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Nucleotide excision repair: from molecular mechanisms to patient phenotypes

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Chapter 1

Nucleotide excision repair leaves a mark on chromatin: DNA damage detection in nucleosomes

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Abstract

Global genome nucleotide excision repair (GG-NER) eliminates a broad spectrum of DNA lesions from genomic DNA. Genomic DNA is tightly wrapped around histones creating a barrier for DNA repair proteins to access DNA lesions buried in nucleosomal DNA. The DNA-damage sensors XPC and DDB2 recognize DNA lesions in nucleosomal DNA and initiate repair. The emerging view is that a tight interplay between XPC and DDB2 is regulated by post-translational modifications on the damage sensors themselves as well as on chromatin containing DNA lesions. The choreography between XPC and DDB2, their interconnection with post-translational modifications such as ubiquitylation, SUMOylation, methylation, poly(ADP-ribos)ylation, acetylation, and the functional links with chromatin remodelling activities regulate not only the initial recognition of DNA lesions in nucleosomes, but also the downstream recruitment and necessary displacement of GG-NER factors as repair progresses. In this review we highlight how nucleotide excision repair leaves a mark on chromatin to enable DNA damage detection in nucleosomes.

Introduction

Damage recognition in nucleotide excision repair

Cells are continually exposed to different sources of DNA damage including solar UV light, environmental chemicals, food-borne mutagens, and reactive metabolites that generate a wide variety of structurally diverse genomic DNA lesions (Gates, 2009; Hoeijmakers, 2009). Dedicated DNA repair mechanisms recognize and remove genomic DNA lesions to maintain genome integrity and prevent disease (Ciccia and Elledge, 2010). Nucleotide excision repair (NER) is a versatile DNA repair pathway that eliminates a wide range of structurally diverse DNA lesions from genomic DNA, including UVinduced photolesions, such as 6–4 pyrimidine–pyrimidone photoproducts (6-4PPs) and cyclobutane pyrimidine dimers (CPDs) (Marteijn et al., 2014).

DNA lesions in transcribed strands are substrates of transcription-coupled repair (TC-NER) (van den Heuvel et al., 2021), while elimination of DNA lesions throughout the genome is carried out by global genome repair (GG-NER) (Scharer, 2013; Sugasawa, 2016). Recognition through both subpathways ultimately leads to a common pathway of verification, excision and re-synthesis of the damaged DNA, involving the same set of core NER proteins, including the TFIIH complex, XPA, RPA and the endonucleases XPG and ERCC1-XPF (Figure 1a) (Marteijn et al., 2014). The mechanisms involved in TC-NER initiation have been reviewed recently (Gregersen and Svejstrup, 2018; Lans et al., 2019; van den Heuvel et al., 2021). In this review we focus on recent insights on the initiation and operation of GG-NER in a chromatin context (see Table 1-3).

The recognition of DNA lesions during GG-NER is critically dependent on the DNA damage recognition complex XPC-RAD23B, which utilizes an indirect recognition mechanism (Camenisch et al., 2009; Maillard et al., 2007; Min and Pavletich, 2007; Sugasawa et al., 2001). Structural studies of Rad4, the yeast homolog of XPC, have shown that the protein uses four domains for DNA- and damage recognition (Min and Pavletich, 2007; Paul et al., 2019). The BHD1 and TGD domains anchor the protein on DNA non-specifically to allow the BHD2 and BHD3 domains to probe for sites of thermodynamic destabilization induced by the lesion. BHD2-3 interact with the lesion site through a binding pocket for two native bases on the undamaged strand and by inserting the tips of BHD3 into the duplex at the site of the lesion, displacing the lesion into an extrahelical position (Mu et al., 2018b; Paul et al., 2019) (Figure

1b). XPC does not make any specific contacts with the lesion itself. This feature of XPC explains the broad substrate specificity of lesion binding by XPC and NER in general (Gunz et al., 1996; Mu et al., 2018a; Mu et al., 2018b). Furthermore, a “kinetic gating” mechanism for Rad4/XPC lesion binding has been proposed, which suggests that lesion recognition primarily depends on the local destabilization of the DNA duplex and the protein's retention time at the lesion site rather than the presence of a particular lesion. These observations explain why the protein binds with high affinity to helix-destabilizing DNA lesions, such as 6-4PPs, while its affinity for the more abundant, but less helix-destabilizing UV-induced CPD photolesions is rather low (Chen et al., 2015).

For the recognition of CPDs, XPC needs the support of the $CRL4^{DDB2}$ complex, consisting of DDB2, the damage-recognition protein, and DDB1, which serves as a link to a CUL4A-RBX1-based (CRL4) E3 ubiquitin ligase complex (Groisman et al., 2006; Groisman et al., 2003; Scrima et al., 2008). DDB2 directly associates with photolesions by extruding the lesion out of the helix into a hydrophobic pocket embedded in its WD40 domain using three residues that form a wedge to take the place of the lesion in the helix (Figure 1c) (Matsumoto et al., 2019; Scrima et al., 2008). An overlay of the structures of XPC and DDB2 bound to 6-4PPs suggests that the two proteins cannot coexist on a lesion. Instead, DDB2 makes the lesion more accessible for XPC by opening the DNA at the lesion to generate a helix destabilizing substrate that is recognized by XPC (Matsumoto et al., 2019; Scrima et al., 2008). The recruitment of XPC is further dependent on direct protein-protein interactions with DDB2 (Sugasawa et al., 2005; Yasuda et al., 2007). These findings suggest that DDB2 is needed to bring XPC in proximity of the lesion, but that the binding of XPC opposite of the DNA lesion requires the displacement of DDB2 to prevent steric clashes between the two damage-recognition proteins.

DNA damage detection in nucleosomes

The process of GG-NER has been fully reconstituted *in vitro* with recombinant purified components and is independent of DDB2 under these conditions (Aboussekhra et al., 1995; Mu et al., 1995). While reconstituted GG-NER operates well on naked DNA, genomic DNA is tightly wrapped around histones creating a barrier for DNA repair proteins to access DNA lesions buried in nucleosomal DNA (Gong et al., 2005; Hara et al., 2000). Earlier biochemical studies showed that chromatin remodelers can alleviate the chromatin barrier to repair proteins, thereby making lesions accessible to NER (Hara and Sancar, 2002; Ura et al., 2001). Before any mechanisms of chromatin rearrangements were known, the repair of

Figure 1

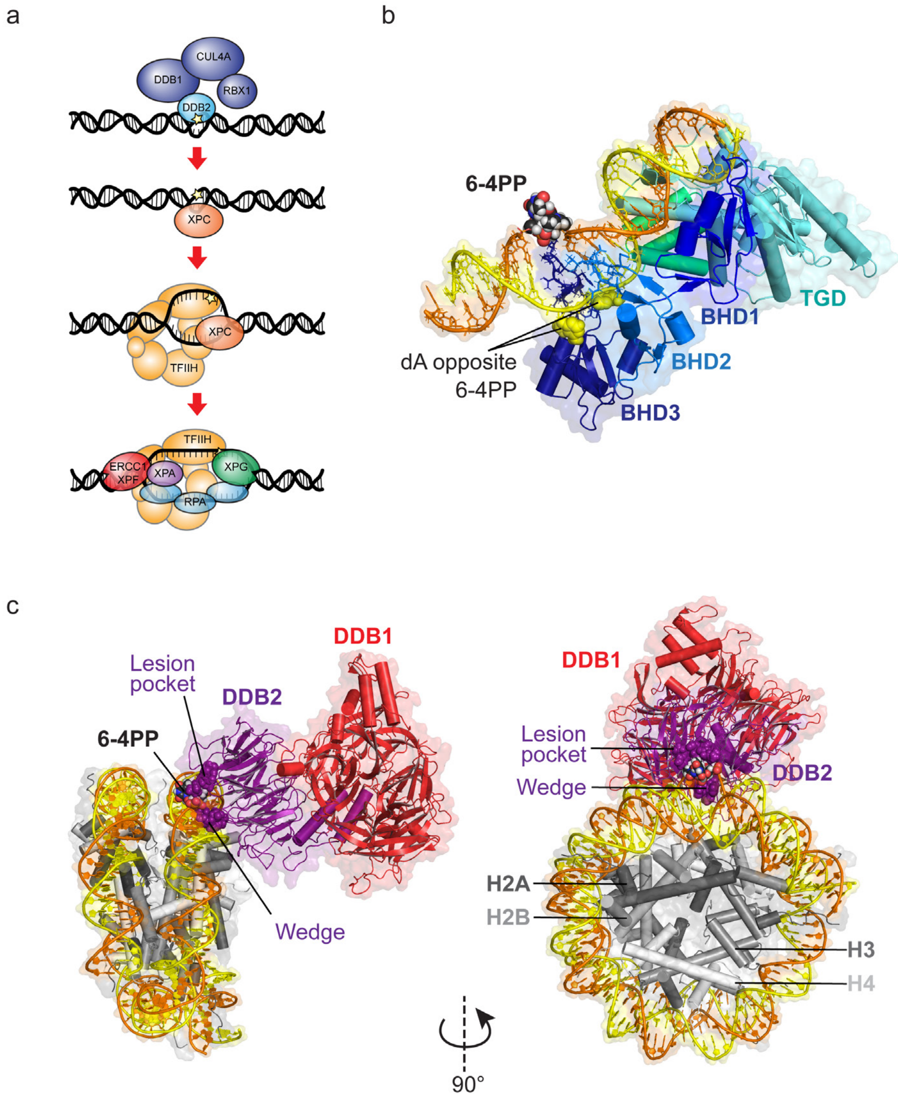

Figure 1. DNA lesion-recognition factors initiate GG-NER. (a) Model of GG-NER initiation by the CRL4^{DDB2} complex (consisting of DDB2-DDB1-CUL4A-RBX1) and the XPC complex (consisting of XPC, RAD23B, CETN2), which is followed by the recruitment of the TFIIH complex, XPA, RPA and the endonucleases XPG and ERCC1-XPF. (b) Structure of yeast Rad4/XPC bound to a 6-4PP lesion. The lesion is displaced from the helix stack using the hairpins of the BHD2 and BHD3 domains. The BHD2/3 domains form a tight binding pocket for the dA residues in the non-damaged strand, but do not contact the lesion directly. The BHD1-TGD domains of Rad4/XPC bind in a damage and sequence non--specific manner and anchor the protein on DNA during the lesion search process. Figure generated using PDB 6CFI with PyMol. (c) Structure of UV-DDB (consisting of DDB2 and

DDB1) bound to a 6-4PP in a nucleosome. The DDB2 protein binds to the nucleosome at a 60° angle and pushes the 6-4PP into a lesion-binding pocket using wedge residues (F334, Q335 and H336). Figure generated using PDB 6R8Y with PyMol.

DNA lesions was envisioned to occur through an access-repair-restore model (Polo and Almouzni, 2015; Smerdon and Lieberman, 1978). It is now becoming clear that DDB2 has a key role in facilitating DNA lesion-recognition in a chromatin context (Adam et al., 2016; Luijsterburg et al., 2012b; Matsumoto et al., 2019). DDB2 directly binds photolesions embedded in nucleosomal DNA (Figure 1c) and mediates slide-assisted site exposure of buried lesions that face the nucleosome core (Matsumoto et al., 2019; Osakabe et al., 2015). Additionally, as discussed extensively below, DDB2 plays a key role in regulating the recruitment and the activity of several chromatin remodelling and modifying enzymes to regulate downstream steps during GG-NER. These findings provide a mechanistic explanation for why DDB2 is essential for the repair of CPDs, while the repair of 6-4PPs is enhanced by, but not dependent on DDB2 (Moser et al., 2005).

The emerging picture is that the interplay between XPC and DDB2 is tightly regulated by post-translational modifications (PTMs) on the damage-recognition proteins themselves as well as on chromatin containing DNA lesions. The tight interplay between these DNA lesion-recognition proteins, their interconnection with PTMs such as ubiquitylation, SUMOylation, methylation, poly(ADPribos)ylation, acetylation, and the functional links with chromatin remodelling activities regulate not only the initial recognition of DNA lesions in chromatin, but also the downstream recruitment and necessary displacement of NER factors as repair progresses.

DNA lesion-recognition proteins and their interconnection with ubiquitylation

The CRL4^{DDB2} ligase and histone H3 and H4 ubiquitylation in response to UV

The E3 ubiquitin ligase activity of the CRL4^{DDB2} complex has been linked to histone ubiquitylation during GG-NER. One study reported that the CRL4^{DDB2} complex mediates the UV-induced ubiquitylation of histone H3 and H4, resulting in a weakened interaction between histones and DNA, thereby facilitating XPC recruitment (Figure 2a, b) (Wang et al., 2006). Although these findings suggest a link between H3 and H4 ubiquitylation and GG-NER, it will be important to identify the precise residues that are targeted for ubiquitylation and determine the mechanistic basis for XPC

recruitment to these ubiquitylated histones.

XPC and DDB2 ubiquitylation and SUMOylation facilitate DNA-lesion recognition

Regulating the interplay and handover between lesion-recognition proteins DDB2 and XPC is crucial to initiate GG-NER in chromatin. The catalytic activity of the $CRL4^{DDB2}$ ubiquitin ligase complex has a key role during these early transactions. The $CRL4^{DDB2}$ complex ubiquitylates XPC in response to UV irradiation (Figure 2b). However, this does not result in its proteasomal degradation, but rather stabilizes the association of the protein with DNA (Sugasawa, 2006; Sugasawa et al., 2005). $CRL4^{DDB2}$ also auto-ubiquitylates DDB2 triggering its degradation (El-Mahdy et al., 2006; Luijsterburg et al., 2007). It is believed that the differential impact of ubiquitylation of the two damage sensors stimulates the handover from DDB2 to XPC, a process required for GG-NER progression. In addition, DDB2 becomes conjugated with SUMO-1 at lysine residue K309 in response to UV irradiation. This modification was shown to stimulate XPC recruitment and regulate efficient repair of CPDs (Han et al., 2017).

DDB2 ubiquitylation regulates its chromatin extraction

The handover of DNA lesions from DDB2 to XPC is tightly regulated at multiple levels. Firstly, the initial transient XPC-mediated recruitment of the TFIIH complex stimulates DDB2 dissociation, thereby promoting the formation of a stable XPC-TFIIH complex (Ribeiro-Silva et al., 2020) (Figure 2c). Furthermore, the ubiquitin-selective segregase VCP/p97 is involved in extracting ubiquitylated DDB2 from damaged DNA to reduce its chromatin dwell-time (Puumalainen et al., 2014) (Figure 2c). The inability to extract DDB2 from chromatin interferes with the stable binding of XPC and TFIIH to DNA lesions (Ribeiro-Silva et al., 2020), suggesting that while the initial binding of DDB2 stimulates XPC recruitment, its prolonged binding actually inhibits subsequent GG-NER progression. The interaction between VCP/p97 and DDB2 is stimulated by the deacetylase SIRT6, suggesting that the UV-induced deacetylation of DDB2 promotes its ubiquitylation and subsequent extraction from chromatin (Geng et al., 2020). Interestingly, the UV-induced SUMOylation of XPC at lysine residues K81, K89 and K183 was suggested to regulate the release of DDB2 in trans. More specifically, an XPC mutant that cannot be SUMOylated (3KR) shows a stronger UV-induced immobilization on chromatin and a more pronounced DNA repair defect, which was partially alleviated by the loss of DDB2 (Akita et al., 2015). These findings suggest that XPC SUMOylation promotes efficient DDB2 dissociation and DNA damage-handover to XPC. While this is an interesting possibility, an

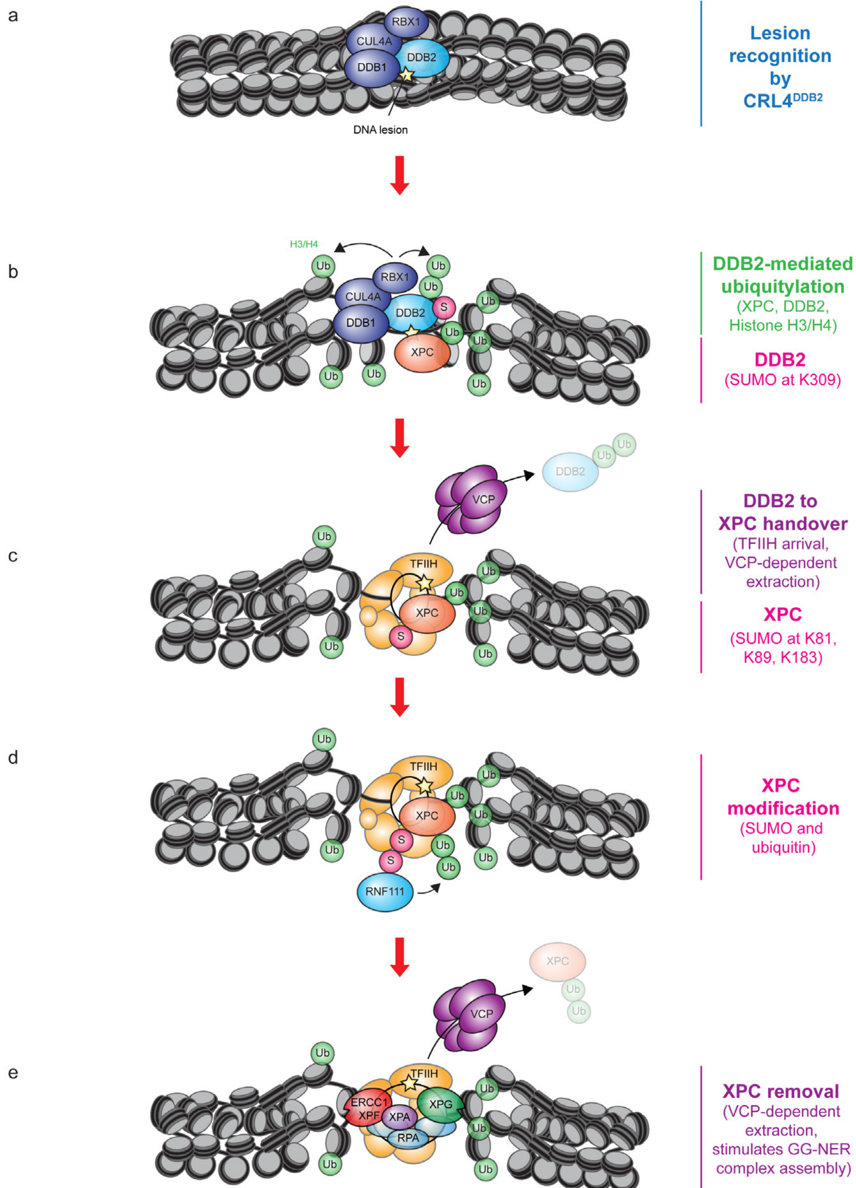

Figure 2. The role of ubiquitylation and SUMOylation in GG-NER. (a) DDB2 is part of the CRL4^{DDB2} ubiquitin ligase complex together with DDB1, CUL4A and RBX1 that binds to photolesions. (b) The CRL4^{DDB2} ligase ubiquitylates H3 and H4 leading to chromatin decompaction through an unknown mechanism, which stimulates XPC recruitment. DDB2 also ubiquitylates XPC, which increases its affinity for DNA lesions. DDB2 becomes SUMOylated at K309, which stimulates XPC recruitment and promotes CPD repair. (c) DDB2

must dissociate to allow stable XPC binding to the DNA lesion. The displacement of DDB2 is stimulated by the recruitment of TFIIH by XPC. The ubiquitin-selective segregase VCP/p97 further stimulates the dissociation of DDB2 through extraction of ubiquitylated DDB2 from chromatin. XPC is SUMOylated at K81, K89 and K183, which was suggested to stimulate the handover between XPC and DDB2. (d) The SUMO-dependent E3 ubiquitin ligase RNF111 recognizes and ubiquitylates the SUMOylated form of XPC. (e) The ubiquitylated form of XPC may also be extracted from chromatin by VCP/p97 to enable efficient recruitment of the endonuclease XPG. This is important because XPG and XPC cannot coexist in the same NER complex.

alternative - but not necessarily mutually exclusive - function for XPC SUMOylation is discussed in the section "XPC extraction from chromatin requires SUMOylation".

XPC ubiquitylation may regulate its chromatin extraction

XPC is possibly also extracted from chromatin by VCP/p97, but conflicting data exist as siRNA-mediated depletion of VCP was found to increase XPC binding to local DNA damage in one study (Puumalainen et al., 2014), while treatment of cells with VCP inhibitor was found to reduce XPC binding in another study (Ribeiro-Silva et al., 2020). Extraction of ubiquitylated XPC may facilitate the assembly of the NER pre-incision complex (Figure 2d,e). In particular the XPG endonuclease and XPC cannot coexist in the same NER complex (Riedl et al., 2003; van Cuijk et al., 2015; Wakasugi and Sancar, 1998). Importantly, ubiquitylated XPC needs to remain bound long enough to recruit the TFIIH complex, which may be regulated by two deubiquitylases, USP11 and USP7, that each interact with and deubiquitylate XPC to prevent its untimely extraction (He et al., 2014; Shah et al., 2017).

XPC extraction from chromatin requires SUMOylation

Although DDB2 was reported to ubiquitylate XPC (Sugasawa et al., 2005), another E3 ligase known as RNF111 (Arkadia) was also shown to act on XPC (Poulsen et al., 2013; van Cuijk et al., 2015). RNF111 is a so-called SUMO-targeted ubiquitin E3 ligase (STUbL) that selectively ubiquitylates substrates that were previously conjugated with SUMO (Figure 2d). Indeed, XPC is modified by SUMO-1 at lysine residues K81, K89 and K183 and by SUMO-2 under unchallenged conditions (Akita et al., 2015; van Cuijk et al., 2015), although one study reported the UV-induced SUMOylation of XPC (Wang et al., 2005). These studies showed that while SUMOylation of XPC did not affect its initial binding to lesions, it was required for the extraction of XPC from chromatin, in conjunction with ubiquitylation by RNF111 (Akita et al., 2015; Poulsen et al., 2013; Puumalainen et al., 2014; van Cuijk et al., 2015). Consistent with XPC and XPG being mutually exclusive in NER complexes, the RNF111-mediated

ubiquitylation of XPC is required for efficient XPG recruitment (van Cuijk et al., 2015) (Figure 2e). As described above, an XPC-3KR SUMOylation-deficient mutant becomes strongly immobilized on chromatin after UV irradiation in a DDB2-dependent manner. This suggests that SUMOylated XPC may regulate the release of DDB2 in trans (Akita et al., 2015). An alternative explanation, which is more in line with results from these other studies (van Cuijk et al., 2015) is that the XPC-3KR mutant itself is not extracted from chromatin in a timely manner and blocks the NER reaction. It is possible that this effect is exacerbated by DDB2, which stimulates XPC recruitment to chromatin after UV irradiation (Nishi et al., 2009), resulting in even higher levels of XPC on chromatin.

The CRL4^{DDB2} ligase and histone H2A ubiquitylation in response to UV

The ubiquitylation of histone H2A has also been linked to GG-NER (Bergink et al., 2006; Gracheva et al., 2016; Kapetanaki et al., 2006; Marteijn et al., 2009), although general consensus about the underlying mechanism is lacking. One study observed a reduction of H2A ubiquitylation within the first 30 min after UV irradiation followed by a DDB2-mediated restoration of H2A mono-ubiquitylation at 2 hours post UV to levels similar as before UV irradiation (Kapetanaki et al., 2006). Whether this reflects the canonical H2A ubiquitylation at K119 (Wang et al., 2004) or perhaps another residue detected by the same antibody is currently unclear. Conceptually, it is not clear how reducing H2A ubiquitylation levels after UV and restoring these levels in a DDB2-dependent manner could facilitate GG-NER. Another study did not observe a decrease in H2A ubiquitylation levels, but did report increased levels in the first 30 min after UV in a manner dependent on DDB2 and the canonical H2A ligase RING1B (Gracheva et al., 2016). To complicate matters further, not CRL4^{DDB2} but the E3 ubiquitin ligase RNF8 was shown to catalyze H2A ubiquitylation as a late DNA damage signalling event during GG-NER (Marteijn et al., 2009). This is consistent with an earlier study showing that H2A ubiquitylation after UV is dependent on functional GG-NER and subsequent ATR activation (Bergink et al., 2006; Hanasoge and Ljungman, 2007), which is required for H2AX phosphorylation and RNF8 recruitment (Marteijn et al., 2009). These findings suggest a mechanism in which damage excision exposes single-stranded DNA that, probably following gap extension by exonuclease EXO1 (Sertic et al., 2011), triggers ATR activation and subsequent DNA damage signalling that is similar to the DNA double-strand break (DSB) response. In the DSB response, RNF8 was shown to target histone H1 (Thorslund et al., 2015), while the subsequent recruitment of RNF168 targets histone H2A at K13/K15 (Mattiroli et al., 2012). Taken together, the

available data suggests that H3/H4 ubiquitylation by CRL4^{DDB2} complex facilitates GG-NER (Wang et al., 2006) (see section 1.1), while a potential role of H2A ubiquitylation by CRL4^{DDB2} during early GG-NER remains more enigmatic.

An alternative E3 ubiquitin ligase complex containing DDB2

One study proposed that the ubiquitylation of H2A during early GG-NER is not carried out by the canonical CRL4^{DDB2} ubiquitin complex, but rather by an alternative E3 ubiquitin ligase complex consisting of DDB2-DDB1-CUL4B-RING1B (CUL4B/RING1^{BDDB2})(Gracheva et al., 2016). RING1B is the catalytic subunit of the polycomb-repressive complex 1 involved in gene silencing during differentiation (Richly et al., 2010). The initial recruitment of CUL4B/RING1B^{DDB2} to DNA lesions by DDB2 was suggested to deposit H2A ubiquitylation, which is recognized by the ubiquitin-binding domain of ZRF1. Upon recruitment to DNA lesions, ZRF1 was suggested to remodel the CUL4B/RING1B^{DDB2} complex and exchange CUL4B-RING1B with CUL4A-RBX1, to turn the CUL4B/RING1B^{DDB2} complex into the canonical CUL4A/RBX1DDB2 complex (Gracheva et al., 2016). Instead of targeting histones, the CUL4A/RBX1^{DDB2} complex was found to ubiquitylate XPC (Gracheva et al., 2016), consistent with previous reports (Sugasawa et al., 2005).

Although the involvement of ZRF1 and the potential remodelling of a DDB2 containing E3 ubiquitin ligase complex with two functional modules - CUL4B/RING1B and CUL4A/RBX1 - in GG-NER is very intriguing, these findings have not been verified by other groups yet and also raise many conceptual questions. For instance, proteomics approaches have identified the presence of the CRL4A^{DDB2} complex containing RBX1 in unirradiated cells (Groisman et al., 2003; Kapetanaki et al., 2006; Ribeiro-Silva et al., 2020), which will be recruited to DNA lesions through DDB2. It is therefore unclear what the added advantage of localized remodelling of a CRL4^{DDB2} complex is. Also, how is the relative recruitment of the CUL4B/RING1B^{DDB2} and CUL4A/RBX1^{DDB2} complexes regulated? Answering these questions will provide a better understanding of the role of the E3 ubiquitin ligase complexes containing DDB2 during early GG-NER.

Chromatin remodelling during the DNA damage-recognition step in GG-NER

The binding of DDB2 triggers chromatin unfolding and opening in response to UV irradiation (Adam et al., 2016; Luijsterburg et al., 2012b), which is thought to facilitate XPC recruitment. Interestingly, while DDB2 recruitment occurs independently of ATP hydrolysis, the recruitment

Figure 3

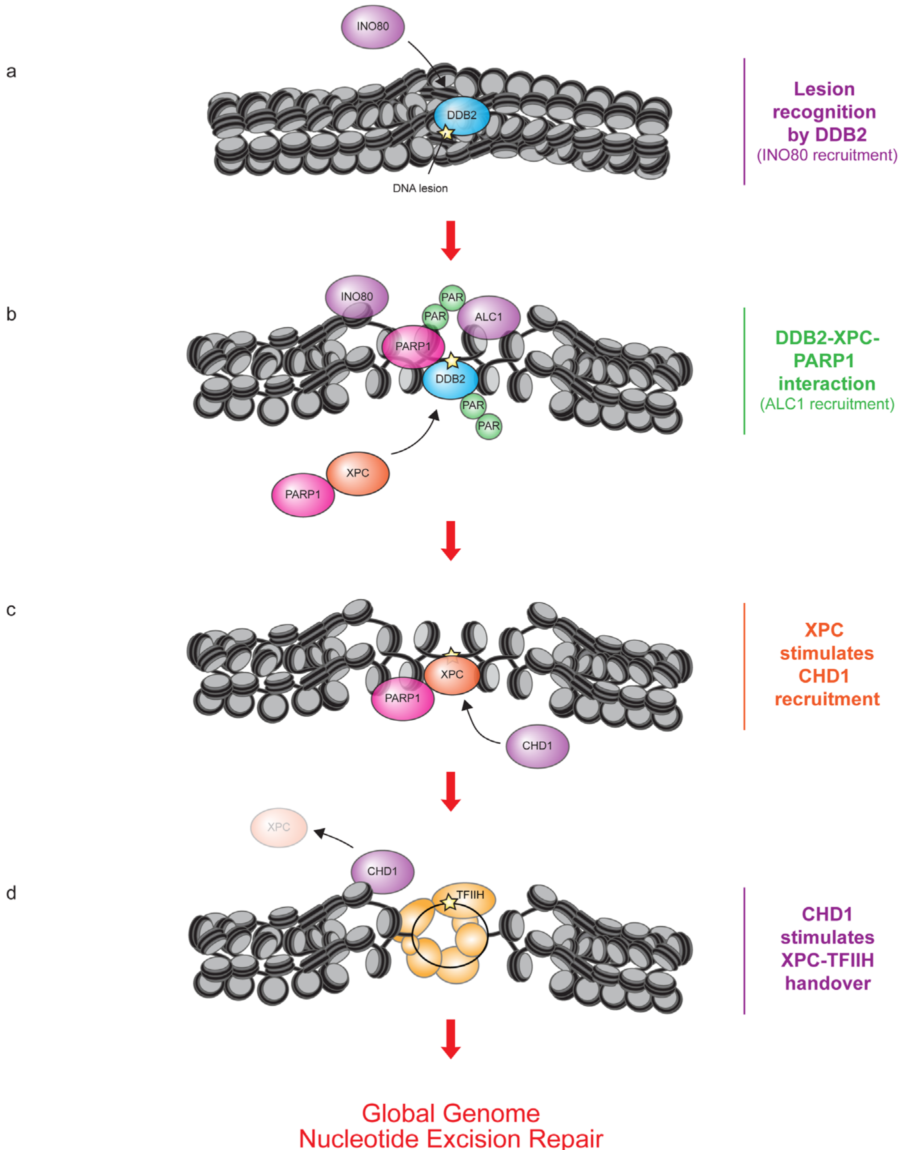

Figure 3. The role of chromatin remodelers and PARylation in GG-NER (a) Lesion recognition by DDB2 may recruit the ATP-dependent chromatin remodeler INO80. While INO80 was shown to be recruited by DDB1, we speculate that this is also dependent on DDB2. (b) DDB2 interacts with PARP1 and stimulates its catalytic activity. Note that PARP1 binds to photolesions independently of DDB2 or XPC. PARP1 modifies itself and DDB2 with PAR chains. The PAR-binding chromatin remodeler ALC1 is recruited and stimulates GG-NER. PARP1 also interacts with XPC already in the absence of DNA damage and facilitates its recruitment to photolesions, particularly at low damage load. (c) XPC

recruits the chromatin remodeler CHD1. (d) CHD1 facilitates the displacement of XPC to stimulate TFIIH recruitment.

of XPC is inhibited when ATP is depleted (Luijsterburg et al., 2012b), suggesting that chromatin accessibility is likely increased by the activity of ATP-dependent chromatin remodelers. In the following sections, we discuss the role of chromatin remodelers during the initiation of GG-NER.

The INO80 complex stimulates XPC recruitment

The INO80 remodeler consists of 10-15 polypeptides and exhibits ATP-dependent chromatin remodelling activity (Jin et al., 2005). Besides its role in DSB repair (van Attikum et al., 2004) and possibly interstrand crosslink repair (Andreev et al., 2019), the INO80 complex is also implicated in GG-NER (Jiang et al., 2010). Both the INO80 and the ARP5 subunits were shown to associate with and stimulate the removal of UV-induced DNA lesions. INO80 interacted with DDB1 and cells depleted of INO80 showed decreased XPC recruitment, suggesting that INO80 may be recruited by CRL4^{DDB2} upstream of XPC (Jiang et al., 2010) (Figure 3a). Because formal proof for this scenario is still lacking, it will be important to establish whether DDB2 is indeed required for INO80 recruitment. Interestingly, yeast INO80 interacts with Rad4 - the yeast orthologue of XPC - and INO80-deficient yeast strains are sensitive to UV irradiation (Sarkar et al., 2010). Nevertheless, in yeast INO80 was implicated in restoring chromatin after repair rather than facilitating lesion removal, making it currently unclear whether INO80 has an evolutionary conserved role or possibly multiple roles in GG-NER.

PARP1, DDB2 and XPC: A ménage à trois

Poly(ADP-ribose) polymerase 1 (PARP1) has been linked to the early stages of GG-NER through its interaction with both DDB2 (Pines et al., 2012; Robu et al., 2013) and XPC (Robu et al., 2017) (Figure 3b). PARP1 uses NAD+ as a substrate to add poly-ADP-ribose (PAR) chains to target proteins. Such PAR chains can contain up to 200 ADP-ribose units (Gibson and Kraus, 2012) and form highly branched structures (Miwa et al., 1979) thereby adding a strong negative charge to target proteins. Interestingly, PARP1 associates with UV-induced DNA lesions independently of XPC and DDB2 (Robu et al., 2017), suggesting that PARP1 may be a third independent sensor of photolesions (Pines et al., 2013; Purohit et al., 2016). The interaction between PARP1 and DDB2 was suggested to stimulate the catalytic activity of PARP1 resulting in PARylation of DDB2, which increased its chromatin retention by inhibiting its ubiquitin-mediated proteasomal degradation (Pines et al., 2012). By preventing

untimely degradation of DDB2, the PARP1-dependent modification of DDB2 stimulates XPC recruitment to DNA lesions (Pines et al., 2012; Robu et al., 2013). This illustrates that the chromatin dwell-time of DDB2 is tightly controlled to ensure that it is sufficiently long to stimulate XPC recruitment (Pines et al., 2012; Robu et al., 2013), without inhibiting full XPC engagement and subsequent TFIIH recruitment (Puumalainen et al., 2014; Ribeiro-Silva et al., 2020). Independently of this PARP1-DDB2 mechanism, PARP1 also directly interacts with XPC in the nucleoplasm of unchallenged cells and stimulates its recruitment to DNA lesions. While the catalytic activity of PARP1 was not required to form the PARP1-XPC complex, it did stimulate the recruitment of XPC to DNA lesions in a DDB2-independent manner (Robu et al., 2017). These findings reveal that PARP1 is tightly linked to early DNA damage recognition by both DDB2 and XPC (Figure 3b). What the exact mechanism of PARP1 in damage recognition is, whether XPC is involved in stimulating the catalytic activity of PARP enzymes and whether other PARP enzymes, such as PARP2 and PARP3, are involved in GG-NER remain open questions for future research.

The poly-ADP-ribose-dependent chromatin remodeler ALC1 regulates GG-NER

The ATP-dependent chromatin remodeler ALC1, also called CHD1L, becomes activated upon binding PAR chains through its macrodomain (Singh et al., 2017), resulting in increased chromatin accessibility through nucleosome sliding (Ahel et al., 2009). ALC1 is recruited to UV-induced DNA lesions in a PARP1-dependent manner and stimulates CPD repair (Pines et al., 2012) (Figure 3b). Given the intricate interplay between PARP1, DDB2 and XPC (Luijsterburg et al., 2012b; Pines et al., 2012; Robu et al., 2013; Robu et al., 2017), these DNA damage sensors are likely involved in regulating ALC1 recruitment or activation in response to UV irradiation (Figure 3b). Depletion of DDB2 was indeed shown to affect the recruitment of ALC1 to sites of UV-induced DNA lesions in XPA-deficient cells (Pines et al., 2012). It is important to note that the detection of the PAR response during GG-NER initiation in these studies often required the depletion of the PARG glycohydrolase, which catalyses removal of PAR chains, in GG-NER-deficient cells to boost PAR levels. Now that more sensitive tools have been developed in the last few years, such as recombinant antibody-like ADP-ribose binding proteins (Gibson et al., 2017), it will be important to confirm these earlier findings and re-evaluate conclusions under more physiological settings.

CHD1 stimulates the XPC to TFIIH handover

CHD1 belongs to the CHD family of ATP-dependent chromatin remodelers and contains a central SNF2- like ATPase domain, a DNA-binding domain in its C-terminal and two tandem chromodomains in its N-terminus (Marfella and Imbalzano, 2007). CHD1 was reported to be recruited to nucleosomes after UV irradiation in an XPC-dependent manner and to stimulate efficient XPC displacement and subsequent TFIIH recruitment (Ruthemann et al., 2017) (Figure 3d). Although clearly detectable, the impact on TFIIH recruitment was only modest and resulted in delayed CPD repair kinetics in CHD1-depleted cells (Ruthemann et al., 2017). Although these findings suggest that CHD1 acts on XPC to favour its displacement or that subsequent TFIIH recruitment may require a different chromatin configuration, these ideas are difficult to reconcile with NER models in which XPC forms a stable DNA damage verification complex together with TFIIH (Mu et al., 2018a; Ribeiro-Silva et al., 2020; Sugasawa et al., 2009). Thus, the precise mechanism underlying CHD1 function in GG-NER and requirement of its ATPdependent chromatin remodelling activity remain to be further verified and established. Also, whether other CHD family members, including CHD2, CHD3 and CHD4 which have been found to be important for DSB repair pathways in different chromatin environments (Goodarzi et al., 2011; Klement et al., 2014; Larsen et al., 2010; Luijsterburg et al., 2012a; Luijsterburg et al., 2016; Polo et al., 2010; Smeenk et al., 2010), have a function in NER remains to be investigated.

The role of SWI/SNF remodelers in GG-NER: a confusing affair

The SWI/SNF chromatin remodelers incorporate either BRM or BRG1 as ATPase subunit to confer ATP dependent chromatin remodelling activity (Pulice and Kadoch, 2016). The loss of either BRM or BRG1 results in a NER defect, highlighting an involvement in GG-NER (Gong et al., 2008; Ribeiro-Silva et al., 2018; Zhang et al., 2009; Zhao et al., 2009). One study reported a UV-induced interaction between BRG1 and DDB2 and suggested that BRG1 stimulates the recruitment of XPC to DNA lesions early during GG-NER (Zhang et al., 2009). Somewhat confusingly, BRG1 was found to accumulate at sites of UV-induced DNA lesions only at very late time-points after UV (8 hours) when DDB2 and XPC are no longer bound to damage sites (Zhang et al., 2009), arguing against direct recruitment of BRG1 by DDB2 to sites of DNA damage. Another study showed that BRG1 can interact with XPC in co-IP experiments and that BRG1 stimulates XPG recruitment without affecting XPC recruitment (Zhao et al., 2009).

More recent work demonstrates that these remodelers likely affect GG-NER through an indirect mechanism (Ribeiro-Silva et al., 2018). The SWI/SNF ATPases BRM and BRG1 were found to promote the

Figure 4

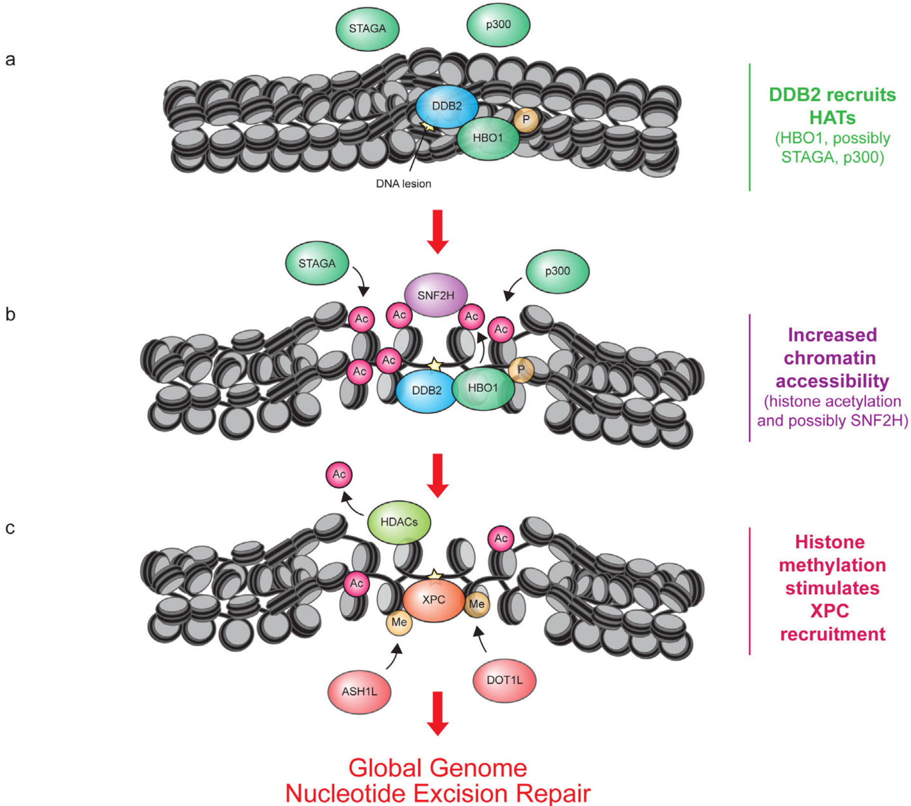

Figure 4. A model of the role of acetylation and methylation in GG-NER. (a) UV-induced lesions in chromatin are recognized by DDB2 resulting in the recruitment of three histone acetyltransferases (STAGA, p300 and phosphorylated HBO1). (b) These enzymes catalyse histone acetylation leading to increased chromatin accessibility. Phosphorylated HBO1 recruits the chromatin remodeler SNF2H. (c) Efficient recruitment of XPC also requires histone deacetylation, which is facilitated by DDB2 through the proteolytic degradation of p300 and HBO1, as well as through the recruitment of histone deacetylases (HDAC1-4). Finally, DDB2 also recruits the methyltransferase ASH1L and possibly DOT1L, which methylate H3K4 and H3K79, respectively. XPC preferentially associates with nucleosomes containing methylated histones.

transcription of the GTF2H1 gene encoding the p62 core subunit of the TFIIH complex by binding to its promoter. Depletion of either BRM or BRG1 indeed downregulates p62 expression and therefore compromises TFIIH stability and the recruitment of GG-NER proteins that bind downstream of TFIIH, including XPG (Ribeiro-Silva et al., 2018). This is consistent with reduced XPA and XPG recruitment reported earlier (Watanabe et al., 2017; Zhao et al., 2009). Importantly, the DNA damage sensitivity of BRM/BRG1-depleted cells correlates with p62 levels and re-expression of p62

restores their phenotype (Ribeiro-Silva et al., 2018), revealing an indirect involvement of SWI/SNF chromatin remodelers rather than a direct role during DNA damage recognition in GG-NER. Loss of SWI/SNF subunits was also found to confer UV hypersensitivity in yeast and C. elegans, suggestive of functional evolutionary conservation (Gong et al., 2006; Lans et al., 2010). Although the reported interaction of two subunits with Rad4 in yeast may point to a more direct role in GG-NER in this species, mapping of genome-wide repair in yeast lacking SWI/SNF subunits shows that this complex is only required for GG-NER in a small subset of genes (Bohm et al., 2021). Instead, the related RSC ATP-dependent remodeling complex was found to promote GG-NER in both nucleosomal and non-nucleosomal DNA throughout the yeast genome.

DNA damage-recognition proteins and their interconnection with histone modifications

DDB2 triggers histone acetylation in response to UV irradiation

The acetylation of histones at various lysine residues is associated with increased chromatin accessibility (Grunstein, 1997) due to a weakened electrostatic interaction between DNA and histones tails (Brower-Toland et al., 2005; Kim et al., 2015). In response to UV irradiation there is a strong increase in global H4 and H3 acetylation, suggesting that this modification acts to stimulate DNA repair in chromatin (Kim et al., 2009; Niida et al., 2017). However, the precise roles of histone acetylation in response to UV irradiation are not yet fully understood. For instance, there is a strong increase in H4 and H3 acetylation immediately as well as several hours after UV (Kim et al., 2009; Ramanathan and Smerdon, 1986), while cycling cells also degrade acetylated histones independently of NER in response to replication stress (Mandemaker et al., 2018).

Histone acetyltransferases (HATs) transfer an acetyl-group from acetyl-coenzyme A onto acceptor proteins such as histones. DDB2 interacts with a number of HATs and targets their histone acetyltransferase activity to chromatin containing DNA lesions. Earlier studies revealed that DDB2 interacts with the HATs p300 (Datta et al., 2001; Rapic-Otrin et al., 2002) and the STAGA complex (Martinez et al., 2001), containing the GCN5 catalytic subunit which predominantly acetylates H3 (Kuo et al., 1996) (Figure 4). In addition, DDB1 was found to interact with a GCN5-containing complex that acetylates H3 (Brand et al., 2001). Although GCN5 has been implicated in promoting NER via acetylation of H3K9 in both yeast and mammals (Guo et al., 2010; Waters et al., 2015; Yu et al., 2016), the exact roles of these HATs in GG-NER requires further

investigation. Nonetheless, these findings clearly highlight the connection between DDB2 and histone acetyltransferase activities. In further support of such a connection, DDB2 itself was found to be acetylated (Choudhary et al., 2009) and deacetylated by SIRT6 in response to UV irradiation (Geng et al., 2020).

More recent findings suggest that DDB2 interacts with the histone acetyltransferase HBO1, also called KAT7, from the MYST family in a UV-dependent manner and facilitates its recruitment to CPDs (Niida et al., 2017). Once recruited by DDB2, the HBO1 enzymatic activity stimulates acetylation of H4 and H3K14 and recruits the ATP-dependent chromatin remodeler ACF1-SNF2H through protein-protein interaction in response to UV irradiation, which facilitates XPC recruitment to photolesions (Niida et al., 2017) (Figure 4). It should be mentioned however, that an earlier study found that ACF1-SNF2H functions in TC-NER without an apparent role in regulating GG-NER efficiency (Aydin et al., 2014). DDB2 was suggested to specifically interact with and recruit phosphorylated HBO1 to sites of DNA damage, which is a substrate of the ATR protein kinase (Matsunuma et al., 2016). It is however unclear how HBO1 can be precisely phosphorylated by ATR. While ATR has been implicated during the damage recognition step (Ray et al., 2013; Ray et al., 2009), multiple studies have shown that ATR activation is triggered later in NER in a manner that is dependent on dual incision (Hanasoge and Ljungman, 2007; Marini et al., 2006; Marteijn et al., 2009; Matsumoto et al., 2007; Vrouwe et al., 2011). One potential explanation could be that successful repair of 6-4PP triggers ATR activation, which would stimulate the HBO1-DDB2 interaction and facilitate CPD repair.

Histone deacetylation stimulates XPC recruitment

While DDB2 may stimulate UV-induced histone acetylation during early repair, DDB2 may also promote the reversal of this chromatin mark at later time-points by regulating the proteolytic degradation of HATs and the recruitment of histone deacetylases (HDACs). DDB2 is incorporated in the $CRL4^{DDB2}$ E3 ubiquitin ligase complex (Groisman et al., 2003) that ubiquitylates phosphorylated HBO1 leading to its proteasomal degradation after UV irradiation (Matsunuma et al., 2016). Similarly, p300 is also degraded by the proteasome in a UV-dependent manner (Wang et al., 2013), but to what extent this is regulated by DDB2 remains to be determined.

DDB2 was also reported to facilitate recruitment of histone deacetylases HDAC1 and HDAC2 to UV-induced DNA lesions resulting in deacetylation of H3K56 (Zhu et al., 2015). Indeed, acetylation levels of both H3K56 and H3K9 were reduced in response to UV irradiation (Tjeertes et

al., 2009). At late time-points after UV H3K56 acetylation was increased, a step suggested to shut-down the induced cell cycle checkpoint (Battu et al., 2011). The precise function of H3K9 and H3K56 deacetylation during the early steps of GG-NER remains to be elucidated.

Besides HDAC1 and HDAC2 (Zhu et al., 2015), additional histone deacetylation steps by HDAC3 and HDAC4 have been implicated in GG-NER. In fact, all four HDACs were found to stimulate recruitment of XPC to UV-induced DNA lesions (Kakumu et al., 2017; Li et al., 2020; Nishimoto et al., 2020), possibly by lowering the inhibitory impact of histone acetylation on XPC binding to nucleosomes (Kakumu et al., 2017) (Figure 4). Although the precise recruitment mechanism of HDAC3 and HDAC4 and the potential involvement of DDB2 is currently unclear, HDAC3 was specifically linked to H3K14 deacetylation in response to UV irradiation, which was found to stimulate CPD repair in chromatin (Li et al., 2020; Nishimoto et al., 2020). How the HBO1-dependent H3K14 acetylation and the HDAC3-dependent H3K14 deacetylation are orchestrated and synergize to stimulate CPD repair remains to be elucidated. Although current literature suggests that DDB2 stimulates recruitment of HDAC1, HDAC2 and possibly other deacetylases resulting in local histone deacetylation (H3K9, H3K14, H3K56, H3K27) necessary for efficient XPC recruitment, further studies are needed to confirm these findings and provide a mechanistic basis for how histone deacetylation facilitates XPC binding. Importantly, it remains to be determined how a combinatorial chromatin code involving specific acetylated and deacetylated histone tails shapes the optimal chromatin landscape for GG-NER. Considering that UV irradiation also triggers replication stress that causes proteasomal degradation of acetylated histones (Mandemaker et al., 2018) and that both DDB2 and XPC are rapidly recruited to DNA damage sites within seconds (Hoogstraten et al., 2008; Luijsterburg et al., 2007), it will be important to determine the histone PTM code immediately after UV irradiation and independently of DNA replication.

Histone methylation stimulates the DDB2 – XPC handover

Histone methylation is catalysed by histone methyltransferases that mono, di or tri-methylate histone tails (Gong and Miller, 2019). DDB2 was found to interact with and recruit the ASH1L histone methyltransferase to UV-induced DNA lesions resulting in increased H3K4 tri-methylation levels in chromatin containing DNA lesions, which is required for the repair of CPDs (Balbo Pogliano et al., 2017). H3K4 tri-methylation, in turn, stimulates the association of XPC with nucleosomes involving a short β-turn motif (XPC residues 741–757) located between the two well-characterized β-hairpin domains BHD2 and BHD3 involved in DNA binding (Balbo Pogliano et

al., 2017)(see Figure 1b). Conversely, DDB2 preferentially associates with unmethylated nucleosomes, suggesting that H3K4 tri-methylation may stimulate the DDB2 - XPC handover at CPDs (Figure 4). The tri-methylation of H3K4 is associated with active transcription and serves as a binding platform for chromatin remodelers (Flanagan et al., 2005). Thus, UV-induced histone methylation could possibly trigger chromatin remodelling to facilitate GG NER besides directly influencing XPC binding as well.

In addition to H3K4 tri-methylation, UV irradiation was also found to trigger increased H3K79 tri-methylation by methyltranferase DOT1L (Zhu et al., 2018). In contrast to K4 which is located in the H3 tail, the K79 residue is located in the H3 core. The action of DOT1L is thought to facilitate XPC recruitment in part through depositing H3K79 tri-methylation to trigger XPC binding and in part through a direct protein-protein interaction between XPC and DOT1L (Zhu et al., 2018). Similarly, yeast DOT1L was found to promote GG-NER via H3K79 tri-methylation (Bostelman et al., 2007; Tatum and Li, 2011). However, unlike in mammalian cells, which show increased H3K79 tri-methylation (Zhu et al., 2018), UV irradiation does not appear to increase H3K79 tri-methylation in yeast (Rossodivita et al., 2014; Tatum and Li, 2011). By contrast, another study in mouse embryonic fibroblasts challenged the view that DOT1L is important for GG-NER, suggesting it rather acts in transcription recovery after UV (Oksenych et al., 2013). Interestingly, mice genetically deleted for DOT1L develop melanomas upon UV irradiation, consistent with the frequent deletion of DOT1L observed in human melanomas (Zhu et al., 2018). Thus, how the XPC-DOT1L interaction contributes to GG-NER and whether DNA damage detection by XPC is directly influenced by its interaction with histones needs confirmation and further investigation.

The spatial organization of GG-NER in distinct chromatin domains

The cell nucleus is a highly compartmentalized structure that contains distinct structural domains. Chromosomes consists of several dense chromatin domains of about 100-500 nm that each consist of several megabase pairs of DNA. An approximately 100-nm-wide shell at the surface of condensed chromatin domains - known as the perichromatin region - contains partly decondensed chromatin where GG-NER was shown to mainly take place (Fakan and van Driel, 2007; Solimando et al., 2009). Electron microscopy experiments revealed that XPC is only moderately enriched in condensed chromatin domains, while both XPC and XPA became strongly enriched in the perichromatin region

following UV irradiation. These findings suggest that DNA lesions are recognized in condensed chromatin domains and subsequently relocate to the perichromatin region to be repaired. Indeed, electron microscopy experiments show that UV-damaged chromatin domains undergo significant expansion, which might promote this translocation (Solimando et al., 2009). Similarly, DNA double strand breaks in heterochromatin were also found to relocate to the periphery of condensed chromatin domains to be repaired (Chiolo et al., 2011; Tsouroula et al., 2016).

In line with these findings, the repair of CPDs in heterochromatin is slower than in euchromatin and strongly depends on DDB2 for efficient repair (Adar et al., 2016; Han et al., 2016). Live-cell imaging revealed that DDB2 mediates extensive heterochromatin decompaction that is accompanied by linker histone displacement (Fortuny et al., 2021). Interestingly, the UV-induced rapid heterochromatin decompaction occurred within 30 min, is fully compatible with the recruitment of GG-NER proteins within heterochromatin domains, and was followed by a much slower heterochromatin recompaction phase within 12 hours (Fortuny et al., 2021).

While CPDs form in both eu- and heterochromatin, it appears that UV irradiation selectively triggers 6-4 PP formation in euchromatin (Han et al., 2016), with a preference for internucleosomal regions over nucleosome core particles (Fei et al., 2011). Interestingly, DDB2 preferentially associates with internucleosomal regions and directs XPC to these sites in a ubiquitin-dependent manner to suppress the association of XPC with nucleosome core particles (Fei et al., 2011). According to this model, DDB2 prioritizes GG-NER in internucleosomal regions to ensure rapid repair of 6-4PPs and CPDs in these genomic regions, while the repair of CPDs in nucleosome core particles is stimulated by protein-protein interactions between DDB2 and XPC in a ubiquitin-independent mechanism (Fei et al., 2011).

Concluding remarks

The last few years have witnessed the identification of many new links between chromatin modulators and GG-NER. This review focused on recent insights into the coordinated DDB2-dependent recruitment of histone acetyltransferases (Datta et al., 2001; Niida et al., 2017) and histone methyltransferases (Balbo Pogliano et al., 2017) that together with the DDB2-associated E3 ubiquitin ligase (Gracheva et al., 2016; Wang et al., 2006) extensively modify histone tails to create a local chromatin environment that facilitates early XPC recruitment. Identifying the specific histone tail residues that are modified during GG-NER and their interconnections will be important future goals, together with mechanistic studies to unravel how exactly histone PTMs influence the binding of XPC to DNA and its detection of DNA lesions. These events are aided by the association of a number of ATP-dependent chromatin remodelers that probably mediate further chromatin opening to facilitate not only early recognition of DNA lesions (Jiang et al., 2010; Niida et al., 2017; Pines et al., 2012), but possibly also DNA damage handover to promote progression of the GG-NER reaction (Ruthemann et al., 2017). To better understand their precise involvement, it will be necessary to study histone and nucleosome occupancy and dynamics in response to UV-lesion induction, which has thus far been difficult because NER substrate lesions cannot be induced at a predefined location. Electron and fluorescence microscopic techniques have found clear evidence for chromatin expansion, histone eviction and chromatin expansion and restoration during GG-NER and TC-NER initiation, and after completion of repair (Adam et al., 2016; Adam et al., 2013; Dinant et al., 2013; Duan and Smerdon, 2010; Luijsterburg et al., 2012b; Solimando et al., 2009), but thus far no clear functional requirement in this process for ATP-dependent chromatin remodelers or histone chaperones during GG-NER was observed. Possibly, techniques to map the nucleosomal landscape at single nucleotide resolution, applied after UV in both yeast and mammals (Nakata et al., 1989; van Eijk et al., 2019), may be helpful. A third seemingly independent DNA lesion-recognition protein - PARP1 - also acts in GG-NER (Luijsterburg et al., 2012b; Pines et al., 2012; Robu et al., 2013; Robu et al., 2017), but its precise links with XPC and DDB2 need further exploration.

An emerging theme is that DNA lesion-recognition factors also need to dissociate in a timely fashion to prevent them from inhibiting subsequent repair steps. Timely removal from chromatin is tightly coordinated

through ubiquitylation of both XPC and DDB2 and their subsequent ubiquitin-dependent extraction by the VCP segregase (Puumalainen et al., 2014; Ribeiro-Silva et al., 2020). These ubiquitylation events, in turn, are also subjected to tight regulation and require prior SUMOylation of XPC (Poulsen et al., 2013; van Cuijk et al., 2015) or can be prevented by competitive PARylation of DDB2 (Pines et al., 2012). Powerful new methods including sensitive proteomic approaches (Branon et al., 2018) and genome-wide CRISPR screens (Olivieri et al., 2020) will not only identify the full repertoire of chromatin modulators of GG-NER, but will also facilitate subsequent structural studies of how GG-NER operates in nucleosomes by cryo-EM (Matsumoto et al., 2019). New developments now allow the study of GG-NER in intact organisms (Sabatella et al., 2021), providing insights into developmentally regulated chromatin modulators. A better understanding of how these posttranslational modifications and remodelers progressively modify chromatin in a stepwise fashion during the different stages of repair will further reveal how GG-NER leaves its mark on chromatin.

Table 1. Chromatin changes triggered by DDB2

Protein	Modification	Impact on chromatin	References
ALC1	Chromatin remodeler	DDB2 stimulates the recruitment of the ATP-dependent chromatin remodeler ALC1 to UV damage	(Pines et al., 2012)
ASH1L	Histone methyltransferase	DDB2 interacts with and recruits ASH1L to UV-induced DNA lesions resulting in increased H3K4 tri-methylation levels in chromatin containing DNA lesions. Loss of ASH1L leads to a CPD repair defect	(Balbo Pogliano et al., 2017)
H2A	Ubiquitylation	DDB2 forms a complex with CUL4B-RING1B that ubiquitylates H2A at K119. Ubiquitylated H2A is a docking platform for ZRF1	(Gracheva et al., 2016)
H3, H4	Ubiquitylation	DDB2 forms complex with CUL4A-RBX1 that ubiquitylates H3 and H4 in response to UV	(Gracheva et al., 2016; Wang et al., 2006)
HBO1	Acetylation (HAT)	DDB2 interacts with phosphorylated HBO1 which acetylates H3K14. HBO1 recruits the chromatin remodeler ACF1-SNF2H. DDB2 ubiquitylates HBO1 triggering its degradation at late time-points	(Niida et al., 2017)
HDAC1, HDAC2	Deacetylation (HDAC)	DDB2 interacts with HDAC1 and HDAC2 resulting in H3K56 deacetylation	(Zhu et al., 2015)
INO80	Chromatin remodeler	INO80 interacts with DDB1 and associates with UV-induced lesions, suggesting that its recruitment is mediated by DDB2. Loss of INO80 leads to a CPD repair defect	(Jiang et al., 2010)
p300	Acetylation (HAT)	DDB2-DDB1 interacts with p300 (through DDB1)	(Datta et al., 2001; Rapic-Otrin et al., 2002)
PARP1	PARylation	PARP1 interacts with DDB2, which PARylates DDB2 to regulate its ubiquitylation and chromatin retention	(Pines et al., 2012; Robu et al., 2013)
SIRT6	Deacetylation (HDAC)	SIRT6 interacts with DDB2 and deacetylates lysines K35 and K77 in response to UV. Deacetylation promotes ubiquitylation and VCP/p97-mediated chromatin extraction	(Geng et al., 2020)
STAGA	Acetylation (HAT)	STAGA interacts with DDB1, and thus indirectly with the DDB2-DDB1 complex. The STAGA complex acetylates H3	(Martinez et al., 2001)

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Table 1. Proteins that affect the recruitment of XPC to DNA lesions

Protein	Impact on XPC recruitment to DNA lesions	References
ASH1L	ASH1L-mediated H3K4 tri-methylation stimulates the association of XPC with nucleosomes. This involves a short β-turn motif (XPC residues 741–757) located between the two well-characterized β-hairpin domains BHD2 and BHD3 involved in DNA binding	(Balbo Pogliano et al., 2017)
DDB2	DDB2 stimulates chromatin unfolding and XPC recruitment to photolesions.	(Luijsterburg et al., 2012b; Moser et al., 2005)
DOT1L	DOT1L stimulates XPC recruitment in part through depositing H3K79 tri-methylation to trigger XPC binding and in part through a direct protein-protein interaction between XPC and DOT1L	(Zhu et al., 2018)
HDAC3	HDAC3 deacetylates H3K12 which facilitates the recruitment of XPC. There are no detectable interactions between HDAC3 and XPC	(Nishimoto et al., 2020)
HDAC4	HDAC4 interacts with XPC. The recruitment of XPC to photolesions is stimulated by HDAC4-mediated deacetylation	(Li et al., 2020)
INO80	XPC recruitment is stimulated by the DDB1-mediated interaction with the chromatin remodeler INO80.	(Jiang et al., 2010)
PARP1	XPC and PARP1 interact. The recruitment of XPC to DNA lesions is stimulated by PARP1-mediated PARylation	(Luijsterburg et al., 2012b; Robu et al., 2017)
DDB2	The SUMOylation of DDB2 at K309 stimulates XPC recruitment to sites of local UV damage	(Han et al., 2017)

Table 1. Proteins and modification that regulate XPC retention at DNA lesions

Protein	Modification	Impact on XPC retention at DNA lesions	References
CHD1	Recruitment	XPC recruits the chromatin remodeler CHD1 to nucleosomes to stimulate XPC displacement and TFIIH recruitment	(Ruthemann et al., 2017)
DDB2	Ubiquitylation	DDB2 ubiquitylates XPC which stimulates its binding to DNA	(Sugasawa et al., 2005)
RNF111/ Arkadia	Ubiquitylation	RNF111 ubiquitylates SUMOylated XPC. RNF111-mediated ubiquitylation stimulates chromatin extraction and promotes XPG and ERCC1/XPF recruitment	(Poulsen et al., 2013; van Cuijk et al., 2015)
SUMO-1	SUMOylation	XPC is SUMOylated by SUMO-1 at residues K81, K89, K183. XPC SUMOylation stimulates XPC ubiquitylation	(Akita et al., 2015; Wang et al., 2005)
TFIIH	Protein	TFIIH recruitment by XPC promotes DDB2 dissociation and stabilizes XPC chromatin binding	(Ribeiro-Silva et al., 2020)
USP11	Deubiquitylation	USP11 deubiquitylates XPC to prevent the VCP/p97-mediated extraction of XPC from chromatin	(Shah et al., 2017)
USP7	Deubiquitylation	USP7 deubiquitylates XPC to prevent the VCP/p97-mediated extraction of XPC from chromatin	(He et al., 2014)

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