Chapter 6

Chromatin Remodeling in Nucleotide Excision Repair in Mammalian Cells

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1. Introduction

The chromatin basic structure named nucleosome contains 147 DNA base pairs wounded 1.65 times around an octamer of histone proteins which consist of two copies of H2A, H2B, H3, and H4, separated by linker regions of 20-110 nucleotides. Nucleosome assembly in the nucleus proceeds in two stages. At first, hetero-tetramer H3/H4 integrates into the DNA and at the second stage the heterodimer H2A/H2B is added. Nucleosomes are further condensed into 30 nm fibers through the incorporation of histone H1, located in the linker regions, achieving an additional 250-fold structural compaction in metaphase chromosomes. Nucleosome packaging restricts protein binding and obstructs DNA-templated reactions. Therefore, local modulation of DNA accessibility is necessary for the fundamental processes of transcription, replication and DNA repair to occur. In this sense, chromatin structure is not static but subject to changes at every level of its hierarchy. Nucleosomes are considered dynamic and instructive particles that are involved in practically all chromosomal processes, being subjected to highly ordered changes considered as epigenetic information, which modulates DNA accessibility [1, 2]. Nucleosomes exhibit three dynamic properties: a) covalent histone post-translational modifications, b) change of composition due to removal of histones and c) movement along DNA. The latter two are carried out by ATP-dependent chromatin remodeling complexes [3]. Histone post-translational modifications (PTMs) such as the addition of acetyl, methyl, phosphate, ubiquitin, and sumo groups change the properties of histones, modifying histone-DNA or histone-histone interactions [4]. Modifying complexes add or remove covalent modifications on particular residues of the N- and C-terminal domains of histone pro-

teins, altering the structure of chromatin and creating "flags" which can be recognized by different regulatory proteins. Many chromatin-associated proteins contain protein domains that bind these moieties such as the bromodomain that recognizes acetylated residues and chromodomains, Tudor, Plant Homeo Domain (PHD) fingers, Malignant brain tumor (MBT) domains that bind to methylated lysines or arginines [5].

In the regulation of gene expression a "code of histones" has been determined, where different PTMs allow the recruitment of different factors specifying determined functions on chromatin [2]. Certain histone modifications can even induce or inhibit the appearance of other modifications in adjacent aminoacidic residues [6]. ATP-dependent chromatin remodeling factors use ATP hydrolysis to slide or unwrap DNA. These multi-subunit complexes can also catalyze eviction of histone octamers to promote histone variant replacement [7]. Eukaryotic cells also contain alternative versions of the canonical histones, differing in the aminoacidic sequences. One of these isoforms is histone H2AX, which differs from the canonical H2A histone by the presence of a short C-terminal tail. Nucleosomes containing canonical histones are formed during replication, and non-canonical histones replace canonical ones in the course of DNA metabolic processes not associated with replication, such as transcription and repair. Other protein complexes participating in the process of nucleosome assembly/disassembly such as histones chaperones like the chromatin assembly factor 1 (CAF-1), composed by three subunits: p150, p60 and p48, which has been suggested to play a pivotal role in chromatin assembly after DNA replication and repair [8]. During DNA replication, CAF-1 complex binds to newly synthesized histone H3 and H4 and deposits the histone tetramers onto replicating DNA to form the chromatin precursor in a PCNA-dependent manner. The replicated precursor then serves as the template for deposition of either old or new histone H2A and H2B.

In response to both DNA damage and replication stress, a signal transduction cascade known as the checkpoint response is activated. This phenomenon is also referred to as the DNA damage response. It is becoming clear that DNA damage sensors can recognize the chromatin-associated signals of DNA damage. This information is then transmitted via signal transducers, including diffusible protein kinases, to effector molecules such as the checkpoint kinases that mediate the physiological response of the cell to DNA damage, which ultimately promotes efficient repair and cell survival. The primary target of this pathway is the arrest or slowing of the cell cycle, providing time for DNA repair to take place. Depending on the type of DNA damage induced, different repair mechanisms can be activated, such as non-homologous end joining and homologous recombination in case of double strand breaks induction and excision repair mechanisms in case of nucleotide or base damage. As for DNA transcription, a regulatory role of the epigenetic code in DNA repair has been proposed [3, 4, 9, 10]. Chromatin remodeling processes not only influence access to DNA but also serves as a docking site for repair and signaling proteins [7, 10-12]. Chromatin plays a pivotal role in regulating DNA-associated processes and it is itself subject of regulation by the DNA-damage response. In this chapter, we summarize the current knowledge on the involvement of chromatin remodeling processes in nucleotide excision repair in mammalian cells.

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2. Chromatin structure after UVC-induced DNA damage

Endogenous and exogenous DNA damaging agents modify DNA. One of the most common environmental stresses that produce lesions in DNA is UV light. UVC irradiation induces cyclobutane pyrimidine dimers (CPDs) and pyrimidine 6-4 pyrimidone photoproducts (6-4PP) which result in an abnormal DNA structure that signals the lesion [7], [13-15]. However, they can be distributed differently along the chromatin structure. CPDs are mainly found in the minor groove of DNA facing away from the histone surface and 6-4PPs are preferentially formed in linker DNA but can also be seen throughout the histone core region. This indicates that nucleosomes can actually confer partial protection against this type of DNA damage. Moreover, an *in vitro* study in specific sites with mono-nucleosomes showed that elimination of UVC-induced lesions is highly inhibited by nucleosomes [16, 17]. Chromatin plays a role not only in the spectrum of DNA damage formation but also in the repair of these lesions. In this respect, it has been shown that chromatin structure has an inhibitory effect on the repair of both CPDs and 6–4PPs [18]. For instance, excision activity in the nucleosome core center is nearly sevenfold lower than that in free DNA [15].

Access to these lesions in chromatin can be achieved mainly by the action of ATP-dependent chromatin remodeling factors and the addition of post-translational modifications on histones [19], which could facilitate their removal. However, like DNA repair enzymes, both chromatin remodeling proteins and histone modification factors require initial localization to damaged sites, but the mechanism by which UVC-damaged DNA in chromatin is recognized by these factors and how damaged from undamaged chromatin can be distinguished remain unclear. A recent study using reconstituted nucleosomes containing DNA with CPDs or 6–4PPs showed that the presence of these lesions does not affect the reconstitution of nucleosomes *in vitro*, but the dynamic equilibrium of DNA unwrapping-rewrapping around the nucleosome switches toward the unwrapped state. These *in vitro* experiments suggest that intrinsic nucleosome dynamics, specially increased unwrapping of the DNA around damaged nucleosomes, facilitate the access of factors involved in recognizing damage and/or those involved in chromatin remodeling. Therefore, once remodeling factors are recruited to the damaged nucleosomes, disruption of local chromatin structure could initiate the recruitment of the multiple repair proteins [14]. Nevertheless, it is important to take into account that *in vivo*, in the context of all chromatin factors, the recognition step of the photolesions may be more complex. Apart from the DNA distortion, other factors also actively contribute to reveal and mark lesion sites for recruitment of the repair machinery.

3. Nucleotide excision repair in chromatin

Nucleotide excision repair (NER) system is more efficient in naked DNA than in chromatin and it is inhibited by the presence of nucleosomes and heterochromatin, which limit the access of repair proteins to DNA [20]. Thus, for NER to recognize, excise and repair DNA damage efficiently, chromatin needs to be adapted [21]. Therefore, a chromatin rearrangement is a

necessary step in the access of repair proteins to DNA damage sites and led to the ''access, repair, restore'' model of NER in chromatin. This model suggests that early chromatin remodeling steps and/or intrinsic dynamic changes in chromatin may allow the access of repair complexes to damaged sites, followed by restoration of the original nucleosomal organization after DNA repair [1, 22]. In NER, lesions that are located in linker regions are more accessible for binding by the recognizing proteins. A plausible scenario for DNA repair implies that the lesion is recognized and eliminated in the most accessible sites for repair proteins. Therefore, nucleosome modification and initiation of chromatin relaxation around the repair site start at considerable distances from the initiation point of DNA repair. As a result, other lesions, particularly those in the core of nucleosomes, become more accessible. Thus, proteins responsible for recognizing UVC-induced DNA lesions can recognize and bind them even if they are located in the core of the nucleosome [23, 24].

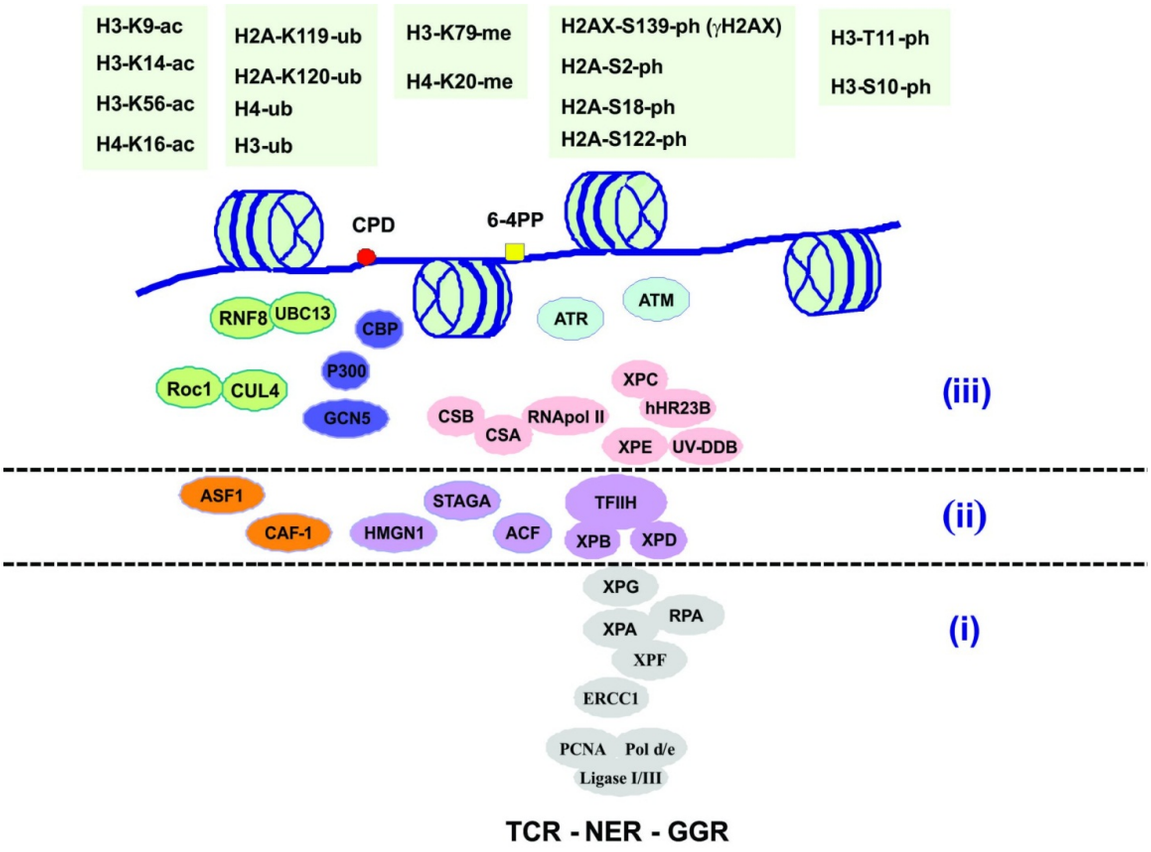

Figure 1. Nucleotide excision repair in the chromatin context. Nucleotide damage induced by UVC (CPDs and 6-4-PPs) is represented on a 11 nm chromatin fiber. Main proteins acting during the cellular response to UVC-induced damage are presented: (i) key proteins implicated in nucleotide excision repair (NER) (TCR and GGR) in mammalian cells (grey); (ii) chromatin assembly or remodeling factors recruited by chromatin modifications (violet) and histone chaperons involved in NER (orange); (iii) sensor proteins belonging to TCR (CSA, CSB, RNApolII) or GGR (XPC-HHR23B, XPE-UV-DDB) (pink); and histone modifying enzymes responsible for post-translational covalent modifications (PTMs): histone acetyl transferases (HATs) (blue), enzymes that conjugate ubiquitin moieties (green) and kinases (light-blue). Known PTMs appearing in response to UVC-induced damage are highlighted in green on top of the figure. See text for more details concerning the activities of every protein. Ac: acetylation, Ph: Phosphorylation, Ub: ubiquitylation, K: lysine, S: serine, T: threonine.

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NER removes a wide range of bulky DNA adducts that distort the double helix of DNA, including those induced by UVC. NER system can be divided into two pathways: transcriptional coupled repair (TCR) pathway, that repairs lesions that occur in transcriptionally active genes and global genome repair (GGR) that acts into lesions in non transcribed DNA [1, 25, 26]. Both pathways involves the action of about 20-30 proteins (Figure 1) in a "cut-and-paste-like" mechanism [26, 27] divided in five steps: a) lesion detection; b) recruitment of TFIIH-XPB-XPD complex, which directs DNA unwinding around the damaged nucleotide; c) recruitment of ERCC1- XPF, XPG, XPA and RPA that induce 5′ and 3′ breaks around the lesion and remove the damaged nucleotide; d) DNA synthesis directed by DNA polymerase δ/ε, PCNA and other accessory factors and e) strand ligation (ligase I/III) [1, 26]. Both pathways use the same cellular machinery in all steps except from lesion recognition. At this initial step, in TCR CSA and CSB direct the basic repair machinery to RNA polymerase II stalled at the lesion [28]. On the other hand, in GGR damage site recognition is carried out by XPC-hHR23B and UV-DDB/XPE complexes [13, 25, 29-31]. The defect in one of the NER proteins is the consequence of three rare recessive syndromes: Xeroderma pigmentosum (XP), Cockayne syndrome (CS) and the photosensitive brittle hair disorder trichothiodystrophy (TTD) [26, 31, 32].

Apart from ATP-dependent chromatin remodeling factors and histone modifications, repair factors themselves could cause chromatin rearrangements. Particularly good candidates for this type of function in the NER system are the transcription-coupled repair factor CSB, which has homology to SWI/SNF chromatin remodeling proteins, and the TFIIH complex that contains the helicase subunits XPD and XPB [33]. However, a non-mutually exclusive suggestion is that global chromatin relaxation increases accessibility over the whole genome in response to damage in order to expose the individual damage sites for recognition [34]. After removal of the DNA lesion and completion of new DNA synthesis by DNA polymerase and DNA ligase, the original structure of chromatin is restored by the action of CAF-1 [22, 31]. The recruitment of mammalian CAF-1 is restricted to damaged sites and depends on NER, binding concomitantly with repair synthesis [8]. Chromatin restoration does not simply recycle histones, but also incorporate new histones and histones with distinct post-translational modifications into chromatin. For example, new histone H3.1, deposited during DNA replication, is incorporated into chromatin as a marker of sites of UVC-induced DNA damage repaired by NER [35].

4. Histone covalent modifications in NER

One of the most important chromatin remodeling processes that occur during NER is histone covalent modification, which constitutes a reversible process. The most frequent histone tail modification is the histone acetylation/deacetylation process, which is controlled by histone acetyltransferases (HAT) and histone deacetylases (HDAC), determining either gene activation or inactivation, respectively. Meanwhile, histone methylation is carried out by histone methyl-transferases (HMT) and histone demethylases (HDM) are used for the reverse reaction.

Finally, kinases like ATR are responsible for histone phosphorylation, and histone ubiquitination is driven by histone ubiquitin ligases.

4.1. Histone acetylation

The acetylation of the ε-amino group of lysine (K) side chains is a major histone modification involved in numerous cellular processes, such as transcription and DNA repair. Acetylation neutralizes the lysines positive charge and this action may consequently weaken the electrostatic interactions between histones and DNA. Thus, acetylated histones could enhance chromatin accessibility by reducing the attractive force between the nucleosome core and negatively charged DNA. For this reason, histone acetylation is often associated with a more ''open'' chromatin conformation. UVC irradiation induces global and local changes in chromatin structure in order to increase accessibility for repair proteins and hence a proper NER occurs [34]. Early studies demonstrated that acetylated nucleosomes enhance NER efficiency [36]. In this respect, UVC-induced acetylation of H3 K9 and H4 K16 has been observed [37, 38]. H3 K9 acetylation after UVC irradiation requires the recruitment of the transcription factor E2F1, which interacts with the HAT GCN5. In fact, inactivation of GCN5 in human cells decreases recruitment of NER factors to damaged sites, which demonstrates that GCN5 is important for a timely and efficient NER [38]. Besides, UV-DDB complex (DDB1–DDB2) recruits two HATs, such as CBP/p300 and STAGA (a SAGA-like complex containing GCN5L) [39, 40], whose activities induce chromatin remodeling to allow recruitment of the repair complexes at the UVC-induced damage sites. By the same token, it has also been observed that p33ING2, a member of the inhibitor of growth (ING) family proteins, enhances NER in a p53-dependent manner by inducing chromatin relaxation following UVC irradiation, increased acetylation of histone H4 and recruitment of NER factors to sites of damage [41]. Actually, it has also been observed that CBP/p300 is recruited to UVC damaged sites in a p53-dependent manner via its interaction with CSB, accompanied by an increase in H3 acetylation [34, 42]. Hence, increased histone acetylation at the NER site is likely to contribute to the p53-induced chromatin relaxation that is induced by DNA damage, suggesting that the function of UVC-induced histone acetylation is to promote opening up on the chromatin to facilitate repair. However, employing the *in situ* nick translation technique, we have observed that chromatin decondensation is also induced in p53 mutant Chinese hamster (CHO) cell lines, either proficient or deficient in TCR (simile Cockayne's Syndrome B or CSB cells), and that this chromatin decondensation process is related to histone acetylation (data not published yet). Actually, it seems that the extent and type of histone acetylation may vary depending on the structure of chromatin associated with repair sites and the type of NER pathway (GGR or TCR). On the other hand, we have demonstrated in Chinese hamster chromosomes that acetylated histone H4 regions are preferred sites for radiation- and endonucleases-induced chromosome lesions [43, 44]. Altogether, these results could indicate that certain chromatin modifications can take place independently of NER, acting as a signal for the recruitment of chromatin remodeling factors. Moreover, it has been proposed that H3 K56 deacetylation is an early event triggered by DNA damage upon UVC irradiation in mammalian cells [45]. According to this, DNA damage results in the prompt deacetylation of H3 K56, which contribute to the recruitment of different factors including chromatin remodelers to relax the chromatin structure for

allowing easy access to the NER complex and cell cycle checkpoints. Upon successful completion of DNA repair, the histone chaperone anti-silencing function1A (ASF1A) is recruited in an ATM-dependent manner, facilitating the recruitment of HATs needed for the restoration of native H3 K56 acetylation status, but the molecular mechanism of ASF1A recruitment is not clear yet [45]. Finally, High mobility group protein B1 (HMGB1), a multifunctional protein that, influences chromatin structure and remodeling by binding to the internucleosomal linker regions in chromatin [46] and facilitating nucleosome sliding [47], has been shown to affect DNA damage-induced chromatin remodeling. It was observed that after UVC irradiation of the HMGB1 knockout MEFs cells, their ability to remove UVC-induced DNA damage and the increasing of histone acetylation was significantly affected [48]. This distortion may assist the NER system in recognizing the damage [49] and facilitating repair of the lesion. HMGB1 also affects chromatin remodeling after DNA damage, so its binding to the lesion could increase the accessibility of repair factors to the site of DNA damage.

4.2. Histone phosphorylation

The phosphorylation of serine (S), threonine (T), and tyrosine (Y) residues has been documented on all core and most variant histones. Phosphorylation alters the charge of the protein, affecting its ionic properties and influencing the overall structure and function of the local chromatin environment [50]. Although there is no evidence that PI3K enzymes could be activated by DNA lesions repaired by NER, when DNA replication fork is stalled, NER protein foci are formed, creating single strand breaks (SSBs) which can be covered by RPA/ATRIP and activate the kinase activity of ATR [51]. However, these NER intermediates (SSBs arising from excised lesions) can activate ATR, even outside S-phase [52]. Several histone phosphorylation changes after UVC irradiation have been observed, such as H2AX histone variant which is phosphorylated at S139 (named gamma-H2AX) [52]. H2AX phosphorylation upon UVC in non-S-phase cells depends on ATR and active processing of the lesion by the NER machinery [53], suggesting that NER-intermediates trigger this response. The notion that gamma-H2AX formation occurs in response to NER and that NER is proficient in H2AX-deficient cells, suggests that this modification mainly plays a role in checkpoint activation during the repair of UVC lesion. Besides, S2, S18 and S122 H2A residues play important roles in survival following UVC exposure [54]. Two aminoacidic residues of histone H3, S10 and T11, appear to be a target of differential phosphorylation during NER. H3 S10 and H3 T11 in mouse are dephosphorylated by UVC irradiation and rephosphorylated after DNA damage repair. Hypophosphorylation of H3 S10 and H3 T11 are associated with transcription repression, and this histone modification might be one of the mechanisms that cells employ to inhibit transcription at UVC-damaged sites [25].

4.3. Histone methylation

Histone methylation is carried out by a group of enzymes called histone methyltransferases HMT, which covalently modify the lysine and arginine (R) residues of histones by transferring one, two or three methyl groups to the ε-amino group of lysine residues or to the guanidino group of arginine residues [6]. Methylation, unlike acetylation and phosphorylation, does not

alter the overall charge of histones. Histone methylation in combination with acetylation creates specific modification signatures which can influence transcription [55, 56]. Lysine methylation has a different impact on transcription, depending on the positions and degree of methylation (mono-, di-, tri-methylation). Methylation of H3 lysine (H3 K4 and 36) is associated with transcribed domains, whereas methylation of H3 K9, H3 K27 and H4 K20 appears to correlate with transcriptional repression. Human Chd1 binds to methylated H3 K4 through its tandem chromodomains, linking the recognition of histone modifications to non-covalent chromatin remodeling [57]. In contrast, methylated H3 K9 and H3 K27 are recognized by heterochromatin protein 1 (HP1) and polycomb repressive complexes (PRC). Different from histone acetylation, which has been known to be implicated in NER for a long time, histone methylation was found to be implicated in NER recently [58, 59]. The knockdown of the best known methyltransferase of histone H3 K79 (called Dot1 in yeast or DOT1L in mammals), results in complete loss of methylation on this site either in yeast [60], flies [61] or mice [62]. In mammaliam cells, several enzymes target histone H4 K20 methylation. Mouse cells lacking the Suv4-20h histone methyltransferase have only mono-methylated but essentially no di- and tri-methylated H4 K20. These mutant mouse cells are sensitive to DNA damaging agents, including UV and defective in repair of DSBs [63]. However, if methylation of histone H4 K20 also plays a role in NER is unknown. Moreover, there is not much knowledge about its role in DNA repair in mammalian cells. Finally, it has not been determined yet if global histone methylation levels change in response to DNA damage, although it is well known that they affect cell cycle checkpoints through interactions with checkpoint components.

4.4. Histone ubiquitination

All of the previously described histone modifications result in relatively small molecular changes in the aminoacid side chains. In contrast, ubiquitination results in a much larger covalent modification. Ubiquitin itself is a 76-amino acid polypeptide that is attached to histone lysines via the sequential action of three enzymes, E1-activating, E2-conjugating and E3-ligating enzymes [6]. Histones H2B, H3 and H4 are constitutively ubiquitinated, but at very low levels (0.3% of the total H3, 0.1% for H4) [64]. In an effort to purify and characterize histone ubiquitin ligases, it was found an ubiquitin ligase activity capable of ubiquitinating all histones *in vitro* [65]. The ligase was later characterized as CUL4–DDB–ROC1 complex, an enzyme that is known for ubiquitinating DDB2 and XPC at UVC damaged sites [66, 67]. A small fraction of histone H3 and H4 (0.3% and 0.1%, respectively) is found ubiquitinated *in vivo* and siRNA mediated knockdown of CUL4A, B and DDB1 decreases the H3 and H4 ubiquitination levels. In addition, the dynamics of CUL4–DDB–ROC1-mediated H3 and H4 ubiquitination is similar to that of XPC. Actually, further biochemical studies indicate that the H3 and H4 ubiquitination weakens the interaction between histones and DNA, and facilitates the recruitment of XPC repair factor to damaged DNA [65]. These studies point out the role of H3 and H4 ubiquitination in chromatin disassembly at the sites of UVC lesions. However Takedachi et al. [68] found that ubiquitination of H3 and H2B by the CUL4A complex was not sufficient to destabilize the nucleosome and proposed that ubiquitination around damaged sites functions as a signal that enhances the recruitment of XPA repair protein to lesions. Moreover, as well as H2B, H3 and H4, H2A displays some constitutive ubiquitination being the primary targets

K119 and K120. H2A ubiquitination by UBC13/RNF8 ubiquitin ligase complex also occurs at the sites of UVC-induced DNA damage [69]. Depletion of these enzymes causes UVC hypersensitivity, without affecting NER, suggesting that UBC13 and RNF8 are involved in the UVC-induced DNA damage response. It has also been reported the recruitment of uH2A to sites of DNA damage as a post-excision repair event, in which transiently disrupted chromatin is restored through repair synthesis-coupled chromatin assembly [31], showing that the formation of uH2A foci do not involve pre-incision events mediated by Cul4A-DDB ubiquitin ligase, but require successful NER through either GGR or TCR subpathway. In this respect, it was recently shown that monoubiquitination of H2A K119 and K120 by DDB1-CUL4B^{DDB2} is critical for destabilization of the photolesion-containing nucleosomes, leading to eviction of H2A from the nucleosome, and that the partial eviction of H3 from the nucleosomes also depends on ubiquitinated H2A K119/K120. Furthermore, nucleosomal structure has consequences for the binding of E3 ligase complex; polyubiquitinated DDB2 is only released from the destabilized nucleosome, presumably releasing space around the lesion to load the NER pre-incision complex and proceed with repair. These results reveal how post-translational modification of H2A at the site of a photolesion initiates the repair process, which affects the stability of the genome [70].

5. ATP-dependent chromatin remodeling during NER

Chromatin remodeling complexes (CRCs) in contrast to PTMs utilize the energy of ATP to disrupt nucleosome DNA contacts, move nucleosomes along DNA and remove or exchange nucleosomes [71]. Thus, they make DNA/chromatin available to proteins that need to access DNA or histones during cellular processes [72]. A large array of different chromatin-remodeling complexes has been identified, which play important roles in controlling gene expression by regulating recruitment and access of transcription factors [73]. ATP-dependent chromatin remodelers belong to the SWI2/SNF2 (switching/sucrose non fermenting) superfamily and can be divided into several subfamilies on the basis of their ATPase domain structure and protein motifs outside the ATPase domain [74]. Among the different complexes identified in different species, four structurally related families have been described: SWI/SNF (switching defective/sucrose non fermenting), INO80 (inositol requiring 80), CHD (chromodomain, helicase, DNA binding) and ISWI (imitation SWI). Each family is defined by its characteristic catalytic ATPase core enzyme from the SWI2/SNF2 [5]. The essential role of these enzymes is reflected in the fact that many of them are required for diverse but specific aspects of embryonic development including pluripotency, cardiac development, dendritic morphogenesis and self-renewal of neural stem cells. However, in adults, deletion or mutation of these proteins often leads to apoptosis or tumorigenesis as a consequence of dysregulated cell cycle control. In recent years, it has become clear that ATP-dependent chromatin remodeling factors not only are involved in transcription regulation, but also play an important role in a number of DNA repair pathways including double strand break repair, base excision repair as well as nucleotide excision repair (NER) [71]. UVC damage itself enhances unwrapping of nucleosomes, which normally exist in a dynamic equilibrium between wrapping and unwrapping [75]. This

enhanced "DNA breathing" may assist the repair of lesions in chromatin by increasing the time window for repair factor access and their binding to lesions might further unwrap the DNA [14]. ATP-dependent chromatin remodeling may play a role in opening the chromatin structure for access during DNA damage repair, facilitating the early step of NER in the recognition of the damage [76]. In this respect, three SWI2/SNF2 subfamilies have been implicated in the cell response to UVC radiation as it is shown in Table 1 [71, 77]. Several factors have been implicated on stimulating the repair of UVC-induced DNA damage by increasing chromatin accessibility. Numerous studies showed that there is an association between histone hyperacetylation and chromatin relaxation in response to UVC-irradiation that enhances NER [76]. GCN5-mediated acetylation of histone H3 contribute to the recruitment of the SWI/SNF chromatin remodeling complex via the bromodomains of BRG1 or hBRM [38]. CSB/ERCC6, one of the major TCR proteins, contains a SWI2/SNF2 ATPase domain, which is essential for recruitment of the protein to chromatin [78]. CSB is able to remodel chromatin *in vitro* in an ATP-dependent manner and is required for the recruitment of NER factors to sites of TCR [42, 79], suggesting that repair enzymes and remodeling complexes may work in concert to allow access of DNA lesions to the repair machinery.

FAMILY	COMPLEX	ATPase	ROLE IN NER
SWI/SNF	BAF	SMARCA4/BRG1, SMARCA2/BRM	Stimulates the removal of 6–4PPs and CPDs in a UVC-dependent histone H3 hyperacetylation manner [71]
	PBAF	SMARCA4/BRG1, SMARCA2/BRM	
INO80	INO80	INO80	Promotes the removal of UVC lesions (CPDs,6–4PPs) by NER in not transcribed regions [71]
	TRRAP/Tip601	EP400/p400	
ISWI	ACF	SMARCA5/hSNF2H	Not fully understood [71]
	CHRAC	SMARCA5/hSNF2H	
	WICH	SMARCA5/hSNF2H	
	NURF	SMARCA1/hSNF2L	
OTHER	ERCC6/CSB		Remodels chromatin *in vitro* in an ATP-dependent manner. Required for the recruitment of NER factors to sites of TCR [73]

Table 1. Mammalian ATP-dependent chromatin remodeling complexes identified as taking part in nucleotide excision repair.

5.1. SWI/SNF

The SWI/SNF chromatin-remodeling complex plays essential roles in a variety of cellular processes including differentiation, proliferation and DNA repair. Loss of SWI/SNF subunits has been reported in a number of malignant cell lines and tumors, and a large number of experimental observations suggest that this complex functions as a tumor suppressor [80]. Interestingly, inactivation of the SWI/SNF-like BRG1/BRM-associated factors (BAF) complexes renders human cells sensitive to DNA damaging agents, such as UVC and ionizing radiation [81]. The mammalian SWI/SNF complexes contain either of two ATPase subunits, BRM (brahma) or BRG1 (Brahma Related Gene). Both of them form a discrete complex by interacting with other BAFs and may have distinct roles in cellular processes [65, 81].

Several studies have indicated that the SWI/SNF complex plays an essential role in the removal of UVC-damage by NER [82]. In mammals, the SWI/SNF ATPase subunit BRG1/SMARCA4 stimulates efficient repair of CPDs but not of 6-4PPs. For Example, BRG1 interacts with XPC and it is recruited to an UVC lesion in a DDB2 [83] and XPC [76] dependent manner. BRG1, in turn, modulates UVC-induced chromatin remodeling and XPC stability and subsequently promotes damage excision and repair synthesis by facilitating the recruitment of XPG and PCNA to the damage site [76], suggesting the essential role of Brg1 in prompt elimination of UVC-induced DNA damage by NER in mammalian cells. Finally, BRG1 may also transcriptionally regulate the UVC-induced G1/S checkpoint, as loss of BRG1 leads to increased UVC-induced apoptosis [81]. Besides BRG1, the mammalian SWI/SNF subunit SNF5/SMARCB1 also interacts with XPC. Inactivation of SNF5 causes UVC hypersensitivity and inefficient CPD removal [82]. Intriguingly, BRG1/BRM, but none of the other subunits, is also important to the UVC response in germ cells, suggesting that the involvement of individual SWI/SNF subunits may differ between cell types. Interestingly, UVC hypersensitivity resulting from BRG1 inactivation depends on the presence of the checkpoint protein TP53, extending the complexity of the involvement of BRG1 in UVC-induced DNA damage response [83]. Several lines of evidence suggest that recruitment of factors like SWI/SNF and their functional participation help to recruit downstream factors for processing DNA damage.

5.2. INO80

The INO80 family of CRCs function in a diverse array of cellular processes, including DNA repair, cell cycle checkpoint and telomeric stability [84, 85]. The INO80 complex also contains three actin-related proteins (ARPs). ARP5 and ARP8 are specific to the INO80 complex. Deletion of either INO80-specific ARP compromises the ATPase activity of the remaining complex and gives rise to DNA-damage-sensitive phenotypes indistinguishable to the INO80 null mutant [86]. Purification of human INO80 revealed a complex with virtually identical core components and a role in transcription [87, 88], indicating that the INO80 complex is highly conserved within eukaryotes [89]. The role for various remodeling activities is likely to promote the timely repair of lesions, rather than being an essential component for lesion removal. For example, some observations suggest that loss of remodeling activity leads to attenuation of photolesion repair, but not a complete impairment. Thus, it supports the idea that INO80 carry out an important chromatin remodeling activity for an efficient NER [74].

The link between INO80 and NER function may reflect the underlying mechanism for the UVC hypersensitivity of INO80 mutant cells and the broadening connections between chromatin remodeling and DNA repair in general [89]. The mammalian INO80 complex functions during earlier NER steps facilitating the recruitment of early NER factors such as XPC and XPA and, in contrast to yeast, it localizes to DNA damage independently of XPC [89]. Furthermore, INO80 facilitates efficient 6-4PPs and CPDs removal and together with the Arp5/ ACTR5 subunit, interacts with the NER initiation factor DDB1, but not with XPC. These discrepancies may reflect interspecies differences, but may also point out multiple functions of INO80 chromatin remodeling during NER that are experimentally difficult to dissect. INO80 may function to facilitate damage detection as well as to restore chromatin after damage has been repaired [5]. A recent study shows that the INO80 complex plays an important role in facilitating NER by providing access to lesion processing factors, suggesting a functional connection between INO80-dependent chromatin remodeling and NER [89].

5.3. ISWI

ISWI complexes are a second major category of ATP-dependent chromatin remodeling complexes. In mammals, two ISWI-homologs, named SNF2H and SNF2L, have been described. While most of the complexes contain SNFH; up to now, SNF2L has only been found in the human NURF complex [90, 91]. Subunits related to ACF1 are similar to these ISWI-containing remodeling complexes, which contain PHD and bromodomains [92]. Snf2h is a gene essential for the early development of mammalian embryos, suggesting that ISWI complexes [93] may be required for cell proliferation [94]. Besides, ISWI cooperates with histone chaperones in the assembly and remodeling of chromatin [95]. These complexes accumulate at sites of heterochromatin concomitant with their replication, suggesting a role for ISWI chromatin remodeling functions in replication of DNA in highly condensed chromatin [96]. ISWI complexes also may have a role in facilitating repair and recombination of DNA in chromatin. Several experiments have suggested that ISWI-mediated chromatin remodeling also functions to regulate NER, although its precise role remains unknown [5]. Moreover, SNF2H interacts with CSB [97], and the ACF1 subunit is recruited to UVC-induced DNA damage [98]. Knockdown of the mammalian ISWI ATPase SNF2H/SMARCA5 or its auxiliary factor ACF1/BAZ1A also leads to mild UVC sensitivity [99]. However, further experimental evidence is required to understand how ISWI chromatin remodeling functions in the UVC-DNA damage response.

6. Discussion and perspectives

When DNA is damaged, the chromatin, far from acting as an inhibitory barrier to lesion removal, can actively signal its presence, promoting the overall physiological response of the cell to damage, which stimulates the removal of the DNA damage itself. By the same token, the most challenging step in NER is the recognition of DNA lesions in their chromatin context. Nucleosomes on damaged DNA inhibit efficient NER and a functional connection between chromatin remodeling and the initiation steps of NER has been described [18].

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In this respect, the relevance of the histone acetylation balance and some ATP-dependent chromatin remodeling complexes to facilitate the early damage-recognition step of NER has been demonstrated, since changes in chromatin conformation could interfere with the correct interactions between repair proteins and DNA lesions which are immersed in a dynamic chromatin structure [38, 76, 100]. Besides, neuronal survival has been related to the balance between HAT and HDAC activities [101]. For example, it has been shown that in the presence of histone deacetylase inhibitors, normal neuron cells increase the frequency of apoptosis. Moreover, in transgenic mice, carrying neurodegeneration diseases characterized by histone hypoacetylation, their neurodegeneration phenotypes can be diminished in the presence of HDAC inhibitors [102, 103]. By the same token, alterations in the acetylation/deacetylation balance by changes in HATs or HDACs activities have been associated with the development of different cancers [104].

Another interesting issue in favor of the relevance of chromatin remodeling is the fact that transcription coupled repair (TCR) seems not to be responsible for the higher UVC sensitivity evidenced through the increased frequency of chromosomal aberrations observed in Cockayne's Syndrome (CS) simile cells exposed to UVC [105]. In this respect, we have found that chromosome breakpoints were distributed more random in CS simile cells than in normal ones instead of being concentrated on the transcribed chromosome regions as expected [106]. Since DNA accessibility for DNA repair proteins is limited in nucleosomes [16, 75], different chromatin organization after UVC exposure in CS simile cells could influence the distribution of CPDs in eu- and heterochromatic regions as well as their removal by TCR, leading to increased frequencies of chromosomal aberrations in these cells.

Although many of the chromatin remodeling factors observed in yeast have also been found in mammals, different functions have been attributed to some of them (i.e. H3K56 acetylation and INO80 mentioned previously), indicating that in spite of being quite well evolutionary conserved, they could have another function in mammals. Moreover, due to the multifunctional role of chromatin remodeling complexes become still very difficult to arise questions such as by which mechanism the damage is sensed or how the cell is able to choose a particular repair pathway, by which mechanisms chromatin remodelers are directed to a specific repair pathway or by which mechanisms chromatin reassembly takes place. Therefore, it is clear that we just begin to understand the DNA repair in the context of chromatin and, therefore, further work it is needed to elucidate either the individual functions or the coordinated activities of chromatin remodeling in all DNA repair pathways.

Abbreviations and acronyms

6-4PP	Pyrimidine 6-4 pyrimidone photoproducts
ARPs	Actin-related proteins
ASF1A	Histone chaperone anti-silencing function1A
ATM	Ataxia telangiectasia mutated

ATR	Ataxia-telangiectasia Rad3-related
ATRIP	ATR interacting protein
BAF	BRG1/BRM-associated factors
BRG1	Brahma Related Gene
BRM	Brahma
CAF-1	Chromatin assembly factor 1
CBP	Creb-binding protein
CPDs	Cyclobutane pyrimidine dimers
CRCs	Chromatin remodeling complexes
CS	Cockayne syndrome
CSB	Cockayne syndrome group B protein
CUL4–DDB–ROC1	Culin 4- DNA damage-binding protein- RING finger protein
CHD	Chromodomain
CHO	Chinese hamster cell lines
E2F1	Transcription factor
ERCC1	Excision repair cross complementing 1
ERCC6	Excision repair cross complementing 6
GCN5	General control non-derepressible 5
GGR	Global genome repair
HAT	Histone acetyltransferases
HDAC	Histone deacetylases
HDM	Histone demethylases
hHR23B	Human homologue of the yeast protein RAD23
HMGB1	High mobility group protein B1
HMT	Histone methyl-transferases
HP1	Heterochromatin protein 1
ING	Inhibitor of growth
INO80	Inositol requiring 80
ISWI	Imitation SWI
K	Lysine
MBT	Malignant brain tumor
NER	Nucleotide excision repair
NURF	Nucleosome remodeling factor
p300	Histone acetyltransferase named p300
p53	Tumor supressor p53 gene
PCNA	Proliferating cell nuclear antigen
PHD	Plant Homeo Domain
PI3K	Phosphoinositide 3-kinase
PTMs	Histone post-translational modifications
R	Arginine
RNF8	Ring finger protein 8
RPA	Replication protein A
S	Serine
SMARCA4	Transcription activator BRG1

SNF2H and SNF2L	ISWI-homologs
SNF5/SMARCB1	Mammalian SWI/SNF subunit
SSBs	Single strand breaks
STAGA	SAGA-like complex containing GCN5L
SWI/SNF	Switching defective/sucrose non fermenting
SWI2/SNF2	Switching/sucrose non fermenting
T	Threonine
TCR	Transcriptional coupled repair
TFIIH	Transcription factor II H
TP53	Tumor suppressor protein 53
TTD	Trichothiodystrophy
UBC13	Ubiquitin-conjugating enzyme
UVC	Ultraviolet light C
UV-DDB	UV-damaged DNA binding protein consisting of two subunits (DDB1 and DDB2)
XP	Xeroderma pigmentosum
XPA	Xeroderma Pigmentosum group A
XPB	Xeroderma Pigmentosum group B
XPC	Xeroderma Pigmentosum group C
XPD	Xeroderma Pigmentosum group D
XPE	Xeroderma Pigmentosum group E
XPF	Xeroderma Pigmentosum group F
XPG	Xeroderma Pigmentosum group G
Y	Tyrosine

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