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# What happens at the lesion does not stay at the lesion: Transcription-coupled nucleotide excision repair and the effects of DNA damage on transcription *in cis* and *trans*

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ABSTRACT

Unperturbed transcription of eukaryotic genes by RNA polymerase II (Pol II) is crucial for proper cell function and tissue homeostasis. However, the DNA template of Pol II is continuously challenged by damaging agents that can result in transcription impediment. Stalling of Pol II on transcription-blocking lesions triggers a highly orchestrated cellular response to cope with these cytotoxic lesions. One of the first lines of defense is the transcription-coupled nucleotide excision repair (TC-NER) pathway that specifically removes transcription-blocking lesions thereby safeguarding unperturbed gene expression. In this perspective, we outline recent data on how lesion-stalled Pol II initiates TC-NER and we discuss new mechanistic insights in the TC-NER reaction, which have resulted in a better understanding of the causative-linked Cockayne syndrome and UV-sensitive syndrome. In addition to these direct effects on lesion-stalled Pol II (effects *in cis)*, accumulating evidence shows that transcription, and particularly Pol II, is also affected in a genome-wide manner (effects *in trans*). We will summarize the diverse consequences of DNA damage on transcription, including transcription inhibition, induction of specific transcriptional programs and regulation of alternative splicing. Finally, we will discuss the function of these diverse cellular responses to transcription-blocking lesions and their consequences on the process of transcription restart. This resumption of transcription, which takes place either directly at the lesion or is reinitiated from the transcription start site, is crucial to maintain proper gene expression following removal of the DNA damage.

The eukaryotic genome is transcribed by different RNA polymerases. These polymerases consist of multiple subunits, are structurally alike and function in a similar manner although they all transcribe a different part of the genome [1]. In this perspective, we will focus on RNA polymerase II (Pol II), the RNA polymerase responsible for transcription of protein-coding genes and synthesis of most non-coding snRNAs and miRNAs [1]. Correct temporal and spatial regulation of gene expression is crucial for proper cell function and homeostasis. To safeguard this, transcription is tightly controlled at almost each step of the dynamic transcription cycle, ranging from initiation, promoter proximal pausing, productive elongation to transcription termination [2,3]. However, the DNA template transcribed by Pol II is compromised on a daily basis by numerous types of DNA damaging factors. Several types of these DNA lesions can block or strongly impede progression of Pol II and are therefore referred to as transcription-blocking lesions (TBLs). If TBLs are not resolved properly, prolonged stalling of Pol II can lead to severely disrupted cellular homeostasis due to absence of newly synthesized RNA molecules or the appearance of mutant RNA molecules [4,5]. In addition, prolonged stalled Pol II induces R-loops and may result in collisions with advancing replication forks [6]. Altogether, these TBLs may result in genome instability, severe cellular dysfunction, premature cell death and senescence [7,8] which finally may result in DNA-damage induced, accelerated aging [9].

## 1. The effects of different transcription blocking lesions on Pol II

TBLs can originate from both endogenous and exogenous sources. The main examples of DNA damage of endogenous origin are by-products of metabolic processes in mitochondria. These reactive oxygen species can for example generate 8,5′-Cyclopurine-2′-deoxynucleosides

*Abbreviations:* Pol II, RNA polymerase II; TC-NER, transcription-coupled nucleotide excision repair; TBLs, transcription-blocking lesions; CPDs, cyclobutane-pyrimidine dimers; CSA, cockayne syndrome protein A; CSB, cockayne syndrome protein B; UVSSA, UV-stimulated scaffold protein A; CRL4, cullin-RING ubiquitin ligases 4; TFIIH, transcription factor II H; ALE, alternative last exon; AS, alternative splicing

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or 8-oxo-7,8-dihydroguanine (8-oxo-G) lesions [10–12]. Damage from exogenous sources which cause TBLs include clinically used chemotherapeutics like cisplatin which causes inter- and intrastrand crosslinks, or ultraviolet (UV) radiation mainly causing 6-4 pyrimidine-pyrimidone photoproducts (6-4PPs) and cyclobutane-pyrimidine dimers (CPDs) [13]. While all these structurally different types of damage can interfere with elongating Pol II [9,14], the stalling is mechanistically different for these diverse types of lesions [15]. For example, Pol II most likely does not stall at 8-oxo-G lesions itself but is affected by base excision repair intermediates after the action of lesion-specific DNA glycosylase, such as OGG1 [16–18]. Cisplatin-induced crosslinks do not pass through the so-called Pol II translocation barrier. This impairs delivery of this bulky lesion to the active site of Pol II and stalls Pol II in front of the lesion [19]. In contrast, UV-induced CPD lesions can pass the translocation barrier and therefore enter the active site of Pol II. This results in direct stalling of Pol II, thereby completely covering the lesion with a 35-nucleotide footprint; 10 nucleotides downstream and 25 nucleotides upstream of the CPD lesion [13,20,21]. These UV-induced CPDs form a stable road block for Pol II, as shown by extreme stability of CPD-stalled Pol II complexes, with half-lives of approximately 20 h *in vitro* [22]. As a consequence of the different effects on elongating Pol II, the diverse types of lesions also trigger different response mechanisms such as transcriptional bypass for cyclopurines or transcription-coupled nucleotide excision repair (TC-NER) for CPDs (Fig. 1) [13,23,24].

In this perspective we will give an overview on how cells cope with TBLs and provide insight in the cell-wide consequences of DNA damage on Pol II and transcription. First we will discuss how cells can efficiently remove TBLs by using the dedicated TC-NER pathway. Furthermore, we will discuss new insights on the consequences of TBLs *in trans*. These effects include both TBL-induced signaling events but also effects of DNA damage on non-lesion stalled Pol II by regulating the transcription cycle or affecting splicing. Finally, we will discuss factors and mechanisms involved in the last crucial step of overcoming the cytotoxic effects of TBLs; restart of transcription.

## 2. Transcription-coupled nucleotide excision repair

The concept of TC-NER was discovered almost three decades ago by the observation that UV-induced DNA damage in an actively transcribed gene was removed faster compared to damage in a non-transcribed genomic region [25,26]. Follow-up studies showed that preferential repair of active genes was specifically observed in the transcribed strand [25,27]. Since the discovery of TC-NER, many factors have been identified that play an important role in removal of TBLs and their discovery resulted in a better understanding of the molecular mechanism of TC-NER.

### 2.1. CSB senses lesion-stalled Pol II and initiates repair

TC-NER is initiated by recognition of lesion-stalled Pol II by the three main TC-NER factors: cockayne syndrome protein A and B (CSA and CSB) and UV-stimulated scaffold protein A (UVSSA) (Fig. 2) [28–30]. CSB is considered to be a master regulator of TC-NER as it plays a key role in recruitment of several proteins to the TC-NER complex. For example, CSB is essential for translocation of CSA to the nuclear matrix [31,32] and recruitment to the TC-NER complex [33]. In addition, CSB, together with CSA, recruits other factors to the TC-NER complex including the pre-mRNA splicing involved protein XAB2, nucleosome binding protein HMGN1 and p300 histone-acetyl transferase [33]. However, the exact mechanism of how this 1493 amino acid long multifunctional CSB protein contributes to the repair of TBLs remained elusive for a long period. While the C-terminal domain of CSB is required for its interaction with Pol II and translocation of CSA to the nuclear matrix [34], the SWI2/SNF2 DNA-dependent ATPase activity located in the central region of CSB was expected to play a crucial role

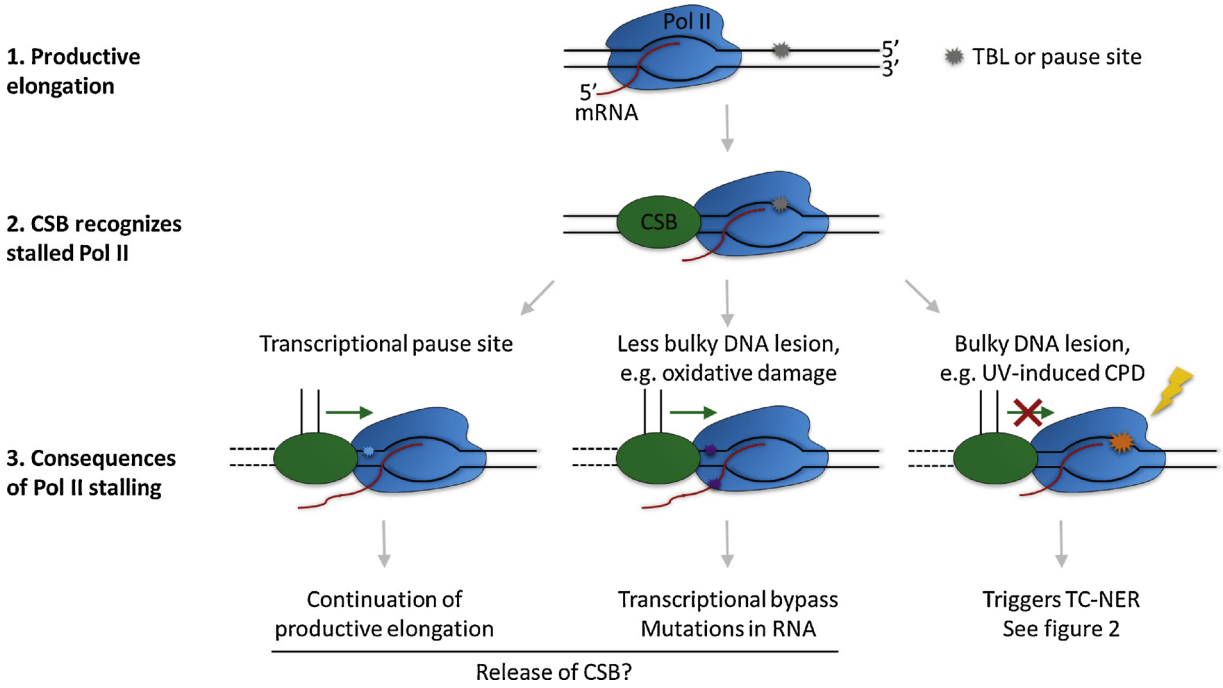


**Fig. 1. CSB probes Pol II for lesion recognition. (1)** During productive elongation Pol II may run into DNA damage or natural occurring pause sequences that consequently impede Pol II forward translocation. **(2)** CSB recognizes and binds stalled Pol II. **(3)** Binding of CSB will result in an 80° bending of the DNA. Consequently, the ATPase activity of CSB is suggested to pull on the template DNA thereby mediating Pol II forward translocation. **(3, left and middle panel)** Translocation can be successful in case of natural occurring pause sites and less bulky DNA lesions, including oxidative damage, resulting in continuation of productive elongation or transcriptional bypass respectively. After the CSB-mediated forward movement, CSB might be released from Pol II. **(3, right panel)** Pol II cannot be translocated over bulky, transcription-blocking DNA lesions like UV-induced CPDs. This unsuccessful forward translocation of Pol II likely increases the residence time of CSB and thereby functions as a trigger for the initiation of TC-NER as illustrated in Fig. 2.

during TC-NER-mediated TBL removal [35] and was shown to mediate chromatin remodeling after UV-induced DNA damage [35–37]. Interestingly, its key function during TC-NER was only recently disclosed by unraveling the structure of the yeast homolog of CSB, Rad26, in complex with lesion-stalled Pol II using cryo-EM studies [38].

This lesion-stalled structure showed that Rad26 binds to DNA upstream of Pol II and the TBL, causing a CSB-mediated 80 ° bending of the extruding DNA. Importantly, the 3′-5′ ATP-dependent translocase activity of Rad 26 pulls the DNA away from Pol II in a similar manner as Snf2, another member of the SWI2/SNF2 ATPase family, pulls DNA from nucleosomes [39]. This "DNA pulling" is suggested to stimulate forward translocation of Pol II over for example naturally occurring pause sites or small blocking lesions (Fig. 1). However, Rad26 cannot translocate Pol II over bulky DNA lesions that lead to a transcription block, like CPDs [38]. This study provides important new insights in the long lasting question how TC-NER, and CSB specifically, could discriminate between normal paused Pol II and TBL-stalled Pol II in such a way that TC-NER is only initiated when needed. Since Rad26 is highly

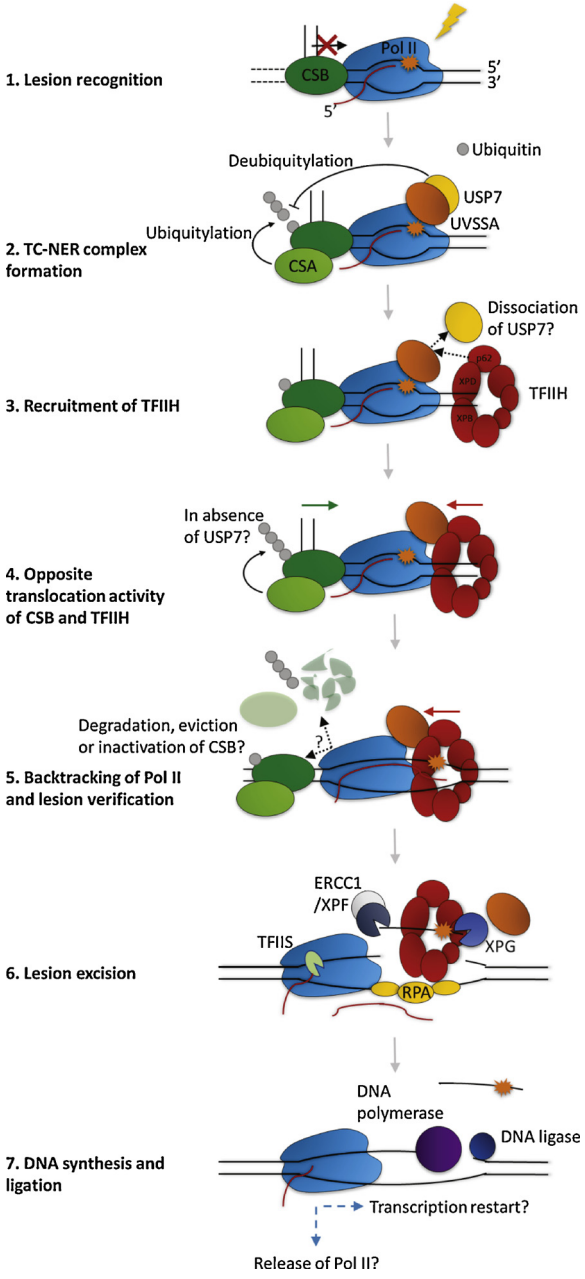


**Fig. 2. A model of transcription-blocking lesion (TBL) removal by transcription-coupled nucleotide excision repair (TC-NER). Step 1,** UV-induced TBLs result in stalling of Pol II and the inability of CSB to forward translocate Pol II. This results in an increased residence time for CSB on Pol II and most likely results in recruitment of the TC-NER factors CSA, UVSSA and USP7. **Step 2,** CSA is part of the CRL4$^{CSA}$ E3 ligase complex and is recruited to the stalled Pol II complex via CSB resulting in polyubiquitylation of CSB. The deubiquitylating enzyme USP7 is recruited to the TC-NER complex by UVSSA and stabilizes CSB via deubiquitylation. **Step 3,** subsequently, TFIIH is recruited, most likely via a direct interaction with UVSSA. As USP7 and TFIIH bind the same domain of UVSSA, TFIIH binding might compete with USP7, resulting in the loss of USP7 activity in the TC-NER complex. **Step 4,** the forward translocating activity of CSB might counteract the reverse translocating helicase activity of the XPB and XPD subunits of TFIIH. To overcome these counteracting forces, either the ATPase activity of CSB needs to be inhibited, or CSB can be degraded or evicted from the TC-NER complex. Increased CSB ubiquitylation due to absence of USP7 might contribute to one of these processes. **Step 5,** due to the loss of CSB or its ATPase activity, TFIIH is able to efficiently reverse translocate (backtrack) Pol II, while at the same time the TFIIH complex verifies the DNA lesion. **Step 6,** following successful Pol II backtracking and damage verification, the DNA lesion is efficiently removed by dual incision of the damaged strand by the ERCC1/XPF and XPG nucleases. RPA binds the undamaged strand. **Step 7,** the ssDNA gap is filled by DNA synthesis and ligated to finalize repair. Subsequently, transcription has to be restarted. This can be initiated either directly at the lesion or by new Pol II initiation at the transcription start site when lesion-stalled Pol II is removed from the template DNA during the repair reaction.

homologous to mammalian CSB, a similar key role for CSB in sensing damage-paused Pol II in mammalian cells is proposed. Interestingly, this model suggests that CSB is constantly probing Pol II to sense for an obstruction, indicating that CSB interacts both with lesion-stalled as well as unperturbed elongating Pol II. In line with this, it was observed that CSB transiently interacts with chromatin in a transcription-dependent manner in non-damaged conditions, most likely by binding to Pol II. A larger fraction of CSB was bound when cells were challenged with Pol II-stalling agents including UV-induced DNA damage or actinomycin D [40]. Interestingly, the binding affinity of Rad26 to Pol II upon stalling at TBLs was not increased *in vitro* [38]. This suggests that the observed increased CSB binding in cells might be caused by its prolonged binding to lesion-stalled Pol II, which could be the trigger for TC-NER complex assembly and subsequent repair of the TBL (Fig. 1) [22,38].

### 2.2. The role of CSA and UVSSA in TC-NER

A key protein which is recruited by CSB to the TC-NER complex is DDB1- and Cul4-associated factor (DCAF) CSA [33] which forms the CRL4$^{CSA}$ E3 ligase complex together with DDB1, Cul4A and Roc1 [41]. In this CRL4$^{CSA}$ complex, CSA is a dedicated substrate receptor, providing the complex its essential target specificity [42]. CSA contains a seven-bladed WD40 propeller and binds via its helix-loop-helix motif to DDB1 [28,42–44]. A recent study uncovered that the chaperonin TCP-1 ring complex (TRiC) interacts with CSA, especially those CSA proteins that are not incorporated in CRL4$^{CSA}$ complexes. TRiC interaction is important for stability of CSA and most likely mediates CSA handover to DDB1 to form properly functioning CRL4$^{CSA}$ [45]. In unperturbed conditions, the ligase activity of CRL4$^{CSA}$ is inhibited by binding of the COP9 signalosome [41,46]. However, upon DNA damage, the COP9 signalosome dissociates, resulting in activation of CRL4$^{CSA}$ ligase activity. Consequently, CSB, the substrate of the CRL4$^{CSA}$ ligase, is ubiquitylated and targeted for proteasomal degradation (Fig. 2) [47,48]. However, also other, yet unknown, targets of the CRL4$^{CSA}$ complex may exist and function during TC-NER.

The third main factor in TC-NER initiation is UVSSA, which interacts with both CSA and Pol II [30,49]. One of the roles of UVSSA during the TC-NER reaction is to specifically recruit ubiquitin-specific protease

7 (USP7) (Fig. 2) [30,49,50]. USP7 was, just as UVSSA, shown to be crucial for TC-NER [30]. The deubiquitylating activity of USP7 plays an important role in several different pathways following DNA damage. For example, Mdm2, XPC, p53, ALKBH3 [51–54] but also many factors outside the DNA damage response are described as USP7 substrates [55]. In a large number of these processes, USP7 is recruited to its substrate as part of a relatively stable complex. This seems to be a common mode of action for USP7 and might be essential to specifically target this abundant and pleiotropic deubiquitylating enzyme to its substrate [56,57]. In addition, complex formation of USP7 stimulates its deubiquitylating activity. This can be facilitated by remodelling its structure to a more competent state mediated by its binding partner [56,58–60]. Strikingly, in contrast to stimulation of USP7 activity following complex formation, the UVSSA-USP7 interaction was reported to inhibit the deubiquitylating activity of USP7 [61]. Following induction of TBLs, USP7 is specifically recruited via UVSSA to the TC-NER complex, where it counteracts $CRL4^{CSA}$-mediated CSB ubiquitylation, thereby most likely increasing the half-life of CSB in the TC-NER complex (Fig. 2) [30,50]. In addition, recently it was shown that USP7 also deubiquitylates UVSSA, which is important for efficient TC-NER [62].

Even though UVSSA has high affinity for USP7, it also has functions during TC-NER for which thus far no role for USP7 is described. For example, the largest subunit of Pol II, RPB1, was shown to be ubiquitylated in a UVSSA-dependent manner but this modification does not lead to proteasomal degradation of Pol II [63]. However, thus far it remains unclear whether this is a direct or indirect consequence of UVSSA. In line with previously observed interactions between UVSSA and subunits of transcription factor II H (TFIIH) [63], it was recently shown that UVSSA directly interacts with the PH domain of TFIIH subunit p62, via a short, highly conserved, acidic region in the central part of UVSSA [64]. Interestingly, this acidic region in UVSSA was identified as it was highly similar to the p62 PH-binding region of global genome nucleotide excision repair (GG-NER) DNA damage sensor XPC [64,65] (Fig. 2). This observation suggests that TFIIH is recruited to TBLs by UVSSA following TC-NER initiation via a similar mechanism as used by XPC to recruit TFIIH during GG-NER initiation [63,64]. TFIIH, which is also involved in transcription initiation, is a stable complex of ten subunits, including the helicases XPB and XPD [66]. The ATPase activity of XPB was suggested to recruit TFIIH to damage and initiate opening of DNA around the lesion. The helicase activity of XPD helps to extend unwinding of the DNA in a 5′ to 3′ direction and is thought to verify the lesion with help of the weaker helicase activity of XPB [67–71]. XPB is suggested to co-translocate with XPD and helps to scan the non-damaged complementary DNA strand since it has opposite directionality of XPD and thereby stimulates unwinding and lesion verification (Fig. 2) [68,70]. XPA promotes lesion recognition by enhancing stalling of XPB and XPD and helps to detect chemically altered nucleotides [68,72]. After proper lesion verification, TFIIH together with replication protein A (RPA) recruits the structure-specific endonucleases ERCC1/XPF and XPG in the correct orientation to excise the damaged strand [73,74]. Repair is finished by refilling the gap with DNA synthesis and ligation (Fig. 2) [75,76].

### 2.3. New insights in the TC-NER pathway

The recently acquired insights on the mode of action of these TC-NER initiation factors may have implications for current TC-NER models. One of the most important findings is that CSB, mediated by its ATP-dependent translocase activity, can discriminate between Pol II stalled at a DNA lesion or at pause sites by constantly probing the Pol II complex for its ability to forward translocate [38]. This indirect recognition of lesion-stalled Pol II instead of detection of the DNA lesion itself allows detection of a large spectrum of structurally different types of DNA damage. However, at the same time this mechanism may result in different outcomes for lesion-stalled Pol II, depending on the type of DNA damage. For example, CSB forward translocation of Pol II could promote transcriptional bypass of less bulky, oxidative damage like 8-oxo-G lesions (Fig. 1) [24,38,77]. In contrast, upon stalling at bulky lesions like CPDs, Pol II cannot be translocated by CSB, resulting in a longer residence time of Pol II and CSB at the lesion, which eventually results in initiation of TC-NER (Fig. 1) [38]. The increased residence time of CSB suggests that CSB has to be stabilized, since it is normally targeted for proteasomal degradation by the $CRL4^{CSA}$ complex following UV-induced DNA damage [48]. Protection from degradation could be mediated by concerted action of UVSSA and deubiquitylating enzyme USP7 and thereby likely provides time for CSB to recruit downstream TC-NER machinery (Fig. 2) [30,49,50,63,78].

UVSSA was recently suggested to be involved in recruitment of TFIIH to Pol II [63,64]. TFIIH, with its XPD 5′-3′ and XPB 3′-5′ helicase activity [68], is hypothesized to bind downstream of Pol II for DNA damage verification. This not only suggests that UVSSA and CSB bind to opposite sides of Pol II, but also suggests that the helicase activity of TFIIH might be involved in reverse translocation (backtracking) of Pol II [38,70]. This would indicate that proofreading of the lesion and backtracking of Pol II is mediated by the exact same complex, namely TFIIH, assuring efficient subsequent removal of the TBL by excision. Of note, in this model TFIIH-mediated backtracking of Pol II is counteracted by the Pol II forward translocating property of CSB (Fig. 2). It is therefore tempting to speculate that after TFIIH recruitment, CSB needs to be removed in order for Pol II to be efficiently backtracked by TFIIH. Eviction of CSB from the TC-NER complex might be mediated by ubiquitylation, as CSB was shown to be degraded following $CRL4^{CSA}$-mediated ubiquitylation [48]. However, this may also be mediated by other E3 ligases like BRCA1-BARD1, as this heterodimer was previously implicated to ubiquitylate CSB and target it for proteasomal degradation [79]. Interestingly, USP7 and TFIIH are described to bind a similar region of UVSSA [61,64], which might suggest competitive binding of these proteins. This putative mutual exclusive binding of either TFIIH or USP7 to UVSSA might suggest that USP7-mediated CSB deubiquitylation activity is lost following TFIIH recruitment. This will result in increased CSB polyubiquitylation, which subsequently might result in removal of CSB from the TC-NER complex by proteasomal degradation. This may enable TFIIH to reverse translocate Pol II and verify the DNA damage [68,70].

Although it is tempting to speculate that CSB needs to be degraded in order to allow Pol II backtracking and damage verification by TFIIH, it cannot be excluded that the ATPase activity of CSB is inhibited, or that CSB is evicted from the chromatin without being degraded. In line with this last possibility, the C-terminal ubiquitin-associated (UBA) domain of CSB, which interacts with ubiquitin chains, plays a role in eviction of CSB from the TC-NER complex. CSB mutants lacking this UBA domain remain trapped at TC-NER complexes, resulting in increased UV-sensitivity and reduced transcription restart, indicating that removal of CSB is a crucial step during TC-NER [34,80,81]. In line with a specific role in eviction of CSB at later stages in the TC-NER reaction, deletion of the UBA domain does not interfere with TC-NER complex assembly or ATPase activity of CSB [80,81], although CSA translocation to the nuclear matrix was affected [34]. However, thus far the exact mechanism of CSB eviction and the ubiquitylated substrates which are recognized by the UBA domain of CSB remain elusive. Future experiments are necessary to test the above described model.

### 2.4. Pol II degradation

In addition to backtracking and lesion bypass, cells have evolved an additional mechanism to ensure clearance of lesion-stalled Pol II. The largest Pol II subunit, RPB1, was shown to be degraded by the proteasome following UV-induced DNA damage. This degradation is hypothesized to be a ‘last resort’ pathway, which only happens in conditions where TC-NER fails or when the damage load is too high [82–84]. Pol II degradation is a highly inefficient process, as cells have to

generate new elongating Pol II complexes to restart transcription. In addition, degradation may result in a global decrease of the total Pol II pool that will likely influence transcription in general. However, degradation of Pol II prevents severe cytotoxic effects caused by persistent Pol II-stalling at DNA damage which forms genomic roadblocks for advancing replication forks and other chromatin involved processes and may induce the formation of R-loops [6–9,85]. In addition, degradation of Pol II will make the DNA lesion accessible for another round of TC-NER or for additional repair pathways to remove the TBL, for example by GG-NER.

During the last resort pathway, RPB1 is polyubiquitylated by the E3 ubiquitin ligase NEDD4, which generates lysine 63-linked polyubiquitin chains [86]. These chains are subsequently trimmed down by deubiquitylating enzymes until a monoubiquitin modification remains on RPB1. This monoubiquitin can be extended with lysine 48-linked polyubiquitin chains by the Elc1/Cul3 ligase complex. Next, this chromatin bound, ubiquitylated RPB1 is recognized by the ubiquitin-selective segregase valosin-containing protein (VCP/p97) which removes RPB1 from the stalled complex and results in its proteasomal degradation [46,82,87].

### 2.5. Clinical consequences and phenotypical differences

The above described new insights in TC-NER may also have implications for understanding TC-NER-linked disorders. The importance of functional TC-NER is clearly illustrated by the Cockayne syndrome (CS), a human disorder with defective TC-NER, caused predominantly by mutations in CSA and CSB [88]. CS is characterized by sensitivity to UV light, progressive neurodevelopmental symptoms, growth and developmental problems, mental retardation and severe premature aging [89–91]. Strikingly, UV-sensitive syndrome ($UV^{S}S$), which is mainly caused by mutations in UVSSA, is also characterized by absence of TC-NER-mediated removal of UV-induced TBLs [92], but displays only mild cutaneous UV sensitivity in sharp contrast to the premature and developmental features observed in CS [74,78,93]. The phenotypical differences between these two syndromes may partially be explained by additional functions of CS proteins compared to UVSSA. For example, CS proteins were proposed to be implicated in specific transcriptional programs [94], transcription initiation [95], redox balance [96], repair of double strand breaks [97,98] and maintenance of mitochondrial DNA stability [99,100], while thus far no such roles are described for UVSSA. Importantly, it was also suggested that the additional CS features may be derived from a defect in repair of (endogenously produced) oxidative DNA damage interfering with transcription [25,101] as it was shown that CS cells but not $UV^{S}S$ cells are sensitive to oxidative DNA damage (Fig. 3) [102,103]. CSB deficient cells lack the ability to forward translocate Pol II, which in case of an oxidative lesion will result in the inability to bypass this lesion [38]. This might result in persistent stalling of Pol II, thereby preventing access for base excision repair proteins to remove the lesion (Fig. 3). On top of that, persistent stalling of Pol II can eventually lead to collisions with replication forks or result in onset of R-loops [7,104] which may contribute to the CS phenotype. Recently, it was indicated that also UVSSA is involved in repair of oxidative lesions [105]. However, in absence of UVSSA, CSB is expected to still induce transcriptional bypass of oxidative lesions which suggests that the reduced repair rate of oxidative lesions due to loss of UVSSA might be less cytotoxic than persistently stalled Pol II complexes (Fig. 3) [24,38,77,78,90]. It has to be noted that mutations in CSA and CSB result in similar phenotypes [90], however thus far no role for CSA in lesion bypass of oxidative damage has been reported. In addition, loss of UVSSA might result in destabilization of CSB, due to impaired recruitment of USP7 to the TC-NER complex. Stabilization of CSB by UVSSA/USP7 might only be essential when the ATPase activity of CSB is needed for prolonged time, for example on UV-induced lesions to initiate TC-NER [38,78]. However this stabilization might not be essential during the most likely more rapid lesion bypass of oxidative lesions (Fig. 3). A different but not mutually exclusive explanation for observed phenotypical differences between the TC-NER disorders might be that CSA and CSB are involved in degradation or removal of Pol II [106]. Absence of CS proteins might lead to persistent stalling of Pol II with the lesion trapped in the active site thereby completely covering the lesion and preventing repair. In contrast, $UV^{S}S$ cells might still be able to remove Pol II from the lesion and repair UV-induced transcription blocking lesions with alternative repair pathways. In this scenario, 6-4PP lesions will be quickly repaired by GG-NER. However, CPD lesions are less efficiently repaired by GG-NER and their prevalence might explain the UV-sensitivity and failure to restart transcription as observed in $UV^{S}S$ cells (Fig. 3) [74].

To obtain a better understanding of the contribution of TBLs to the phenotypes of TC-NER linked disorders, genome instability and DNA damage-induced aging, it is of great importance to understand the exact mode of action of the various TC-NER factors during the different stages of this repair pathway. New insights in the spatio-temporal TC-NER complex composition might give important indications when the different activities of TC-NER factors are crucial, or alternatively, when specific factors need to be evicted from damaged chromatin to allow progression to subsequent reaction-steps. In addition, more in-depth experiments are needed to unravel the exact functions of TC-NER factors. For example, even though the E3 ligase activity of the $CRL4^{CSA}$ complex is crucial for TC-NER, its exact role and substrates remain elusive. In addition to this important ubiquitin-mediated regulation [46], other post-translational modifications are expected to provide additional layers of control to allow efficient damage recognition and removal. For example, SUMOylation has recently been shown to target CSB and this modification is essential for efficient TC-NER [34]. To be able to explain the striking differences observed in TC-NER phenotypes [74,78,93], it is important to identify putative differential activities of TC-NER factors or changes in the TC-NER complex composition following exposure to different types of TBLs. For example, recently it was shown that CSB is differentially ubiquitylated following UV-induced or oxidative lesions [81], indicating that depending on the type of lesion, the TC-NER complex is regulated in a different manner.

## 3. Genome-wide consequences of transcription-blocking lesions on transcription

Since TC-NER is initiated via recognition of lesion-stalled Pol II, most research on the effects of transcription-blocking DNA damage has been focused on this specific, damage-engaged subset of elongating polymerases [25,90]. However, in addition to direct consequences of DNA lesions that impede Pol II forward progression - effects *in cis* -, accumulating evidence shows that several important regulatory mechanisms exist that also affect non-lesion stalled Pol II in a genome-wide manner - effects *in trans* -. Both these *cis* and *trans*-effects are expected to be vital for cells to cope with the severe consequences of TBLs [85,107]. In this section, we will focus on genome-wide regulation of Pol II following DNA damage. We will discuss examples of TBL-induced effects that result in specific transcriptional programs, induced by either targeting the transcription cycle or by affecting mRNA splicing. Especially the highly regulated process of Pol II-mediated transcription offers several important control steps that can be targeted to regulate transcription, prevent genome instability and reduce cytotoxicity following exposure to TBLs.

Pol II-mediated transcription is initiated by general transcription factors that facilitate recruitment of Pol II and assembly of the pre-initiation complex (Fig. 4) [108]. During initiation, the CDK7 kinase activity of TFIIH phosphorylates serine 5 of the C-terminal domain (CTD) of RPB1, the core catalytic subunit of Pol II. This allows Pol II to engage the DNA template and start transcribing a short stretch of RNA followed by a transient pause ~60 bp downstream of the transcription start site (TSS) (Fig. 4) [3,109]. The release of Pol II from promoter proximal pause sites into productive elongation is mediated by the

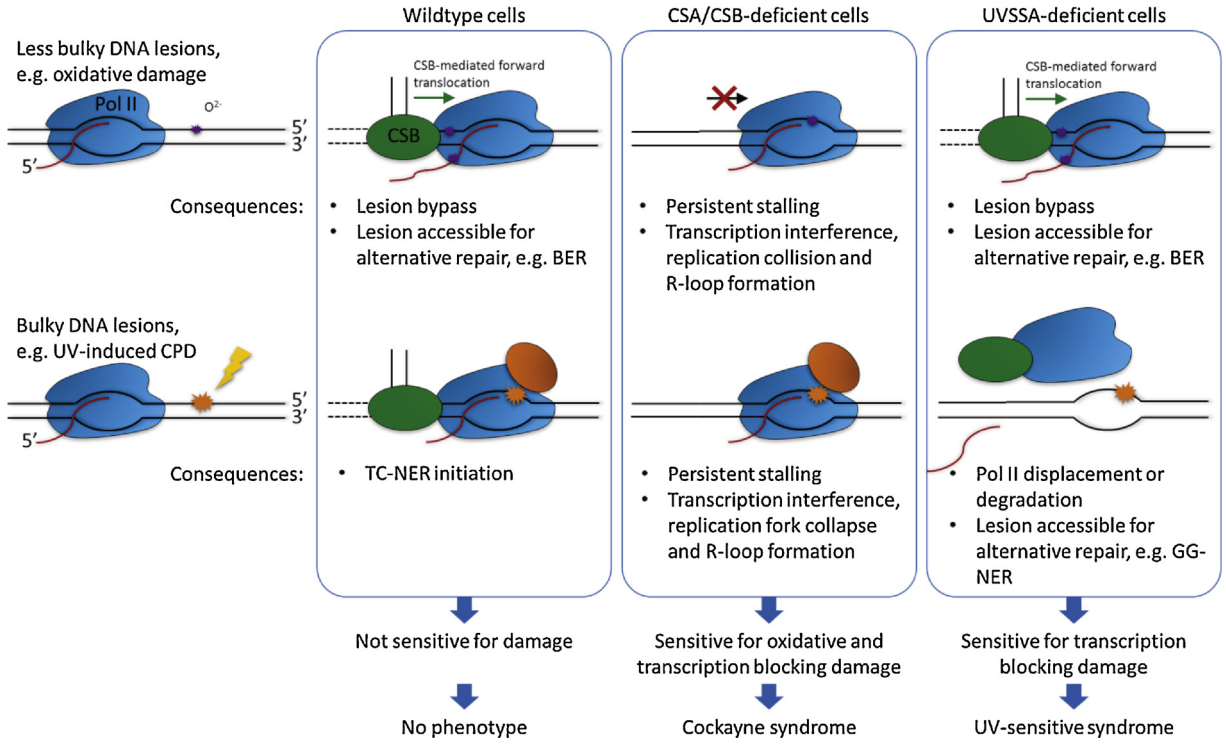


**Fig. 3. Differential processing of TBLs may explain differences in Cockayne Syndrome and UV sensitive syndrome.** Less bulky lesions like oxidative damage (**top row**) and transcription-blocking damage including UV-induced CPDs (**middle row**) will lead to stalling of Pol II. In **wildtype cells**, CSB will bind TBL-stalled Pol II and induce its forward translocation. In case of oxidative lesions, translocation of Pol II by CSB can successfully bypass the lesion making it accessible for alternative repair, e.g. by BER. In contrast, CSB cannot translocate Pol II over TBLs and this will initiate TC-NER to remove the lesion and restart transcription. In **absence of CSB**, TBL-stalled Pol II cannot be forward translocated. Therefore, Pol II may not be able to bypass oxidative damage nor trigger TC-NER and will most likely remain stalled on the lesion. Persistent stalling can lead to transcriptional interference, cause replication-transcription collisions and form R-loops. CSB-deficient cells are sensitive to both oxidative damage as well as TBLs most likely causing the severe Cockayne Syndrome phenotype. In **absence of UVSSA**, CSB is still able to bind the DNA and probe Pol II for translocation. This will lead to successful bypass of oxidative damage similar as in wildtype cells. However, most likely due to absence of UVSSA, CSB will be degraded more rapidly. However, as CSB-induced lesion bypass of oxidative damage might be a swift process, it is therefore not expected to be influenced by the decreased CSB half-life. Since there is still CSA and CSB present in absence of UVSSA, lesion-stalled Pol II might be degraded or displaced from the lesion. This will prevent persistent stalling of Pol II and makes the lesion accessible for repair by alternative repair pathways like GG-NER. As a consequence, UVSSA-deficient cells are sensitive for TBLs but not oxidative damage, which might result in the milder UV-sensitive syndrome.

CDK9 kinase activity of the positive transcription elongation factor b complex (p-TEFb). CDK9-mediated phosphorylation converts the DRB sensitivity inducing factor (DSIF) into a positive elongation factor, facilitates the release of the negative elongation factor (NELF) complex, and phosphorylates the CTD of RPB1 on serine 2 [3]. The different phosphorylation statuses of Pol II also mediate the binding and release of splicing factors as previously reviewed [110]. The CTD serves as a 'landing path' for the spliceosome and mediates co-transcriptional splicing [110].

### 3.1. Effects on Pol II transcription upon UV damage

One of the first indications of TBL-induced genome-wide effects on transcription was the observation that TATA-binding protein (TBP) is sequestered at cisplatin- and UV-damaged DNA. This results in a reduced availability of TBP to bind at promoter regions, subsequently leading to less transcription initiation [111]. This observation was followed by the discovery of another *in trans* effect, a massive depletion of the hypophosphorylated initiating form of Pol II upon UV irradiation, with a concomitant increase in the hyperphosphorylated elongating Pol II [112]. Additional research indicated that this shift could be explained by the inhibition of transcription initiation that was detected in UV-treated cell extracts using *in vitro* assays [112]. Although this indicates that DNA damage directly interferes with the transcription cycle, the loss of hypophosphorylated Pol II can also partially be explained by stalling of elongating Pol II at TBLs, thereby increasing the fraction of hyperphosphorylated Pol II. In line with these early observations, more recently published genome-wide Pol II ChIP-seq data showed that directly following UV-induced DNA damage, Pol II was cleared from the promoter [113]. The loss of Pol II ChIP-seq reads near the promoter, which most likely represent promoter paused Pol II, can be explained in different ways: Either (1) promoter paused Pol II is released into the gene body, (2) paused Pol II is specifically evicted from the chromatin or (3) transcription initiation is inhibited.

As this study showed that in addition to the loss of Pol II, TFIIH promoter-binding was reduced following UV irradiation, it was concluded that there is less TFIIH available for transcription initiation [113]. Reduced availability of TFIIH during transcription initiation might be caused by the involvement of this general transcription factor in the TC-NER reaction following DNA damage. In line with this hypothesis, reduced promoter binding of TFIIH and Pol II following UV-induced DNA damage could be rescued by depletion of CSB [113]. This is an intriguing finding since the vast majority of repair-associated TFIIH is active in GG-NER, which makes up the bulk portion of NER [114]. This may suggest that specifically occupation of TC-NER-associated TFIIH is causing inhibition of transcription initiation (Fig. 4). It is interesting to note that, although most of the genes show a decrease in promoter bound Pol II as a result of DNA damage, a specific subset is shown to be regulated differently. Interestingly, this set of genes is shown to have strongly increased binding of Pol II and consists of genes mainly involved in the p53 response, DNA damage response and apoptosis [113], indicating that this mechanism can stimulate the

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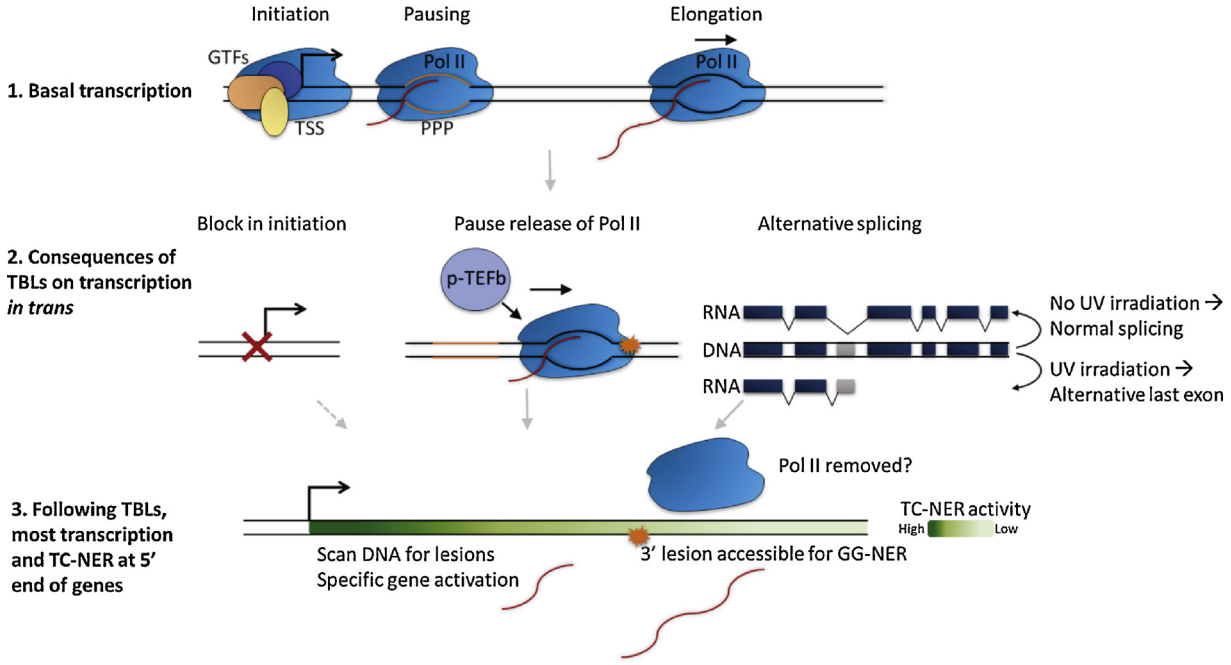


**Fig. 4. Effects of transcription-blocking lesions *in trans*.** **(1)** Basal transcription consists of initiation, pausing and elongation. General transcription factors help Pol II to initiate transcription from the transcription start site (TSS). Pol II pauses on the promoter proximal pause site (orange, PPP) before being released into productive elongation. **(2)** TBLs have different effects on transcription in a genome-wide manner. **(2, left panel)** Upon UV irradiation, transcription initiation is inhibited, decreasing the formation of new pre-initiation complexes, resulting in transcription inhibition. **(2, middle panel)** In addition, p-TEFb is activated independent of transcription. Activated p-TEFb stimulates release of Pol II from the PPP into productive elongation. This might result in increased sensing of TBLs and increased TC-NER. **(2, right panel)** Following UV-induced DNA damage, transcription switches to expression of shorter mRNA isoforms by using alternative last exons. **(3)** Both increased pause release of Pol II from the PPP into productive elongation, in combination with Pol II release from the DNA template following stalling at TBLs, as well as spatial restriction of transcription by the expression of shorter isoforms with alternative last exons, results in preferential transcription and TC-NER in the 5′ end of genes. This might leave the distal part of genes accessible for repair by GG-NER.

expression of specific genes following TBL induction.

### 3.2. p-TEFb activation stimulates transcription of the 5′ end of genes

Another genome-wide effect on the transcription cycle following UV-induced DNA damage is caused by activation of p-TEFb [115]. In unperturbed conditions, a pool of p-TEFb is kept in an inactive state in the 7SK snRNP complex [116–120]. Upon UV-irradiation, most likely not as a direct effect of DNA damage but via the damage-induced $Ca^{2+}$/calmodulin signaling pathway, p-TEFb is released from its inhibitory complex [116,121]. It was recently shown that a rapid increase of active p-TEFb levels following UV exposure resulted in a wave-like release of promoter paused polymerases into productive elongation on almost all active genes (Fig. 4) [122]. This will increase the likelihood of Pol II encountering a lesion, thereby promoting lesion-recognition and initiation of TC-NER. A wave-like release might also partially explain the loss of promoter bound Pol II directly after UVB irradiation as described above [113]. Interestingly, such a *de novo* wave-release of Pol II into the gene body [122] in combination with inhibited transcription initiation [111–113] might be indicative for a “final” round of transcription to ‘sense’ TBLs and swiftly initiate repair. Recently it was suggested that a significant population of lesion-stalled Pol II is released from the DNA template during TC-NER [123]. This suggests that individual elongation complexes will not engage in multiple rounds of TC-NER on successive lesions and indicates that only the first encountered TBL in a gene will be recognized. Such a scenario would result in preferential repair of TBLs close to the transcription start site (Fig. 4). This hypothesis was supported by a meta-analysis of previously performed excision repair sequencing (XR-seq) data showing that most TC-NER is executed in the beginning of genes [122,124]. This is an intriguing finding since TBLs located more downstream will still inhibit gene expression when not repaired properly. Preferential repair of the 5′ end of genes might suggest that the genetic information encoded in this region is especially important to preserve and might play an important role in the DNA damage response.

### 3.3. The role of gene size in response to DNA damage

The idea that the 5′ end of genes is important is supported by the finding that transcription might be spatially restricted to the first 20 to 25 kb of a gene in response to UV [125]. TBL-induced expression of shorter mRNAs is associated with a shift from expression of long mRNAs to shorter isoforms, thereby incorporating alternative last exons (ALEs) that are located closer to 5′ end of the gene (Fig. 4). Expression of shorter isoforms will therefore result in damage-induced, altered gene expression [125]. A key example of altered gene expression due to switching to short isoforms is the Activating Signal Cointegrator 1 Complex Subunit 3 (*ASCC3*). Following UV-damage, the long *ASCC3* isoform (over 370 kb, 42 exons) is replaced by expression of the short *ASCC3* isoform (25 kb) which only shares three exons with the long isoform and has a unique terminal exon. Interestingly, the long *ASCC3* isoform encodes the ASCC3 protein that is involved in repression of transcription [125,126]. In contrast, the short isoform is functioning as a non-coding RNA which is essential for proper transcription restart [125]. These two isoforms have opposing effects on transcription and the changed balance upon UV irradiation can regulate transcription inhibition and restart. The importance of shorter transcripts following TBL-induction might explain the observed preferential repair near 5′end of genes.

The concept that short genes are less susceptible to DNA damage is more commonly observed in the DNA damage response. The human genome consists of over 20.000 genes which vary greatly in gene size. Assuming that TBLs are genome-wide dispersed in a stochastic manner, long genes are more susceptible to gene inactivation due to direct

stalling of Pol II on a TBL than shorter genes [127,128]. A higher chance for TBLs in long genes compared to short genes, which will be especially relevant under physiologically relevant low damage loads, was linked to a shift in gene expression in favor of small genes upon DNA damage exposure [127,129]. Possibly, gene size has been selected during evolution to maintain proficient expression of genes that are important for proper cellular responses following exposure to transcription-blocking DNA damage [129].

A clear example of a small gene that plays an important role following UV-induced DNA damage is the immediate early gene (IEG) activating transcription factor 3 (ATF3) [130–133]. IEGs are in general short genes and their expression can be rapidly induced following cellular stress [130]. In line, also expression of ATF3 is strongly increased following UV-induced DNA damage [131–133]. Upon expression, ATF3 is targeted to CRE/ATF-binding sites which are located near promoters of specific genes, thereby inhibiting specifically the expression of these genes [131,132]. Importantly, this ATF3-mediated transcription inhibition *in trans* needs to be resolved to allow proper transcription restart as discussed below in the transcription restart section. In addition to ATF3, also BMI1 together with the E3 ligase UBR5 was recently shown to repress Pol II elongation and nascent RNA synthesis at UV-induced DNA lesions [134]. Together, the above discussed examples show that different factors actively repress transcription *in trans* following DNA damage, either in general or by targeting a specific subset of genes.

### 3.4. Alternative splicing enhances DNA damage signaling

In addition to the above described selection of alternative last exons, which results in expression of smaller mRNAs following TBL induction, also other alternative splicing (AS) mechanisms play an important role. Damage-induced effects on splicing can induce specific gene expression programs or may contribute to damage-involved signaling. AS-induced expression of different isoforms following DNA damage, has thus far been attributed to changes either in Pol II elongation rate (kinetic coupling) [135,136] or in the interaction between Pol II and the core spliceosome or splicing regulators (recruitment coupling) [104,137,138].

An example of the kinetic coupling model is nicely illustrated by the observed increase in phosphorylation of the C-terminal domain (CTD) of Pol II, which slows down transcription elongation [135]. A reduced elongation rate can result in exon inclusion [135,136] or skipping [139,140]. UV-induced AS is a general mechanism regulating expression of many genes, including several genes specifically involved in regulation of survival and apoptosis. For example, the ratio between anti-apoptotic Bcl-xL and pro-apoptotic Bcl-xS, both isoforms of the Bcl-x gene, is shifted towards the Bcl-xS isoform contributing to a higher UV-induced cell death [135]. Interestingly, it was shown that UV-induced AS also happens on non-damaged genes, indicative for an effect *in trans* on Pol II and co-transcriptional splicing [135].

In line with the finding that regulation of AS by kinetic coupling is regulated *in trans*, it was recently shown that ataxia telangiectasia and Rad3-related (ATR) signaling plays an important role in UV-induced hyperphosphorylation of the CTD of Pol II [141]. ATR is known to be activated upon UV-irradiation in non-cycling cells, following excision of the lesion-containing DNA during the XPF/ERCC1- and XPG-mediated excision step of NER. The residual repair-intermediate, containing a 22–35 nucleotide long piece of ssDNA, is bound by RPA which is subsequently recognized by ATR interacting protein (ATRIP)/ATR complexes thereby triggering ATR signaling [74,142,143]. Of note, the study on ATR signaling used keratinocytes in which the majority of ssDNA intermediates will be generated via the much more active GG-NER sub-pathway [114]. This suggests that stalling of Pol II itself may not be the initiating event, but that Pol II is a target of the ATR-induced effect on elongation speed [141].

Together these studies show that in addition to direct impediment of the forward translocation of elongating Pol II by the lesion [13,16–21], the elongation rate of Pol II is also affected *in trans* by ATR. A reduced transcription elongation rate will subsequently lead to AS events [136], resulting in induction of specific isoforms following DNA damage [135,141]. Whether and how this ATR and DNA damage-induced Pol II hyperphosphorylation is different from the canonical hyperphosphorylated (Pol IIO) remains currently unknown. Of note, most likely ATR affects Pol II in an indirect manner as there are no target sequences known in the CTD for this DNA-damage kinase. Interestingly, in addition to reducing Pol II elongation rate, ATR activation may also affect different axillary factors involved in AS [144–147].

In addition to the above described AS events according to the kinetic coupling model, TBLs also result in AS following the recruitment model [104,137,138]. For example, UV irradiation- or camptothecin-induced TBLs induce co-transcriptional exon skipping of for example the *MDM2*, *CHEK2* and *MAP4K2* transcripts [137,138]. This damage-induced AS is linked to the loss of interaction between EWS, a member of the TET family of RNA and DNA-binding proteins, and its target RNAs [137]. The loss of interaction between these co-transcriptional binding partners might be mediated by the lost interaction between EWS and the spliceosome-associated factor YB-1 upon DNA damage [138]. Also in Drosophila cells, camptothecin induces AS which is mediated by ATR activation and results in proteasome-mediated degradation of splicing regulator Tra2 [146]. Interestingly, in addition to damage-induced AS by targeting splicing regulators, it was recently shown that also the core spliceosome is affected following the induction of TBLs. Pol II stalling on TBLs promotes chromatin displacement of late-stage spliceosomes [104], composed of U2, U5 and U6 small nuclear ribonucleoproteins [148], and initiates a positive feedback loop centered on the signaling kinase ATM. The initial spliceosome displacement results in an increased R-loop formation through hybridization of pre-mRNA with template DNA [104,149]. Interestingly, R-loop formation near the TBL leads to a non-canonical activation of the protein kinase ATM, which signals to impede core spliceosome organization even further, consequently resulting in increased intron retention and altered splicing in a genome-wide manner [104,150].

## 4. Regulation of transcription restart

Even when TBLs are successfully repaired, their induction is expected to remain highly cytotoxic if transcription is not properly resumed. Therefore, transcription restart is important to assure proper *de novo* mRNA production and to maintain cellular homeostasis [85]. Transcription restart was thus far mostly assumed to reconvene at the lesion where Pol II was stalled, as soon as the TBL is removed by TC-NER [25,151]. However, as discussed above, also a significant part of TBL-induced transcription inhibition is caused by effects *in trans* that have direct consequences for the mode of transcription restart. For example, if the TBL-induced block in transcription initiation is reversed [111–113], this will result in transcription restart by new initiation events at the promoter. In line with these findings, genome-wide analyses of nascent RNA sequencing data [152] showed that transcription recovery of RNA synthesis occurred as a wave in the 5′-3′ direction following UV- or camptothecin-induced TBLs. This indicates that a significant part of transcription restarts at the beginning of genes [127,128], which could provide time for the GG-NER pathway to remove TBLs at the more distal parts of genes before the transcription machinery encounters these lesions [127]. This could result in a smooth progression of transcription once restarted. Transcription restart at the promoter might be caused by recovery of *in trans*-mediated transcription initiation blockage but may also indicate that transcription does not always resume from the position where it was initially stalled (*in cis*). In line with the latter, it was recently suggested that a significant population of lesion-stalled Pol II is released from the DNA template during the TC-NER reaction [123], indicating that the observed transcription resumption from the 5′ end of genes might also be a common

mechanism for transcription inhibition *in cis*.

Of note, these findings do not exclude that transcription can also be restarted at the site of the lesion itself which is in line with several factors suggested to be involved in backtracking or 3′-end RNA processing [25,107]. Furthermore, transcription resumption directly at the repaired lesion seems to be the most efficient restart mechanism since the same Pol II complex is able to continue with transcription of the already partially synthesized mRNA.

### 4.1. Factors involved in transcription restart

Thus far, several factors have been suggested to be involved in backtracking of Pol II to allow repair. To resume transcription from this backtracked position it is crucial that protruding nascent RNA is cleaved so that the 3′ end of the RNA is properly realigned with the DNA in the active site of Pol II [153]. This reaction is mediated by transcription factor II S (TFIIS) which is suggested to stimulate the intrinsic 3′–5′ exonuclease activity of Pol II [21,153–155]. TFIIS is recruited in a CSA- and CSB-dependent manner [33]. The Ccr4-Not complex further supports recruitment of TFIIS and enhances its cleaving activity thereby suggesting that TFIIS and Ccr4–Not jointly reactivate arrested Pol II [156]. Absence of TFIIS results in significantly decreased, but not completely absent, transcription resumption. This can be explained by the fact that remaining intrinsic cleavage activity of Pol II is sufficient to cleave the RNA and restart transcription. Even though this restart will happen in a less efficient manner, it is most likely sufficient to prevent increased UV-sensitivity upon depletion of TFIIS [153,157,158]. The intrinsic cleavage activity of Pol II might also explain the observed differences in the role of TFIIS in transcription resumption [157,158], but this may also be caused by the presence of the redundant TFIIS paralogue TCEA2, which is not solely expressed in the testis as originally described [159]. In addition to its stimulating function on TFIIS, Ccr4-Not was suggested to directly promote transcription elongation by binding to the emerging transcript, thereby stimulating Pol II to resume transcription after repair of a lesion [160]. Despite that TFIIS and Ccr4-Not are implied in Pol II backtracking to allow resumption of transcription, it cannot be excluded that their role in facilitating RNA cleavage of the protruding RNA may also be involved in release of Pol II from chromatin following TC-NER initiation [123].

Another factor which was shown to stimulate transcription restart is elongation factor ELL which binds to TFIIH via the CDK7 subunit of the CDK-activating kinase (CAK) complex. Thus far, the exact function of ELL during transcription restart remains unknown. However, it was hypothesized that ELL functions as a docking protein, thereby enabling other proteins to bind and stimulate transcription resumption. ELL was shown to be specifically involved in transcription resumption since depletion of ELL does not affect TC-NER [161]. This uncoupling of repair and transcription restart might also indicate that ELL is involved in transcription restart at the TSS as a consequence of damage-induced transcription inhibition *in trans* [161].

Another important process during transcription restart is resolving ATF3-mediated transcription inhibition, which has been shown to affect approximately 5000 genes [131,132]. Interestingly, CSB and the $CRL4^{CSA}$ E3 ligase complex, possibly together with the E3 ubiquitin ligase Mdm2, were shown to ubiquitylate ATF3 [131]. The subsequent proteasomal degradation of ATF3 at CRE/ATF sites relieves the ATF3-mediated transcriptional repression. This finding also suggests that on top of absence of functional TC-NER in CSA and CSB-deficient cells, loss of transcription restart might be partially explained by maintained transcriptional repression of ATF3-regulated genes and consequently contributes to the severe phenotype observed in CS patients [131,132]. Interestingly, in addition to the well-described function of CSB on stalled Pol II, this finding suggests that CSB has an additional function at the promoter. This might be in line earlier with observations that CSB is involved in regulating gene expression [94].

### 4.2. Chromatin remodeling factors involved in Pol II restart

Histone chaperones and ATP-dependent chromatin remodelers are responsible for histone sliding, eviction and insertion to remodel chromatin and facilitate different DNA transacting processes. Several remodeling factors were identified to be specifically involved in NER-mediated repair [162]. In addition to their role in repair, several of these chromatin involved factors were also shown to play a key role in the restart of transcription [163,164]. For example, nucleosome binding protein HMGN1 and p300 histone-acetyl transferase were shown to be recruited to the TC-NER complex [33]. These factors are hypothesized to induce sliding of upstream nucleosomes resulting in a more open chromatin structure, which might facilitate Pol II backtracking [25,165,166].

In addition, the histone chaperones Histone regulator A (HIRA) and Facilitating Chromatin Transcription (FACT) were identified to remodel histones following TBL induction, a process that was shown to be essential for transcription restart [167,168]. HIRA is recruited to sites of DNA damage where this histone chaperone deposites histone variant H3.3 near the damage [167]. Histone 3.3 is normally involved in promoting transcription or removing inhibitory factors via specific marks [169] and might promote transcription restart via this mechanism. The other chaperone, FACT, consists of the SPT16 and SSRP1 subunits and was shown to exchange histone H2A and H2B which stimulates Pol II transcription along chromatin by destabilizing nucleosomes [170]. Interestinlgy, only the SPT16 subunit of the FACT complex was shown to be important for transcription restart, in line with SPT16-dependent accelerated H2A/H2B exchange at the site of damage [168]. This suggests that SPT16 increases plasticity of chromatin via enhanced incorporation of histone H2A/H2B [171], thereby promoting translocation of Pol II either to enhance repair, reverse translocate Pol II from the lesion or restart transcription after repair [168]. In addition to these two histone chaperones, proteins involved in post-translational modifications of histones may promote transcriptional restart. For example, the lysine methyltransferase DOT1L normally methylates H3K79, a histone mark that regulates transcription [172,173]. DOT1L knock-out cells show increased UV-sensitivity coupled to a deficient recovery of transcription restart following TBL induction without affecting TC-NER [174]. These DOT1L effects can be rescued by treatment with Trichostatin A, which relaxes the chromatin structure, suggesting that DOT1L promotes transcription initation by opening up chromatin of UV-repressed genes and is therefore essential for transcription restart [174]. Interestingly, HIRA and DOT1L are not necessary for transcription restart in response to the reversible transcription inhibitor DRB [167,174], indicative for a specific regulation of transcription restart following removal of TBLs. In line with this additional layer of control during the cellular response to TBLs, it was observed that transcription restart can be regulated in a gene-specific manner [127].

## 5. Outlook

The development of new sequencing approaches, including nascent RNA-seq [127], XR-seq [124] and ChIP-seq [113,122], has resulted in important new insights in the underlying mechanism of transcription inhibition in response to UV-induced DNA damage. In addition to the direct physical block of Pol II once encountering a TBL (inhibition *in cis*), accumulating evidence shows that the highly regulated transcription cycle is targeted at different key steps to efficiently induce transcription inhibition in a genome-wide manner (inhibition *in trans*). Examples are inhibition of transcription initiation [112,113] or induction of immediate response genes (IEGs) like ATF3 that inhibit transcription by binding to their response elements near promoters [131–133]. Most likely many more cellular processes that are involved in transcription inhibition following TBL induction await their discovery. One of the main questions that remains, is why transcripition is inhibited in a genome-wide manner, while cells are equiped with a

highly efficient TC-NER pathway that can directly resolve lesion-stalled Pol II. Apparently, additional back-up mechanims are required for proper cell surival following DNA damage. It is tempting to speculate that these mechanisms have evolved to prevent persistent Pol II stalling, as lesion-stalled Pol II repair intermediates might be more toxic for a cell than the actual TBL itself, for example due to the induction of R-loops [7,8] or transcription-replication collisions [6]. Importantly, by affecting a specific subset of genes, these genome-wide regulatory systems allow cells to regulate transcription of genes essential for cells to cope with TBLs. As a consequence, TC-NER activity is focussed on repair of these important genes that are not inhibited *in trans*.

It has been shown that different types of TBLs have different outcomes on the impedement of Pol II *in cis* [15]. Therefore, it seems logical that also transcription inhibition *in trans* could be differentially affected depending on the type of damage. In line with this idea, recently a rapid accumulation of Pol II near promoters and enhancers was observed following oxidative damage [175]. This is in sharp contrast to rapid release of paused Pol II into productive enlongation observed following UV-induced DNA damage [122]. The differential response between these types of DNA damage could be explained by differences in the activation mechanisms of these pathways. Some of the *in trans* effects are induced by the initial stalling of Pol II at a lesion, including release of the core spliceosome and subsequent ATM activation [104]. In contrast, UV-induced p-TEFb activation by release from its inhibitory complex is a direct consequence of the UV-damage and is thus activated independent of transcription [122]. To obtain a better insight in the biological relevance of the mechanism of transcription inhibition, it is important to study whether different types of TBLs have different outcomes on transcription inhibition *in trans*. In addition, TBLs may also have strikingly different outcomes in different cell types and organs [74,176,177]. This is clearly illustrated by extreme damage-sensitivity of photoreceptor cells in retinas of TC-NER-deficient mice or neurodegeneration in CS patients [178,179]. These differential cellular outcomes to TBLs may be explained by differences in transcription levels, replication or activity of DNA-repair pathways. However, also the presence of multiple mechanisms to inhibit transcription might explain the differential response and sensitivity of different tissues to TBLs.

Improved insights in different modes of transcription inhibition, both *in cis* and *in trans*, is crucial to understand the molecular mechanism of transcription restart. For example, a large contribution of transcription inhibition *in trans* will most likely result in restart from the TSS, while stalling of Pol II *in cis* might result in transcripiton resumption by the same Pol II and RNA molecule that was stalled at the TBL. Even though transcription will be restored in both cases, the molecular mechanisms to restart transcription and the involved factos will be completely different for restart at the beginning of genes compared to transcription resumption at the TBL.

## Conflict of interest

The authors declare that there are no conflicts of interest.

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