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The emerging role of deubiquitination in nucleotide excision repair

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Abstract

Nucleotide excision repair (NER) protects genome stability by eliminating DNA helix distorting lesions, such as those induced by UV radiation. The addition and removal of ubiquitin, namely, ubiquitination and deubiquitination, have recently been demonstrated as general mechanisms to regulate protein functions. Accumulating evidence shows that several NER factors are subjected to extensive regulation by ubiquitination and deubiquitination. Thus, the balance between E3 ligases and deubiquitinating enzyme activities can dynamically alter the ubiquitin landscape at DNA damage sites, thereby regulating NER efficiency. Current knowledge about XPC ubiquitination by different ubiquitin E3 ligases highlights the importance of ubiquitin linkage types in regulating XPC binding and release from damaged DNA. Here, we discuss the emerging roles of deubiquitinating enzymes and their ubiquitin linkage specificities in NER.

Keywords

ubiquitination; deubiquitination; GG-NER; TC-NER; E3 ubiquitin ligase; DUBs; ubiquitin linkage specificity; segregase

Introduction: Ubiquitination in NER

Numerous cellular processes are regulated by the post-translational attachment of ubiquitin, including protein degradation, cell cycle regulation, DNA repair [1-4], transcription, cell signaling and endocytosis [5, 6]. Ubiquitin, a 76 amino acid polypeptide, is used to control protein stability, translocation and activity [7, 8]. Protein ubiquitination is a multi-step process requiring the sequential action of three enzymes: the ubiquitin-activating enzymes (E1s) activate ubiquitin that is subsequently loaded onto ubiquitin-conjugating enzymes (E2s); E2 then recruits the target protein, and complexes with ubiquitin ligase (E3) which finally covalently attaches the activated ubiquitin peptide to the lysine residue of the target

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protein [7, 9]. There are approximately 2 E1 [10], 35 E2 [11] and about 1000 E3 enzymes [12] encoded in the human genome. The linkage specificity and processivity of chain elongation are largely determined by the pairing of specific E2s and E3s. Concerted actions of E1, E2 and E3 result in mono- or polyubiquitination of target proteins. For polyubiquitination, the initial ubiquitin attached to the target is extended by the covalent attachment of additional ubiquitin moieties to form polyubiquitin chains. This involves the use of seven lysine residues (Lys 6, 11, 27, 29, 33, 48 and 63) and the N-terminal residue Met1 on the previously added ubiquitin peptide [6]. Moreover, because any one of ubiquitin's seven internal lysine residues or its amino terminus can potentially serve as sites for further conjugation, the resulting poly-ubiquitin chains can have various, highly distinct topologies with different biochemical and biological functions. For example, the classical function of ubiquitination, primarily through Lys48-linked chains, targets substrate proteins for proteasome-dependent degradation [7]. K63 polyubiquitination, another well-studied linkage, is involved in the recruitment of DNA repair proteins to DNA damage sites [13, 14]. The specific functions of other linkage types (Ly6, Lys11, Lys27, Lys29 and Lys33) are currently less understood [6].

NER is the most versatile form of DNA repair. It repairs helix-distorting DNA lesions that are often caused by UV radiation, reactive oxygen species and cisplatin. CPDs and 6–4PPs, the two major lesions induced by UV radiation, are repaired by the NER pathway [15]. NER consists of two distinct pathways for DNA damage recognition. One is global genome NER (GG-NER) [15, 16], which operates throughout the entire genome, and the other is transcription-coupled NER (TC-NER) [17, 18], which removes lesions specifically from the transcribed DNA strand of transcriptionally active genes. The main difference in these two sub-pathways lies in the DNA damage recognition step [19]. While RNA polymerase II stalling at a damaged site is probably employed as a damage sensor in TC-NER, a complex containing the XPC protein plays an essential role in damage recognition in GG-NER. Subsequent steps after damage recognition are shared by both subpathways: first, transcription factor IIH (TFIIH) unwinds the DNA duplex around the lesion. With the recruitment of XPA and replication protein A, an oligonucleotide of bearing the lesion, around 30 nucleotides in length, is excised by two endonucleases, ERCC1-XPF and XPG, which make incisions at sites 5′ and 3′ to the lesion, respectively. The resulting single-stranded gap is filled by DNA polymerase and the DNA strands are finally rejoined by DNA ligase I or DNA ligase III/XRCC1 [16, 20].

Ubiquitinating NER proteins: The E3 ligases

$CRL4^{DDB2}$ and $CRL4^{CSA}$ are two best-studied CRL4 ubiquitin E3 ligases involved in NER, with DDB2 and CSA being the ligase substrate receptors in the two ligases, respectively [21, 22]. DDB2 is not only a substrate receptor, but also a substrate itself for $CRL4^{DDB2}$. In fact, DDB2 and XPC are two substrates for the $CRL4^{DDB2}$ E3 ligase [23, 24]. Following UV irradiation, DDB2 immediately accumulates on damaged DNA and is ubiquitinated by $CRL4^{DDB2}$ [25]. DDB2 lysine residues 5, 11, 35, 40, and 151 are identified as the main sites for ubiquitination in vitro, using mass spectrometry [26]. Mutation of these seven Lys residues on DDB2 led to increased stability after UV treatment. It is believed that $CRL4^{DDB2}$ forms K48-linked polyubiquitin chains on DDB2, as suggested by K48-linked

ubiquitin accumulation at CPD spots, concurrent with DDB2 binding [27]. Since K48-linked polyubiquitination is generally a degradation signal, K48-linked ubiquitin chains on DDB2 would be consistent with the observation that DDB2 is quickly degraded after UV irradiation [25, 28]. Besides DDB2, another important substrate for $CRL4^{DDB2}$ is XPC. After UV irradiation, XPC is immediately recruited to the site of DNA damage and associates with chromatin in a DDB2-dependent manner [29].

Interestingly, although both DDB2 and XPC are substrates of The $CRL4^{DDB2}$ E3 ligase complex, the fates of two proteins are quite different. Ubiquitination of XPC increases its binding affinity to damaged DNA, but ubiquitination of DDB2 diminishes its strong binding activity to DNA lesion [24]. XPC ubiquitination does not lead to significant XPC degradation and appears to be reversible, whileDDB2 is degraded within hours after UV treatment by the proteasome [24], as noted above. There is evidence suggesting that a small fraction of XPC, like DDB2, can also be degraded by the proteasome in an ubiquitin-independent manner [30]. Based on above observations, a “lesion handover” mechanism between XPC and DDB2 proposed by Sugasawa, et. al. seems very plausible [24].

The crystal structure of $CRL4^{CSA}$ E3 ligase shows high structural similarity to that of $CRL4^{DDB2}$ E3 ligase [26]. The best-known substrate for $CRL4^{CSA}$ E3 ligase is CSB (Cockayne syndrome protein B). Patients suffering from the severe human disorder Cockayne syndrome (CS) have defective TC-NER due to mutations in either the CSA or the CSB gene and both CSA and CSB are TC-NER factors [17]. TC-NER is initiated by lesion-stalled RNA Pol II, which recruits the TC-NER-specific Cockayne syndrome proteins CSA and CSB. CSA and CSB are required for further assembly of the TC-NER machinery. CSA not only interacts with CSB but also is required for UV-induced degradation of CSB. *In vitro* ubiquitin assays further demonstrate that $CRL4^{CSA}$ ubiquitinates CSB [26].

In eukaryotic cells, the NER machinery operates on lesions situated within chromatin. $CRL4^{DDB2}$ has been shown to also target histones for ubiquitination to facilitate DNA repair [31] [32]. Further in vitro characterization of CRL4 E3 ligase shows that this complex can ubiquitinate all forms of histones with similar efficiency and can mono, di-, tri- or multimer-ubiquitinate histone [33]. In response to UV irradiation, the levels of ubiquitinated H3 and H4 increase quickly and the redistribution of ubiquitinated H3 after UV irradiation can be detected, suggesting that H3 and H4 ubiquitination weakens the interaction between histones and DNA to facilitate the recruitment of XPC repair factor to damaged DNA [33]. In summary, the CRL4 E3 ligase is utilized in the DNA lesion recognition step in both GG-NER and TC-NER, and is further involved in histone modifications to facilitate UV-induced DNA damage repair.

The RNF111 E3 ligase

Characterization of RNF111 reveals that it contains three highly conserved, SUMO-interacting motifs in its N-terminal region, suggesting that RNF111 is a SUMO-targeted ubiquitin ligase. Poulsen et al. first reports the involvement of RNF111 in NER, when they demonstrated by $RNF111^{-/-}$ MEFs showing impaired UV-induced DNA repair synthesis [34]. In addition to ubiquitination, XPC is also modified by sumoylation [35] and RNF111 has been shown to ubiquitinate pre-sumoylated XPC [34]. It is important to note that both

CRL4^{DDB2} and RNF111 ubiquitinate XPC in response to UV. However, inhibition of CRL4^{DDB2} decreased XPC accumulation on chromatin after UV radiation [36], while RNF111 depletion led to an increase in XPC accumulation at these UV damage sites [34]. RNF111 promotes NER by regulating the proper release of XPC from damaged sites, therefore generating better access for downstream endonucleases XPG and XPF binding [37]. It appears that ubiquitin linkages mediated by CRL4^{DDB2} (likely Lys48 linkage) and RNF111 (likely Lys63 linkage) [37] are the underlying mechanisms to either promote XPC binding to damaged chromatin or stimulate proper release of XPC from DNA damage to facilitate recruitment of downstream NER factors.

Removing ubiquitinated NER proteins from chromatin: The p97 segregase

The ATP-driven chaperone valosin-containing protein (VCP)/p97/Cdc48 is an ubiquitin selective segregase and serves as an additional layer of regulation to the ubiquitin system [38]. p97 is known to extract mono- or oligoubiquitinated proteins from complexes and delivers them to the ubiquitin proteasome system [39]. After extraction of ubiquitinated substrates from larger complexes, segregated proteins can be polyubiquitinated, resulting in proteasomal degradation, or be deubiquitinated and released into cytosol. A recent report has demonstrated that p97 plays a role in NER [27, 40]. p97 is recruited to CPD sites, and this recruitment is ubiquitin-dependent and DDB2-dependent. As mentioned earlier, DNA damage recognition factors DDB2 and XPC are ubiquitinated upon UV irradiation. p97 segregase is found to extract DDB2 and XPC from chromatin [27]. If p97 is non-functional or depleted, ubiquitinated DDB2 and XPC remain bound on chromatin, resulting in reduced UV lesion repair and increased chromosomal aberrations. This study shows that the p97 segregase is critical for efficient NER by coordinating DDB2 and XPC functions. Another recent study by He et. al further confirms that p97 translocates to UV damage sites where XPC and γH2AX localize [40]. When p97 is inhibited, more ubiquitinated XPC forms are detected in the soluble chromatin fraction, suggesting that p97 aids extraction of ubiquitinated XPC from chromatin. These two studies demonstrate that p97 can stimulate GG-NER by extracting ubiquitinated DDB2 and XPC from DNA damage sites, presumably facilitating recruitment of subsequent NER factors after DNA damage recognition. Taken together, p97 has a very important and dynamic role in NER.

Deubiquitinating NER proteins: The DUBs involved

Ubiquitination is a dynamic and reversible process. A family of enzymes known as DUBs play critical roles in ubiquitin precursor processing and ubiquitin removal from target proteins [41]. DUBs are proteases that catalyze a proteolytic reaction between a Lys ε-amino group and a carboxyl group corresponding to the C-terminus of ubiquitin, therefore removing covalently attached ubiquitin from proteins to control substrate stability and activity. DUBs maintain the balance of ubiquitination dynamics to control substrate protein stability, activity and localization. By doing so, DUBs are involved in a myriad of cellular functions, including cell homeostasis, signaling pathways, transcription, histone modification and DNA repair pathways [42]. The human genome encodes about 90 DUBs

that are divided into five subfamilies based on catalytic mechanism and the fold of the active site domain [43-45]. The following DUBs, namely USP7, USP24 and USP45, have been linked to NER.

USP7 targeting XPC and CSB

Herpes virus-associated ubiquitin-specific protease (HAUSP/USP7) is one of the well-known deubiquitinating enzymes due to its relevance to the Mdm2-p53 pathway [46-49]. USP7 has also been shown to play a role in UV damage response pathway by regulating events in GG-NER and TC-NER. USP7 is implicated in GG-NER by deubiquitinating XPC [40]. As mentioned earlier, XPC is the DNA damage recognition factor in GG-NER. It becomes ubiquitinated by the CRL4 E3 ligase or RNF11 when cells are irradiated with UV, yet ubiquitination of XPC does not lead to significant proteasomal degradation. It appears that ubiquitinated XPC can be converted back to its unmodified state, presumably by one or more DUBs. Inhibition of USP7 slightly increased the XPC ubiquitination level and USP7 and XPC interact *in vitro* and *in vivo* [40]. Without USP7, cells have decreased efficiency in repair UV lesions. Therefore USP7 regulates GG-NER pathway by deubiquitinating and returning XPC to its unmodified state [40].

USP7 also regulates TC-NER by interacting with UVSSA and controlling the stability of CSB/ERCC6 and RNA pol II. Ultraviolet (UV)-sensitive syndrome ($UV^{S}S$) is a human disorder that is associated with TC-NER. Three reports in 2012 identify *UVSSA* gene mutation as being responsible for this disorder using three different approaches [50-52]. Interestingly, USP7 is found to interact UVSSA using mass spectrometry, co-immunoprecipitation assay further confirms the interaction, suggesting a role of USP7 in TC-NER. USP7 can regulate ubiquitination of TC-NER proteins, and stabilizes RNA polymerase II. First, USP7 resides on damaged chromatin with TC-NER factors in a UV-dependent manner, and its recruitment is likely through its interaction with UVSSA. Depletion of USP7 leads to reduced recovery of RNA synthesis and destabilization of CSB protein as seen in $UV^{S}S$-A cells [52]. Therefore, USP7 is delivered by UVSSA to the vicinity of TC-NER factors to regulate their ubiquitination status. Second, RNA pol II is stalled at UV-induced lesion, thereby initiating TC-NER. RNA pol II is ubiquitinated, depletion of UVSSA or USP7 also destabilizes RNA polII [50]. In summary, USP7 and UVSSA cooperate to control the stability of CSB and RNA pol II to ensure efficient TC-NER and transcription resumption.

USP24 targeting DDB2 and p53

USP24 is a 2,620-amino acid ubiquitin-specific protease, containing a UBA domain (ubiquitin-associated domain), a UBL domain (ubiquitin-like domain), and a USP domain (ubiquitin-specific protease domain) [53]. In a yeast-two hybrid screen, USP24 was identified as an interaction partner of DDB2 [54]. Knockdown of USP24 resulted in a decreased level of DDB2, suggesting that USP24 stabilizes DDB2 by removing the ubiquitin moiety from modified DDB2, thereby preventing DDB2 degradation. In multiple cell lines, USP24 protein was found to be induced at 3 hours after UV. [53]. This UV-induced upregulation of USP24 was blocked by ATM inhibitor Ku55933 and siRNA knockdown of ATM, suggesting that upregulation of USP24 is ATM-dependent. USP24 is found to

deubiquitinate p53 both *in vitro* and *in vivo* [53]. p53 is stabilized in response to cellular stress, such as ultraviolet (UV), due to decreased degradation. When USP24 is depleted in HCT116 cells, p53 fails to accumulate after UV, suggesting USP24 plays a role in UV-induced p53 stabilization [53]. Both the UBA domain and the catalytic residue cysteine 1697 are required for USP24 to deubiquitinate p53 [53]. Moreover, knockdown of USP24 affects UV-induced apoptosis in a p53-dependent manner. The hypoxanthine phosphoribosyltransferase (HPRT) gene mutation assay shows that HCT116 cells with USP24 depletion exhibit significantly elevated mutation rates at the endogenous HPRT gene, implying an important role for USP24 in maintaining genome stability[53].

USP45 targeting ERCC1

Like USP24, USP45 is another less understood DUB involved in NER. CPD repair in USP45 knockout cells is significantly impaired compared to control cell lines, suggesting USP45's role in UV-induced damage repair [55]. It is demonstrated that USP45 plays a role in CPD repair, possibly through regulating a NER factor, the ERCC1 endonuclease. Both mass spectrometry and yeast two-hybrid system identify that USP45 interacts with ERCC1, and it was also demonstrated that USP45 deubiquitinates ERCC1 [55]. It seems that USP45 cleaves lys48 and lys63 ubiquitin linkage[55]. Further evidence supporting USP45 involvement in UV damage repair shows that USP45 is recruited to the site of DNA damage, and depletion of USP45 sensitizes cells to DNA damaging agent[55]. USP45 seems to affect UV-induce damage repair by regulating ERCC1's access to DNA damage site.

Conclusions

In this article, we discussed ubiquitination and deubiquitination events in NER and their specific roles in regulation GG-NER and TC-NER. Importantly, we stressed the emerging roles of several DUBs in the regulation of different NER steps. Current evidence suggests that DUBs can target ubiquitinated DDB2, XPC, CSB and RNA Pol II for deubiquitination. Deubiquitination of these factors can regulate their stabilities, protein-protein interactions, as well as protein-DNA binding.

In the example of XPC, currently there are two major E3 ligases that are found to ubiquitinate XPC. RNF111 presumably adds K63-linked ubiquitin to XPC, while the ubiquitin linkage by the $CRL4^{DDB2}$ E3 ligase remains undefined. Because the $CRL4^{DDB2}$ E3 complex responsible for XPC ubiquitination is also responsible for DDB2 ubiquitination and degradation, the K48 linkages of ubiquitin conjugates on XPC are plausible. Intriguingly, mass spectrometry data from Poulsen et al., suggest that XPC ubiquitination involves a variety of ubiquitin chains and ≥ 15 individual ubiquitination sites [34]. Since XPC is relatively stable after UV damage, what are the physiological functions of Lys48 and Lys63 ubiquitination on XPC? It seems that the nature and regulation of XPC ubiquitination is complex, possibly involving different E3 ligases and DUBs to form and remove different ubiquitin linkages on XPC. These different ubiquitin linkages at various sites of XPC may determine XPC affinity for damaged DNA and regulate XPC binding and release from sites of DNA damage. As mentioned above, USP7 is a DUB for XPC [40]. USP7 belongs to low-linkage specificity group [56], it has limited activity toward hydrolyzing K27- and K29-

linked diubiquitin. In contrast, the K6, K11, K48, and K63 ubiquitin topoisomers are hydrolyzed by USP7 relatively efficiently [57]. A yeast two hybrid assay in our lab identified that OTUD4 is a potential interactor of XPC with initial studies showing an increase in XPC ubiquitination after knockdown of OTUD4 [58]. OTUD4 is a largely uncharacterized OTU family DUB and was recently shown to promote resistance to alkylation damage [59]. An *in vitro* deubiquitination assay shows that OTUD4 prefers K48-diubiquitin chains while has much less activity against K11- and K63- diubiquitin linkage [60]. It is likely that redundant DUB activities are involved in cleaving and editing XPC ubiquitination. Future studies will undoubtedly lead to a better understanding of the involvement of DUBs in NER.

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Abbreviations

UV	Ultraviolet
NER	Nucleotide excision repair

TC-NER	Transcription coupled NER
GG-NER	Global Genome NER
XPC	Xeroderma Pigmentosum complementation group C
UV-DDB DUB	Deubiquitinating enzyme
CS	Cockayne syndrome
CSA	Cockayne syndrome protein A
CSB	Cockayne syndrome protein B
CPDs	Cyclobutane–pyrimidine dimers
6–4PPs	6–4 pyrimidine–pyrimidone photoproducts