Nucleotide excision repair : a multi-step mechanism required to maintain genome integrity

Moser, J.

4

DNA REPAIR AND CHROMATIN

DNA REPAIR IN CHROMATIN

Genetic information is packaged with histones and other accessory proteins into chromatin. In order to overcome the chromatin barrier, the transcriptional machinery is assisted by factors called chromatin remodeling complexes that increase the plasticity of nucleosomal DNA (Huertas et al., 2009). Chromatin is organized as a string of repeating nucleosome core particles which consists of 164 DNA base pairs organized around an octomer consisting of two copies of each highly conserved histone protein – H2A, H2B, H3 and H4 (Luger et al., 1997). Chromatin remodeling is essential for key cellular processes such as the regulation of gene expression, apoptosis, DNA replication and DNA repair processes (Downs et al., 2007).

Since DNA repair occurs in a chromatin context, repair factors must overcome the restricted access to DNA in chromatin, particularly in nucleosome cores. As already mention, the first step in DNA repair is lesion recognition, and although proteins that recognize specific lesions in naked DNA have been identified for each of the repair pathways, evidence suggests that changes in chromatin may also play a role in lesion recognition (Huertas et al., 2009; Nag and Smerdon, 2009). Structural changes in the chromatin due to lesions may initiate damage recognition. Alternatively, enzymatic modification and repositioning of histones and nucleosomes may occur to facilitate damage recognition. Chromatin remodeling in NER has been examined using in vitro models such as reconstituted nucleosomes with short DNA fragments containing lesions (Wang et al., 1991; Sugasawa et al., 1993).

Several studies have demonstrated that NER is less efficient in chromatin than in naked DNA, suggesting that DNA repair proteins have limited access to DNA damage buried in nucleosome core regions (Evans and Linn, 1984; Wang et al., 1991). In line with these observations, NER was shown to be more rapid in linker DNA between nucleosomes than in nucleosome cores (Gong et al., 2005). Although UV lesions induce extensive bending of duplex DNA, in vitro studies show that it does not alter the way that DNA wraps around nucleosomes, and for lesions in the nucleosome core, there was no repair specificity for lesions facing either inward or outward from the nucleosome surface (Liu and Smerdon, 2000; Liu et al., 2005; Svedruzic et al., 2005). The rate of repair is therefore dependent on the packaging of DNA in nucleosomes since they restrict the access of repair proteins to DNA strands as well as the lesion itself. It is known that access to bulky lesions such as UV-induced lesions in the chromatin is increased when chromatin is relaxed by histone acetyltransferases, or when nucleosomes are altered or moved by ATP-dependent processes (Peterson and Cote, 2004; Thoma, 2005).

Histone modifications and NER

Multiple modifications of core histones have been identified which are linked to gene activity and repair. These modifications include acetylation, methylation, phosphorylation and ubiquitylation (Jenuwein and Allis, 2001). Acetylation and methylation are important chemical signatures that can alter chromatin activity by recruiting proteins that specifically act on chromatin or on DNA.

Acetylation

Inhibition of histone deactylases has been shown to increase the level of actylation as well as the repair in hyperactylated nucleosomes (Ramanathan and Smerdon, 1989). Histones H3 and H4 were also shown to be acetylated after UV (Brand et al., 2001), further suggesting that UV-induced acetylation of histones is a cellular response which may be required to facilitate repair. Histone acetyltransferases (HATs) such as p300/CBP and GCN5 mediate the acetylation of N-terminal histone tails. The primary modifications associated with histone acetylation may stabilize higher order structures by creating a more open and active chromatin structure (Wolffe and Hansen, 2001). HAT p300/CBP is known to interact with both DDB1, DDB2 (Rapic-Otrin et al., 2002; Datta et al., 2001), CSB (Fousteri et al., 2006), PCNA (Hasan et al., 2001) and p53 (Rubbi and Milner, 2003) which may target p300 to UV damage. However, to date, no direct evidence has shown that p300 is required for efficient NER. TFTC and STAGA are HAT-containing complexes which display an affinity for UV-damaged DNA (Martinez et al., 2001). Both the TFTC and STAGA complexes contain SAP130, a protein which shares high homology to DDB1. SAP130 is also known to interact with DDB1 whereas STAGA has been shown to interact with DDB2 (Brand et al., 2001; Martinez et al., 2001).

Methylation

Histone methylation modifications are carried out by histone methyltransferases which covalently modify the lysine and arginine residues of histones. A combination of histone methylation and acetylation modifications has been shown to influence transcription (Kouzarides, 2007), yet not much is known about their role in DNA repair. However, histone methylation levels have been shown affect cell cycle checkpoints through interactions with checkpoint components such as 53BP1 (Huyen et al., 2004).

Phosphorylation

Phosphoylation of serine residue 139 of H2AX by ATM is known to be a marker for DSBs. Phosphorylated H2AX (γ-H2AX) generates a chromosomal microenvironment that promotes recruitment of repair proteins (Fernandez-Capetillo O et al., 2004) and facilitates DNA repair to reduce the risk of mutations (Bartek & Lukas, 2007). Similarly, H2AX has also been shown to be phosphorylated after UV irradiation (Hanasoge and Ljungman, 2007). ATR kinase was shown to mediate the phosphorylation of H2AX in response to UV damage (Mari et al., 2006). Recently, Xiao et al (2009) and Cook et al (2009) discovered that tyrosine residue 142 (Y142) of H2AX is also phosphorylated but in unstressed cells. Y142 became dephosphorylated after X-ray DNA damage which appears to be a prerequisite for γ-H2AX phosphorylation and the recruitment of MDC1 and the other repair factors (Cook et al., 2009). Nevertheless, if Y142-phosphorylated H2AX persists, protein kinase JNK1 was found to bind, triggering apoptosis (Cook et al., 2009). These results suggest that Y142 phosphorylation may determine whether a cell can be repaired, initiating DNA repair processes or whether the DNA damage is too severe and activating apoptosis in order to get rid of damaged genomes. (Reviewed in Stucki et al., 2009)

Ubiquitination (Ubiquitylation)

The covalent attachment of one or more ubiquitin monomers is called ubiquitination. Ubiquitin is a small 8.5kDa peptide that can label proteins for protosomal degradation. Alternatively, ubiquitination can also alter the function, stability and intracellular localization of a wide range of proteins (Herrmann et al., 2007). Modification of proteins by ubiquitination consists of a series of steps which involves the E1 activating enzyme, E2 conjugating enzyme and the specificity-conferring E3 ubiquitin ligase. E3 ubiquitin ligases are known to work together with several E2 conjugating enzymes which catalyze ubiquitin conjugation via different lysine residues. H2A, H3 and H4 are known to be ubiquitinated in response to UV (Wang et al., 2005; Houtsmuller et al., 2006). Mono-ubiquitination of H2A is mediated by Ring2 ubiquitin ligase which was shown to be dependent on NER and ATR but not ATM (Bergink et al., 2006). UV-DDB is part of an E3 ubiquitin ligase that ubiquinates histones H3 and H4 following UV irradiation. Consequently, the interaction between histones and DNA is relaxed which facilitates the assembly of NER proteins (Wang et al., 2006; Chapter 6). Both XPC and DDB2 are ubiquitinated (Nag et al., 2001; Chen et al., 2001; Matsuda et al., 2005; Sugasawa et al., 2005). Yet, whereas the polyubiquitination of DDB2 triggers its destruction by the 26S proteasome (Fitch et al., 2003a; Rapic-Otrin et al., 2002), polyubiquitinated XPC is not degraded and was even shown to have a higher affinity for both damaged and undamaged DNA *in vitro* (Sugasawa et al., 2005).

ATP-dependent chromatin remodeling and NER

Chromatin remodeling complexes which utilize ATP to mobilize nucleosomes along DNA, evict histones off DNA, or promote the exchange of histone varients. These alterations modulate DNA accessibility and alter nucleosomal structures (Gangaraju and Bartholomew, 2007). The ATP-dependent chromatin remodeling enzymes can be divided into four groups based on distinct domain structures: The SWI/SNF (switching defective/sucrose fermenting) family, the ISWI (imitation SWI) family, the NuRD (nucleosome remodeling and deacetylation)/Mi-2/CHD (chromodomain, helicase DNA binding) family and the INO80 (inositol requiring 80) family. ACF (ATP-utilizing chromatin assembly and remodeling factor) is part of the ISWI family of chromatin-remodeling complexes. ISWI-family complexes are generally involved in regulation of transcription, often in transcriptional repression. Human ACF contains the ATPase subunit SNF2h and a noncatalytic subunit, ACF1 (Ito et al., 1999) and has been shown to facilitate the excision of 6-4PP lesions by the NER core factors, in particular those situated in linker DNA (Ura et al., 2001). In addition to ACF1, SWI/SNF was shown to modulate the accessibility of UV-damaged mono-nucleosomes in vitro (Gaillard et al., 2003; Hara and Sancar, 2002; Hara and Sancar, 2003). Further evidence providing a functional link between chromatin remodeling and repair is demonstrated by the identification of CSB as a DNA-dependent ATPase (Citterio et al., 2000). CSB may therefore have a direct role coupling transcription to repair amoung others via remodeling chromatin at damage sites. It is currently unknown whether CSB directly remodels chromatin *in vivo*. However, CSB has been shown to recruit both p300/CBP and HMGN1 mediating chromatin remodeling in TCR (Fousteri et al., 2006). The ING

(inhibitor of growth) tumor suppressor proteins are known to regulate cellular responses to UV, including cell proliferation, p53-dependent apoptosis and DNA repair. Recently, ING2 was shown to cooperate with p53 to induce histone H4 acetylation, chromatin relaxation, and recruitment of the indispensable damage-recognition XPA protein to photolesion site (Wang et al., 2006). ING1b was similarly shown to promote repair in vivo (Cheung, Jr. et al., 2001) by histone H4 acetylation and chromatin relaxation (Kuo et al., 2004).

Non-chromatin remodelers and NER

Several non-chromosomal proteins have the ability to modify chromatin or to bind to specific histone modifications. For example, GADD45 has a specific affinity for UV-damaged and hyperacetylated DNA and is able to modulate the accessibility of DNA-nucleosome complexes (Carrier et al., 1999). Several studies have shown that GADD45 is required for efficient repair of UV-induced lesions (Smith et al., 1996; Smith et al., 2000; Maeda et al., 2002) suggesting a role of GADD45 in facilitating NER in chromatin. HMGN (high mobility group N) proteins are able to alter higher order chromatin structures by targeting two main elements known to compact chromatin, histone H1 and H3 (Ju et al., 2006; Brown et al., 2006; Catez et al., 2004). Cells deficient in HMGN1 showed diminished repair of CPDs in actively transcribed genes (Birger et al., 2003). In line with these observations, HMGN1 was shown to be recruited to TCR complexes through an interaction with CSB (Fousteri et al., 2006).

Chromatin restoration after NER

As mentioned above, packaging of DNA into chromatin presents a challenge for DNA-repair processes since lesions first have to be made accessible to the repair machinery. Following successful completion of DNA repair the repaired region needs to gain its pre-existing chromatin structure, and checkpoint signaling to switch off the DDR, as described in the Access-Repair-Restore model (Smerdon 1991; Green and Almouzni, 2003). Restoration of the original epigenetic state is essential to maintaining a functional genome and histone chaperones are likely to be involved such as chromatin assembly factor 1 (CAF-1). CAF-1, a complex consisting of p150, p60 and p48 subunits is highly conserved from yeast to human and is known to deposit nucleosomes on newly-synthesized DNA during replication, as well as DNA that has been repaired by NER (Mello and Almouzni, 2001; Gaillard et al., 1996). CAF-1 is recruited to UV-damaged DNA both in vitro and in vivo (Moggs et al., 2000) but dependent on functional NER and possibly by binding via PCNA (Green and Almouzni, 2003). In line with these observations, it is now clear that histones H3 and H4 are incorporated during the repair of UV lesions. Stable de novo incorporation of Histone H3.1 occurs at UV repair sites, dependent on functional NER and CAF-1, providing further evidence for a role of CAF-1 in the chromatin restoration step following repair (Polo et al., 2006). In vitro observations suggest that CAF-1 arrives later than the other post-incision factors and only after ligation is complete (Mocquet et al., 2008). We also observed accumulation of CAF-1 after local UV in wild-type cells as previously described (Chapter 9; Green and Almouzni, 2003). However, CAF-1 accumulation was also found 30 minutes after irradiation in HU and AraC treated cells where DNA synthesis and ligation

is almost completely inhibited (Chapter 8). We therefore conclude that in contrast to in vitro observations by Mocquet et al (2008), CAF-1 is recruited to UV damage prior to completion of DNA synthesis and ligation and therefore cannot carry out nucleosome reassembly when it is first bound (Chapter 8). In line with out observation, Staresincic et al., (2009) found accumulation of late NER factors such as PCNA, DNA pol δ and CAF-1 in cells expressing catalytically inactive XPG, but not in cells expressing catalytically inactive XPF. Hence, 5' incision initiates DNA repair synthesis as well as attracting CAF-1. However, the regulation of CAF-1 seems more complicated, as persistent CAF-1 accumulation was no longer visible 20 hours after irradiation in the presence of DNA synthesis inhibitors, despite the rest of the repair factors still being present (Chapter 8). Asf1, a highly conserved histone H3-H4 chaperone can synergize with CAF-1 in repair and replication-coupled nucleosome assembly *in vitro* (Mello et al., 2002; Tyler et al., 1999), although it is unable to promote DNA-synthesis-dependent histone deposition on its own. Exactly how Asf1 can contribute to DNA-damage responses or if it functions in access, restoration or both processes is currently unknown. Future DNA repair studies in histone structural or modification mutants may improve our understanding of how the histone components and their post-translational modifications influence essential cellular functions such as NER.

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