiquitylation/deubiquitylation of CSB would be required to activate/inactivate or regulate the association/dissociation of the protein through the multistep TC-NER process (Figure 1). Conceivably, an early step in this process could require ubiquitylation while a later one requires deubiquitylation of the same, engaged CSB protein.

**Degradation of RNAPII**

DNA damage-induced ubiquitylation occurs not only on CSB but also on a large number of other proteins, including RNAPII, which is modified at numerous sites in the largest subunits [43–45]. At least some of these ubiquitylation events result in RNAPII degradation, which is likely to be a last-resort mechanism when TC-NER fails. The details of the last-resort mechanism

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**Table 1. (continued)**

| Mammals | Yeast | Bacteria (analogous) | Catalytic activity |
|---------|-------|----------------------|-------------------|
| DDB1–DDB2 complex (XPE) | Not found | Not found | |
| Recognizes DNA lesion directly, kinks the DNA to provide recognition by XPC; also part of the CRL4 E3 ubiquitin ligase complex | | | |

**Gap filling (DNA replication)**

| Protein | Yeast | Bacteria (analogous) | Catalytic activity |
|---------|-------|----------------------|-------------------|
| Proliferating cell nuclear antigen (PCNA) | Pcna/Pol3/Pol2 | | |
| DNA clamp, processivity factor for DNA Pol | Rfc | | |
| Replication factor C (RFC) | | | |
| Clamp loader | | | |
| DNA Pol δ/ε | DNA Pol δ/ε | DNA Pol I | DNA Pol |
| DNA Pol δ/ε (Polδ, Polε) | | | |
| DNA ligase 1 | DNA ligase 1 (Cdc9) | Ligase | DNA ligase |
**Figure 1. Models for Transcription-Coupled Nucleotide Excision Repair (TC-NER).**

1. After RNAPII stalls at a transcription-blocking lesion, CSB is recruited. CSB’s precise role is unclear, but it may remodel the stalled RNAPII complex, for example to dislodge elongation factors such as Spt4/Spt5 (also called DSIF in humans). To make space for NER, RNAPII must be either completely removed from DNA or backtracked. Importantly, if backtracking occurs it is likely to be by as much as 30–40 nucleotides due to the space requirements of RNAPII, repair factors, and the gap-filling DNA polymerase (DNA Pol) on DNA. Such backtracking might require CSB dissociation and could conceivably be facilitated by TFIIH. Repair factors (and probably DNA Pol) are recruited. DNA incisions are made by ERCC1–XPF and XPG and removal of lesion-containing ssDNA oligonucleotides is performed by TFIIH. (3) DNA gap filling, dissociation of NER factors, and marking of chromatin with γH2AZ. (4) Transcript cleavage and forward translocation, probably stimulated by factors such as ELL. A number of unanswered issues about the molecular details of the process are listed on the right. Note that the DNA characteristics of RNAPII and NER (footprint, melted DNA, excised oligo, etc.) are drawn to scale wherever possible. However, nucleosomes, as well as the dramatic bending of DNA in the elongation complex, are omitted for simplicity.
Box 1. Mammalian NER Factors

In GG-NER [87], the DNA lesion is recognized by the DDB1–DDB2 complex and XPC. The DDB1–DDB2 complex (DDB2 is also known as XPE) binds directly to the UV-induced lesion and stimulates the association of XPC, which in turn binds to DNA opposite the lesion causing local helix distortion. This provides a substrate for TFIIH binding and lesion verification. The two TFIIH helicase subunits XPB and XPD are required to simulate the opening of the DNA around the lesion. By contrast, in TC-NER [87] the lesion is recognized indirectly by CSB binding to stalled RNAPII elongation complexes (Figure 1). CSA, UVSSA, and USP7 promote ubiquitination and deubiquitilation of CSB, respectively, to regulate the reaction. The mechanisms of DNA incision and subsequent gap filling are the same in GG-NER and TC-NER [87]. TFIIH promotes the binding of XPA to ssDNA–dsDNA junctions. XPA is involved in damage verification and serves as a scaffold for NER factors. FPA binds the exposed ssDNA. The structure-specific endonuclease XPF–ERCC1 heterodimer (which cuts 5' of the lesion) and XPG (which cuts 3' of the lesion) are recruited by XPA. TFIIH binds and displaces the excised ssDNA oligonucleotide containing the damage and the ssDNA gap of 22–30 nt is then filled by DNA Pol δ or DNA Pol ε and sealed by DNA ligase 1.

Figure 2. Analogous Regulation of Transcription-Coupled Nucleotide Excision Repair (TC-NER) and General Genome Repair (GG-NER) by Ubiquitin. CSB and XPC are specific for TC-NER and GG-NER, respectively. CT-NER and TC-NER pathways regulate their function. The CRL4 ubiquitin ligase complex is required for their ubiquitylation but uses CSA and DDB2, respectively, as targeting subunits. Unsurprisingly, CSA and DDB2 are also known to be specifically required for TC-NER and GG-NER, respectively. Likewise, USP7 is required for deubiquitylation of both, which in the case of CSB is likely to occur through its interaction with a targeting subunit, UVSSA. Abbreviation: ub, ubiquitin. See text for details.

have recently been reviewed [46] and are not outlined in detail here. It is, however, important to underscore that there is a very close connection between transcription, TC-NER, and RNAPII ubiquitylation. Thus, defects in the TC-NER pathway or in transcription can have significant consequences for RNAPII ubiquitylation and degradation [47]. While CSA (CRL4CSA) is not directly involved in RNAPII ubiquitylation/degradation, cells lacking CSA (or CSB) nevertheless have defects in RPB1 degradation [48], at least partly because the transcription response to DNA damage is altered in these cells [49]. Moreover, while RNAPII degradation is not required for TC-NER [46], it is not inconceivable that RNAPII ubiquitylation (perhaps as a non-degradative signaling event) does play a role in the process. Finally, RNAPII ubiquitylation (and degradation) can occur in response to a number of events that halt transcript elongation [46], making it imperative to explore the mechanism in detail before making conclusions on causative connections between DNA damage, DNA repair/transcription factors, and RNAPII ubiquitylation.
CSB in Transcriptional Regulation and Disease

CSB deficiency results in lack of TC-NER and in Cockayne syndrome (CS), but this does not signify that TC-NER deficiency underlies CS a severe neurological disorder [50] (Box 2). If a causal relationship existed, mutation of the basal NER genes (most of which are also absolutely required for TC-NER) would be expected to give rise to the same severe disease. Instead, deficiency in these factors gives rise to xeroderma pigmentosum (XP), a relatively milder disease, with a high incidence of skin cancer. Likewise, UVSSA is required for TC-NER (but not GG-NER), yet mutations in this gene give rise to an even milder disease, UV-sensitivity syndrome (UV^S^) [29,31].

It is important to remember that CSB is part of the SWI/SNF family of ATP-dependent chromatin remodelers [51]. Chromatin remodeling by purified CSB was demonstrated in vitro long ago [52], but it has only recently been shown that CSB also affects chromatin structure in vivo [53]. This may help explain why CSB-deficient cells show altered expression at thousands of genes, also in the absence of DNA damage [54–56]. A striking molecular hallmark of CS versus XP is the marked change in gene expression rather than DNA repair, as also evidenced by the dramatic consequences for transcription of XPD mutations that result in combined CS/XP disease compared with others in the same gene that result only in XP [56]. Importantly, CSB

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Box 2. Syndromes Associated with Defects in GG-NER and TC-NER

**XP**

XP is caused by general defects in NER, with seven complementation groups (XP–A to–G; Table 1) and an XPV variant caused by defective translesion DNA synthesis. XP patients are extremely photosensitive and have a 1000-fold increase in susceptibility to skin and eye cancer. In addition, exposure to sun leads to freckle-like pigmentation in all XP patients. The severity of the symptoms varies between patients and around a third of XP patients also display neurological deficiencies, characterized by microcephaly, hearing loss, and progressive cognitive impairment that is likely to be caused by transcription deficiencies [88].

**CS**

CS patients are characterized by short stature, wrinkled skin, sunken eyes, large ears, a pointed nose, and prematurely thin and grey hair. Although CS is first and foremost a neurodevelopmental disorder, patients also suffer from severe, progressive neurological degeneration. Neurological symptoms include hearing loss, cataracts, retinal dystrophy, mental retardation, and progressive ataxia. CS patients are photosensitive but do not develop marked pigmentation defects and do not have an increased frequency of skin cancer. Some mutations, in XPB, XPD, or XPG, result in combined CS–CS. See main text for details.

**Trichothiodystrophy (TTD)**

TTD is characterized by sulfur deficiency, brittle hair and nails, short stature, and intellectual impairment. Approximately half of TTD patients are photosensitive, but they do not develop pigmentation defects and do not have the predisposition to skin cancer observed in XP patients. Some TTD patients also have neurological symptoms, including microcephaly and dysmyelination. TTD is caused by mutations in the two helicases XPB and XPD and in GTF2H5 (TTDA), which are all subunits of TFIIH (see Table 1 in main text). TTD mutations interfere with TFIIH’s function in transcription [88,89], which is likely to explain the different clinical outcome compared with XP.

**UV^S^**

UV^S^ patients are photosensitive but do not display any of the developmental symptoms present in CS and some XP patients. UV^S^ is caused by a lack of functional UVSSA, as well as specific mutations in CSA and CSB. UV^S^ is likely to be caused by impaired TC-NER. The milder UV^S^ symptoms compared with CS are likely to be explained by the additional involvement of the CS protein in transcription regulation. It is unclear why certain mutations in CSA and CSB lead to UV^S^ while others result in CS, but these might affect TC-NER more than transcription.
affects the expression of an unexpectedly large number of neuronal genes. Cellular reprogramming of CS fibroblasts to cells with neuron-like features is defective and neuroblastoma cells depleted for CSB show defects in neuronal gene expression and fail to differentiate and extend neurites [54,57]. Crucially, CSB function can be partially bypassed by overexpression of specific CSB target genes, most notably SYT9 [58], which controls the release of neurotrophins such as BDNF, which is in turn important for neuronal differentiation and synaptic modulation. Strikingly, addition of BDNF, or pharmacological mimics such as amitriptyline, can compensate for CSB deficiency during neuronal differentiation, and SYT9 and BDNF are downregulated in CS patient brain tissue [58], indicating that suboptimal induction of neurotrophin-regulated gene expression programs, rather than DNA repair deficiency, underlies most neurological defects in CS.

It is worth underscoring, however, that CS is a complex disorder and it is thus likely that some of its other symptoms are caused by TC-NER defects, just as it has been argued that defects in mitochondrial biology and oxidative DNA damage repair may also play a role [59].

The Transcription Response to UV Irradiation

UV-induced DNA damage in mammalian cells triggers the activation of some transcription factors and increases the half-life of p53 [60]. However, although individual genes are consequently highly upregulated by DNA damage, transcription across the rest of the genome is essentially shut down, as measured by a dramatic general reduction in the level of newly synthesized RNA [45,61–63]. Reduced RNA synthesis is sustained for several hours and normal transcription levels are fully restored only 24–48 h after UV exposure [64,65]. One of the identifying characteristics of CS cells is their effect on transcription restart: these cells are unable to recover significant gene expression after DNA damage [63].

Genome-wide measurements of repair kinetics indicate that (6-4) photoproducts are generally repaired quickly (within 4 h) while cyclobutane pyrimidine dimers (CPDs) require 12–48 h for complete removal, even in transcribed regions [66]. At first glance this could indicate that transcription shutdown is merely a consequence of DNA lesions blocking RNAPII progress and that restart occurs when repair has been completed. However, several lines of evidence indicate that shutdown is not simply a consequence of the physical blocking of RNAPII progress by DNA lesions but that it must also be mediated by signalling in trans. Extracts from UV-irradiated human cells have little transcription activity in vitro even on undamaged DNA templates [61] and transfection of an undamaged gene reporter into UV-irradiated cells fails to show significant expression levels until transcription restart occurs in endogenous genes as well [62]. Recent data indicate that merely the transfection of a UV-irradiated plasmid into undamaged cells is sufficient to elicit at least some aspects of the DNA damage response; namely, those related to co-transcriptional mRNA splicing [67].

Recent work shows that transcription shutdown and restart occur in several phases (Figure 3), with transcript elongation slowing already within 10–25 min of UV irradiation while transcriptional initiation is also inhibited shortly afterward [65]. This coincides with the release of promoter-proximal RNAPII [65,68] and almost complete, global loss of the hypophosphorylated form of RNAPII, which is likely to be due to rapid hyperphosphorylation [61,69]. Transcriptional initiation recovers more quickly than elongation, which continues to be slow for many hours [61,64,65,70]. Moreover, transcription appears to be “spatially restricted” for long periods, with the promoter-proximal 20–25 kb showing much more activity than the areas further downstream in genes after DNA damage [64,65,68] (Figure 3). This may help explain the striking observation that virtually all genes induced by DNA damage are short [71]: only short
genes can be highly expressed after UV irradiation. It has been suggested that the release of RNAPII into the gene body might serve as a ‘sensor’ of DNA lesions [68], in that the shift from promoter-proximally paused to slowly elongating RNAPII might allow the TC-NER machinery to rapidly recognize and signal DNA damage when polymerases stall there.

Unsurprisingly, the dramatic change in transcript elongation after UV irradiation has consequences for co-transcriptional RNA-processing reactions such as splicing and termination. For example, UV irradiation leads to increased inclusion of certain ‘weak’ cassette exons, at least partly due to a decrease in elongation rates [72]. However, recent results indicate that splicing is also affected by depletion of certain snRNP spliceosomal proteins from chromatin following
UV-induced damage. The mechanism underlying such displacement remains unclear, but it requires active transcription, is specific for transcription-blocking lesions, and is enhanced by the checkpoint kinase ATM [73]. Examples of UV- and ATM-dependent mRNA splicing are observed and, curiously, ATM is itself activated by R loops. The combination of transcriptional elongation inhibition, R loops, and ATM activation was proposed to form a positive feedback loop that triggers loss of specific splicesomal proteins and thus a change in mRNA splicing on UV irradiation [73]. Intriguingly, another recent report shows that UV-induced CPDs can also result in the activation of ATR-dependent mechanisms, which likewise feed into mRNA splicing [67]. Thus, transcription-obstructing DNA damage elicits a complex cellular response that affects cassette exon splicing, at least partly via DNA damage checkpoint kinases [67,73].

The dramatic changes in transcript elongation and spatial restriction on transcription also result in a marked change in mRNA polyadenylation site selection and transcriptional termination after UV irradiation [65]. This is expressed as a change in alternative last exon (ALE) splicing and results in examples of upregulation of much shorter transcript isoforms, which may at least in some cases function as stable RNAs. The involvement of RNA in the DNA damage response is covered in more detail below.

**Factors Affecting Genome-Wide Transcription Changes**

Several factors involved in chromatin remodeling have been implicated in the shutdown of transcription after UV irradiation. For example, the histone deacetylases (HDACs) SIRT1 and HDAC1 are recruited to several damage-repressed genes [56,74]. Likewise, changes in RNAPII phosphorylation [61] and DNA binding by TBP [75] have been proposed to play a role. More recent evidence suggests that the sequence-specific transcription factor ATF3 is also involved. ATF3 is a transcriptional repressor that is upregulated by DNA damage and that binds to the promoter region of a sizeable fraction of genes repressed by DNA damage (i.e., hundreds of genes) [74]. ATF3 recruits HDACs to repress transcription locally. One important role for CSB outside TC-NER is to counteract the repressive function of ATF3. ATF3-repressed genes such as DHFR take on the characteristics of facultative heterochromatin in CSB-deficient cells [56] and this can be at least partly counteracted by ATF3 depletion [74].

While ATF3 is clearly important for the repression of specific target genes after UV irradiation, the mechanism underlying repression of the rest of the genome is less clear. Recently, it was reported that the E3 ubiquitin ligase UBR5 mediates transcriptional repression in response to UV downstream of the PRC1 component BMI1 [76]. One possible target of the UBR5 E3 ligase was proposed to be the SPT16 component of the FACT complex, a histone chaperone [76]. However, this pathway for damage-induced transcriptional repression requires further investigation.

Unsurprisingly, a number of chromatin factors promoting efficient transcription have been implicated in allowing transcriptional restart after DNA damage. For example, the histone methyltransferase DOT1L [77] and the histone chaperones FACT [78] and HIRA [79] affect the ability of cells to restart transcription after UV irradiation. Moreover, the elongation factor ELL has also been shown to play a role [80]. Deficiency in any factor required for normal restart of transcription after UV irradiation would be expected to result in damage sensitivity; surprisingly, however, while cells with knockdown of DOT1L, FACT, and ELL display UV sensitivity, cells with robust HIRA knockdown do not [79].
The Role of RNA in the Transcription-Related DNA Damage Response

While UV irradiation affects RNA processing, a number of recent papers have shown that RNA pathways in turn affect the cellular response to DNA damage. For example, UV-induced changes in ALE splicing result in upregulation of an RNA isoform, expressed from the ASCC3 gene, that acts as a long noncoding RNA (lncRNA) rather than a protein-coding mRNA [65]. Interestingly, two distinct ASCC3 isoforms have opposite effects on transcription after DNA damage. The protein-coding ASCC3 mRNA encodes the 250-kDa helicase component of the ASC complex [81]. Upon knockdown of ASCC3 or other ASC complex members, cells show elevated levels of transcription 20 h after UV irradiation. By contrast, knockdown (or CRISPR knockout) of the alternative ASCC3 IncRNA transcript, which is normally upregulated by UV irradiation, has the opposite effect: this IncRNA is required to allow normal restart of transcription [65]. Intriguingly, the two ASCC3 isoforms crosstalk: in the absence of the mRNA isoform, the requirement for the IncRNA isoform is markedly reduced. The biochemical mechanisms underlying the functions of the different ASCC3 isoforms remain to be investigated.

Beyond lncRNAs, a role for small noncoding RNA, or the proteins connected to it, has been suggested by the finding that proteins involved in miRNA processing also impact the response to UV irradiation [82–84]. Depletion of either Drosha or its interacting partner DGCR8 thus results in UV sensitivity. UV-induced phosphorylation of DGCR8 at serine 152 is required for the removal of DNA lesions and restart of transcription after UV irradiation [82]. Surprisingly, DGCR8’s RNA-binding, and its Drosha interaction domains, are not required for this role, indicating that DGCR8’s function in the UV response is distinct from that in the miRNA pathway with Drosha. Likewise, an miRNA-independent function has been reported for Dicer to promote chromatin condensation in response to UV irradiation [84]. It remains unclear which RNA species, if any, are important for this response. The recruitment of Dicer to chromatin after UV irradiation is dependent on RNA, whereas the RNA-binding domains of DGCR8 are not required for DGCR8 function in this pathway [82]. The mechanisms underlying the intriguing UV sensitivity observed following Dicer, Drosha, and Ago2 depletion remain to be addressed.

Finally, a recent study found that RNA is extremely rapidly m^6A methylated (within 2 min) by METTL3 in response to UV irradiation [85]. Remarkably, de-methylation by FTO is also rapid, so that m^6A methylations levels have already returned to normal by 8 min after UV irradiation. Lack of METTL3 nevertheless results in delayed DNA repair, slow transcription restart, and UV sensitivity. UV-induced m^6A RNA modification does not affect the recruitment of typical NER factors such as XPA and TFIIH, but results in recruitment of DNA polymerase k (Pol k) to DNA damage sites. Such recruitment is physiologically important as Pol k overexpression is sufficient to suppress the effects of METTL3 depletion. Pol k has previously been shown to play a role in NER, with its recruitment ~30 min after UV irradiation being dependent on XPA [86]. By contrast, the almost immediate m^6A methylation-dependent recruitment of Pol k to lesions is XPA independent. The biochemical mechanisms requiring fast Pol k recruitment remain unclear, but one possibility is that it allows lesion bypass at genes that are being transcribed at the time of DNA damage induction (i.e., they possess nascent RNA for modification by METTL3 in the vicinity of the replicating DNA Pol), so that the replication machinery can clear such damage and allow rapid repair (by TC-NER, presumably). In any case, the two-stage involvement of Pol k in the response to UV-induced DNA damage deserves further investigation.
Concluding Remarks and Future Perspectives
The molecular mechanism of TC-NER has been elusive for several decades, but it seems a fair bet that most, if not all, of the factors required for it have now been uncovered. Therefore, a future challenge is to uncover the precise schedule of events required to remove a transcription-blocking lesion. How is RNAPII moved out of the way for DNA repair? What is the precise role of CSB? Is it required only to prepare the affected area (i.e., the chromatin, the lesion-stalled RNAPII, and/or the proteins associated with it) for the subsequent repair process or is CSB also actively involved in the repair reaction itself? What is the molecular role of CSA-mediated ubiquitination/deubiquitination and of CSB’s UBD? These are key questions that may require biochemical reconstitution or the development of new tools for in vivo discovery (see Outstanding Questions). Likewise, what are the mechanisms and factors responsible for the dramatic shutdown of transcription genome wide after UV irradiation? How is repressin activated and then inactivated to allow transcription to recover? Finally, a fascinating and unexpected role for stable RNAs in the global regulation of transcription after DNA damage has been uncovered. Some of the processes and factors have been identified, but what is their precise mechanism of action? The next few years are certain to bring new exciting findings in this rapidly evolving field.

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References
1. Shankhog, N.M. et al. (2010) ATM-dependent chromatin changes silence transcription in cis to DNA double-strand breaks. Cell 141, 970–980
2. Charaf-Berguerand, N. et al. (2006) RNA polymerase II bypass of oxidative DNA damage is regulated by transcription elongation factors. EMBO J. 25, 5481–5491
3. Donahue, B.A. et al. (1994) Transcript cleavage by RNA polymerase II arrested by a cyclobutane pyrimidine dimer in the DNA template. Proc. Natl. Acad. Sci. U. S. A. 91, 8502–8506
4. Brueckner, F. et al. (2007) CPD damage recognition by transcribing RNA polymerase II. Science 315, 859–862
5. Xu, J. et al. (2017) Structural basis for the initiation of eukaryotic transcription-coupled DNA repair. Nature 551, 653–657
6. Selby, C.P. and Sanzar, A. (1997) Human transcription-repair coupling factor CSS/ERCC6 is a DNA-stimulated ATPase but is not a helicase and does not disrupt the ternary transcription complex of stalled RNA polymerase II. J. Biol. Chem. 272, 1885–1890
7. Tomaletti, S. et al. (1999) Structural characterization of RNA polymerase II complexes arrested by a cyclobutane pyrimidine dimer in the transcribed strand of template DNA. J. Biol. Chem. 274, 24124–24130
8. Mellon, L. et al. (1997) Selective removal of transcription-blocking DNA damage from the transcribed strand of the mammalian DHFR gene. Cell 51, 241–249
9. Bohr, V.A. et al. (1985) 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
10. Mellon, L. and Hanawalt, P.C. (1989) Induction of the Escherichia coli lactose operon selectively increases repair of its transcribed DNA strand. Nature 342, 95–98
11. Smerdon, M.J. and Thoma, F. (1990) Site-specific DNA repair at the nucleosome level in a yeast minichromosome. Cell 61, 675–684
12. Sancar, A. and Reardon, J.T. (2004) Nucleotide excision repair in E. coli and man. Adv. Protein Chem. 69, 43–71
13. Selby, C.P. and Sanzar, A. (1995) Transcription preferentially inhibits nucleotide excision repair of the template DNA strand in vivo. J. Biol. Chem. 265, 21330–21336
14. Park, J.S. et al. (2002) E. coli transcription repair coupling factor (Mfd protein) rescues arrested complexes by promoting forward transcription. Cell 109, 757–767
15. Selby, C.P. and Sanzar, A. (1993) Molecular mechanism of transcription-repair coupling. Science 260, 53–58
16. Epstein, V. et al. (2014) UvrD facilitates DNA repair by pulling RNA polymerase backwards. Nature 505, 372–377
17. Paré, B. and Nuñez, E. (2017) Mechanistic insights into transcription-coupled DNA repair. DNA Repair (Amst.) 56, 42–50
18. Adembal, O. et al. (2017) Mfd translocase is necessary and sufficient for transcription-coupled repair in Escherichia coli. J. Biol. Chem. 292, 18386–18391
19. Adembal, O. et al. (2017) Genome-wide transcription-coupled repair in Escherichia coli is mediated by the Mfd translocase. Proc. Natl. Acad. Sci. U. S. A. 114, E2116–E2125

Outstanding Questions
How is the stalled elongation complex recognized by CSB and the TC-NER machinery?
Can elongation complexes stalled at DNA lesions be distinguished from stalled RNAPII elongation complexes at non-lesion sites and if so, how?
Does ‘remodeling’ of RNAPII elongation complexes occur after UV irradiation? If so, is it necessary to remove elongation factors before TC-NER? Do elongation factors counteract TC-NER in mammalian cells as in yeast? Is the elongation complex merely backtracked away from the lesion or is it taken off the DNA altogether?
What is the functional role of CSB ubiquitination? Does it allow spatial and temporal regulation of CSB protein turnover or activity when associated with stalled RNAPII complexes? What is the precise role of CSA and UVSSA?
Which factors are required for global transcriptional shutdown? How are they activated by DNA damage? What is the signal that operates in trans to slow transcriptional elongation globally and how is it spread and restricted?
What is the role of the ASCS3 lncRNA isoform? Do the multiple other short transcript isoforms that are preferentially expressed after UV irradiation also play functional roles in the DNA damage response?
What is the role in the DNA damage response of short RNA species and the protein machinery that processes them?
42. Sugawara, K. et al. (2005) UV-induced ubiquitylation of XPC protein mediated by UV–DDI–ubiquitin ligase complex. Cell 121, 387–400
43. Povlsen, L.K. et al. (2012) Systems-wide analysis of ubiquitylation dynamics reveals a key role for PAF15 ubiquitylation in DNA-damage bypass. Nat. Cell Biol. 14, 1089–1098
44. Gia, A.E. et al. (2015) Quantitative proteomic atlas of ubiquitination and acetylation in the DNA damage response. Mol. Cell 59, 867–881
45. Boeng, S. et al. (2016) Multicentric analysis of the UV-induced DNA damage response. Cell Rep. 15, 1587–1610
46. Wilson, M.D. et al. (2013) Ubiquitylation and degradation of elongating RNA polymerase II: the last resort. Biochim. Biophys. Acta 1829, 151–157
47. Woudstra, E.C. et al. (2002) A Rad26–Def1 complex coordinates repair and RNA Pol II proteolysis in response to DNA damage. Nature 415, 929–933
48. Brignam, D.B. et al. (1998) UV-induced ubiquitylation of RNA polymerase II: a novel modification deficient in Cockayne syndrome cells. Proc. Natl. Acad. Sci. U. S. A. 93, 11586–11590
49. Anindya, R. et al. (2007) Damage-induced ubiquitylation of human RNA polymerase II by the ubiquitin ligase Nad44, but not Cockayne syndrome proteins or BRCA1. Mol. Cell 28, 386–397
50. Bonke, P.S. (2013) Blinded by the UV light: how the focus on transcription-coupled NER has distracted from understanding the mechanisms of Cockayne syndrome neurologic disease. DNA Repair (Amst.) 12, 656–671
51. Clapier, C.R. and Cairns, B.R. (2009) The biology of chromatin remodeling complexes. Annu. Rev. Biochem. 78, 273–304
52. Citterio, E. et al. (2000) ATP-dependent chromatin remodeling by the Cockayne syndrome B DNA repair–transcription-coupling factor. Mol. Cell. Biol. 20, 7643–7653
53. Cho, I. et al. (2013) ATP-dependent chromatin remodeling by Cockayne syndrome protein B and NAP1-like histone chaperones is required for efficient transcription-coupled DNA repair. PLoS Genet. 9, e1003407
54. Wang, Y. et al. (2014) Dysregulation of gene expression as a cause of Cockayne syndrome neurologic disease. Proc. Natl. Acad. Sci. U. S. A. 111, 14454–14459
55. Newman, J.C. et al. (2006) Cockayne syndrome group B protein (CSB) plays a general role in chromatin maintenance and remodeling. Proc. Natl. Acad. Sci. U. S. A. 103, 9613–9618
56. Velez-Cruz, R. et al. (2013) Sirt1 suppresses RNA synthesis after UV irradiation in combined xeroderma pigmentosum group D/Cockayne syndrome (XP-D/CS) cells. Proc. Natl. Acad. Sci. U. S. A. 110, E212–E220
57. Caffardini, F. et al. (2014) The Cockayne syndrome B protein is essential for neuronal differentiation and neurotogenesis. Cell Death Dis. 5, e1268
58. Wang, Y. et al. (2016) Pharmacological bypass of Cockayne syndrome B function in neuronal differentiation. Cell Rep. 14, 2554–2561
59. Schibye-Knutd, M. et al. (2013) Mitochondrial deficiency in Cockayne syndrome. Mech. Ageing Dev. 134, 275–283
60. Henri, P. et al. (1984) The mammalian UV response: mechanism of DNA damage induced gene expression. Adv. Enzyme Regul. 24, 381–395
61. Rocka, D.A. et al. (2000) UV-induced inhibition of transcription involves repression of transcription initiation and phosphorylation of RNA polymerase II. Proc. Natl. Acad. Sci. U. S. A. 97, 10503–10508
62. Proietti-De-Santis, L. et al. (2006) Cockayne syndrome B protein regulates the transcriptional program after UV irradiation. EMBO J. 25, 1915–1923
63. Mayne, L.V. and Lehmann, A.R. (1982) Failure of RNA synthesis to recover after UV irradiation: an early defect in cells from individuals with Cockayne’s syndrome and xeroderma pigmentosum. Cancer Res. 42, 1473–1478
64. Andrade-Lima, L.C. et al. (2015) DNA repair and recovery of RNA synthesis following exposure to ultraviolet light are delayed in long genes. Nucleic Acids Res. 43, 2744–2756
65. Williamson, L. et al. (2017) UV irradiation induces a non-coding RNA that functionally opposes the protein encoded by the same gene. Cell 168, 843–855 e813
66. Adar, S. et al. (2016) Genome-wide kinetics of DNA excision repair in relation to chromatin state and mutagenesis. Proc. Natl. Acad. Sci. U. S. A. 113, E2124–E2133
67. Munoz, M.J. et al. (2017) Major roles for pyrimidine dimers, nucleotide excision repair, and ATR in the alternative splicing response to UV irradiation. Cell Rep. 18, 2868–2879
68. Lavigne, M.D. et al. (2017) Global unleashing of transcription elongation waves in response to genotoxic stress restricts somatic mutation rate. Nat. Commun. 8, 2076
69. Luo, Z. et al. (2017) Ultraviolet radiation alters the phosphorylation of RNA polymerase II large subunit and accelerates its proteasome-dependent degradation. Mutat. Res. 866, 259–274
70. Gyenis, A. et al. (2014) UVB induces a genome-wide acting negative regulatory mechanism that operates at the level of transcription initiation in human cells. PLoS Genet. 10, e1004483
71. McKay, B.C. et al. (2004) Regulation of ultraviolet light-induced gene expression by gene size. Proc. Natl. Acad. Sci. U. S. A. 101, 6582–6586
72. Munoz, M.J. et al. (2009) DNA damage regulates alternative splicing through inhibition of RNA polymerase II elongation. Cell 137, 708–720
73. Tresini, M. et al. (2015) The core spliceosome as target and effector of non-canonical ATM signalling. Nature 523, 53–58
74. Kristensen, U. et al. (2013) Regulatory interplay of Cockayne syndrome B ATPase and stress-response gene ATF3 following genotoxic stress. Proc. Natl. Acad. Sci. U. S. A. 110, E2261–E2270
75. Con, F. et al. (1998) TATA binding protein discriminates between different lesions on DNA, resulting in a transcription decrease. Mol. Cell. Biol. 18, 3907–3914
76. Sanchez, A. et al. (2016) BM1–UBR5 axis regulates transcriptional repression at damaged chromatin. Proc. Natl. Acad. Sci. U. S. A. 113, 11243–11248
77. Oksenykh, V. et al. (2013) Histone methyltransferase DOT1L drives recovery of gene expression after a genotoxic attack. PLoS Genet. 9, e1003611
78. Dinant, C. et al. (2013) Enhanced chromatin dynamics by FACT promotes transcriptional restart after UV-induced DNA damage. Mol. Cell 51, 469–479
79. Adam, S. et al. (2013) Transcription recovery after DNA damage requires chromatin priming by the H3.3 histone chaperone HIRA. Cell 155, 94–106
80. Mourgues, S. et al. (2013) ELL2, a novel TFIH partner, is involved in transcription restart after DNA repair. Proc. Natl. Acad. Sci. U. S. A. 110, 17927–17932
81. Jung, D.J. et al. (2003) Novel transcription coactivator complex containing activating signal convertransor 1. Mol. Cell. Biol. 23, 5203–5211
82. Caires, P.C. et al. (2017) DGCR8 mediates repair of UV-induced DNA damage independently of RNA processing. Cell Rep. 19, 162–174
83. Pothof, J. et al. (2009) MicroRNA-mediated gene silencing mediates the UV-induced DNA damage response. EMBO J. 28, 2090–2099
84. Chitele, S. and Richly, H. (2017) DICER and ZRF1 contribute to chromatin decondensation during nucleotide excision repair. Nucleic Acids Res. 45, 5911–5912
85. Xiang, Y. et al. (2017) RNA m^6A methylation regulates the ultraviolet-induced DNA damage response. Nature 543, 573–576
86. Ogi, T. and Lehmann, A.R. (2008) The Y-family DNA polymerase kappa (Polk) functions in mammalian nucleotide excision repair. Nat. Cell Biol. 8, 640–642
87. Spivak, G. (2015) Nucleotide excision repair in humans. DNA Repair (Amst.) 36, 13–18
88. Singh, A. et al. (2015) TFIH subunit alterations causing xeroderma pigmentosum and trichothiodystrophy specifically disturb several steps during transcription. Am. J. Hum. Genet. 96, 194–207
89. Dubaele, S. et al. (2003) Basal transcription defect disrupts between xeroderma pigmentosum and trichothiodystrophy in XPD patients. Mol. Cell 11, 1633–1646