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Nucleotide excision repair : complexes and complexities : a study of global genome repair in human cells

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Chapter 5

Chromatin, chromatin remodelling and NER

5 Chromatin, chromatin remodelling and NER

It has long been recognised that the major obstacle to overcome for a repair system – indeed, for any process intimately interacting with DNA – in a human nucleus is the chromatin structure into which the DNA is condensed. At the lower level of chromatin organisation, 146 bp of DNA are wrapped around histone octamers (two each of the histones H2A, H2B, H3 and H4) to form the nucleosome core; these in turn are further compacted into higher-order structures such as the 10-nm fibre and the 30-nm fibre. These higher levels of chromatin structure are still poorly characterised, and their effects on repair have yet to be investigated.

The effect of the lower levels of chromatin structure on repair has been best characterised for the NER pathway, both *in vivo* and *in vitro*. *In vivo*, chromatin interacts with NER at two levels. At the level of the nucleosomes DNA lesions can be situated in linker DNA or in the histone core, whereas at the level of higher-order structure DNA lesions might reside in (transcriptionally) active or inactive DNA. A large number of studies conducted in the last decades have consistently found that lesions in the linker of nucleosomes and in active DNA are repaired significantly faster. This is not surprising when one realises that these DNA structures are more open and therefore the repair system has better access to detect and repair them. In the case of TCR, apart from better access to the lesion due to more relaxed chromatin structures, NER also enhances its repair rates actively, employing RNA polymerase stalled on a lesion as a damage sensor (see chapter 2.1).

From the early 90s of the previous century onward, *in vitro* systems have been available to complement *in vivo* research. Utilising cell-free extracts, reconstituted systems with purified proteins or a combination of both, repair from naked DNA has been compared with repair from chromatinised templates. Since the level of DNA packaging in these experiments does not exceed that of the nucleosome, these assays measure exclusively the difference in repair rates between linker and core DNA. As *in vivo*, repair is more rapid from naked DNA than from chromatinised templates (Araki et al., 2000; Hara et al., 2000; Sugasawa et al., 1993; Wang et al., 1991).

For a long while it has been known that during NER *in vivo*, chromatin rearrangements are made (Smerdon and Lieberman, 1978). It was postulated that these rearrangements were at least partly aimed at opening inaccessible chromatin domains to repair; similarly, following repair these rearrangements could restore the chromatin structure to its original state (Smerdon and Lieberman, 1978). The model that was derived from these and corresponding observations was first postulated by Smerdon as the access-repair-restore (ARR) model and has proven very useful for the understanding and study of NER in the context of chromatin (Smerdon, 1991).

Although originally chromatin was thought of as a rigid structure with the sole purpose of compacting DNA, it has become clear that in fact, chromatin is a highly dynamic, 'fluid' structure that actively influences DNA metabolising processes such as transcription. One major factor contributing to the accessibility of chromatin is a group of enzymes referred to as chromatin remodellers, whose function is to change the structure of chromatin in order to alleviate its restrictive effects. Chromatin remodelling enzymes are divided into two major classes: ATP-dependent non-covalent remodellers and enzymes that covalently link attachments to histone tails. Following the investigations of the effects of the chromatin structure on NER, the effects of its remodelling have likewise been assayed. The effect that several chromatin remodelling enzymes have on NER, both *in vitro* and *in vivo*, is discussed below.

5.1 ATP-dependent non-covalent chromatin remodelling

The type of chromatin remodelling performed by the ATP-dependent non-covalent remodellers involves the breaking and reformation of contacts between histones and DNA, resulting in a mobilisation of nucleosomes along the chromatin template. All non-covalent chromatin remodellers belong to the SWI2/SNF2 superfamily of ATPases. Based on the identity of their catalytic ATPase subunit 3 subfamilies can be discerned: SWI/SNF, ISWI, and Mi-2. The prevailing mechanistic model for these enzymes is that they interconvert chromatin between different states in a random manner. As such, the outcome of conversion may be beneficial or detrimental to processes acting on the chromatin. Furthermore, contacts between DNA and histones will only be disturbed transiently, meaning that any positive (or negative) effect on the accessibility of the DNA can easily get lost. It has for instance been found that for transcription the effects of SWI/SNF remodelling are temporal, unless the opened structure is bound by a transcription factor (Owen-Hughes et al., 1996).

SWI/SNF and ISWI
So far, two ATP-dependent chromatin remodelling enzymes have been found to stimulate NER *in vitro*: SWI/SNF (Hara and Sancar, 2002; Hara and Sancar, 2003) and ACF (Ura et al., 2001), which consists of ISWI and acf-1. Both factors enhance transcription by 'loosening up' the chromatin structure. In addition, evidence has been presented that nucleosomal inhibition of photoreactivation by *E. coli* photolyase (Gaillard et al., 2003), and incision by T4 endonuclease V and *Micrococcus luteus* UV endonuclease (Lee et al., 2004) is relieved upon the addition of ISWI (Gaillard et al., 2003) and SWI/SNF (Gaillard et al., 2003; Lee et al., 2004). These data strongly suggest that the stimulation by chromatin remodellers on human NER is not specific for human repair or for the NER system.

CSB
A special case worth noting is the CSB protein, of which the ATP-dependent chromatin remodelling capacity appears not to be strictly required for functional TCR (Citterio et al., 2000); discussed in chapter 2.1. This may suggest that instead, CSB activity is required for another process; indeed, several observations indicate a role for CSB in transcription, where it might stimulate RNA pol II to proceed past transcriptional pause sites and/or other obstructions (Balajee et al., 1997; Lee et al., 2002; van Gool et al., 1997).

5.2 Histone tail modifications

The second type of chromatin remodellers encompasses enzymes that covalently link attachments to histone tails. These modifications include acetylation, methylation, ubiquitination and SUMOylation, and others. The different modifications are thought to form a 'histone code' which fine-tunes and orchestrates the binding of transcription factors and chromatin-remodelling enzymes, resulting in either activation or repression of transcription.

It would lead to far to discuss in detail the various effects that each of these modifications can have. In brief, ubiquitination or SUMOylation of histones is in general associated with an increase or decrease in transcriptional activity, respectively (as is the case for transcription

factors). Methylation appears to be an irreversible modification that is primarily used to maintain a certain repressed chromatin state for prolonged periods of time, such as in terminally differentiated cells (the permanent repression of *DDB2* in cultured rodent cells mentioned in chapter 3.1 being an example). In contrast, acetylation is a reversible dynamic process that decreases interactions between nucleosomes and between the tails and linker DNA, thus leading to an increased accessibility to the DNA. For example, it has long been known that acetylation of histones generally results in increased transcription. Constitutive acetylation of histones H3 and H4 is also associated with increased rates of NER and DSBR. Correspondingly, the opposite process – deacetylation – is associated with repression of transcription. Although the effect that chromatin remodelling has on transcription has been studied for a long time, its effect on repair is only beginning to emerge.

Histone acetylation and NER

Of the various covalent modifications of the histone tails, only acetylation activity has so far been associated with NER. In the first hours following UV irradiation and in the presence of sodium butyrate, histones are hyperacetylated in human fibroblasts (Ramanathan and Smerdon, 1986) resulting in higher rates of NER (Ramanathan and Smerdon, 1986). In HeLa cells histones H3 and H4 are acetylated following UV treatment even in the absence of sodium butyrate (Brand et al., 2001), although in this situation the effect on NER was not tested. These data suggest that UV-induced (hyper)acetylation of histones is a cellular response to facilitate repair. *In vitro* there is as yet only circumstantial evidence to corroborate this: excision of a cisplatin adduct by Chinese hamster ovary cell-free extracts was found to be 2-fold more efficient when the DNA was wrapped in purified human histones compared to recombinant human histones (Wang et al., 2003). The human histones in this situation may have been acetylated, facilitating repair, whereas the recombinant histones were most certainly not.

Interestingly, an intimate link appears to exist between histone acetylation and NER damage recognition. Firstly, the histone acetyltransferase (HAT) p300/CBP interacts with both DDB1 (Rapic-Otrin et al., 2002) and DDB2 (Datta et al., 2001). Secondly, two human HAT-containing complexes display an affinity for UV-damaged DNA: TFTC (Brand et al., 2001) and STAGA (Martinez et al., 2001). Both these complexes contain the spliceosome-associated protein SAP130, which shares a high homology (>50% similarity) with the DDB1 subunit of UV-DDB. SAP130 interacts with DDB1, and the STAGA complex interacts with both subunits of UV-DDB. Both TFTC and STAGA bind preferentially to UV-damaged DNA, in the case of TFTC causing acetylation of histone H3 assembled on the damaged DNA. Exactly through which protein(s) binding to damaged DNA occurs is not clear yet. Brand and co-workers found that SAP130 as a separate factor can bind to UV-damaged DNA, and this binding activity is stimulated in the TFTC complex (Brand et al., 2001). On the other hand, Martinez and co-workers reported that SAP130 in the absence of STAGA compounds shows hardly any preference for UV-damaged DNA and accordingly, STAGA without SAP130 still displays an affinity for UV-damaged DNA (Martinez et al., 2001).

Despite these (as yet) contradictory findings it is clear that there might be a strong interplay between the 'access' and 'repair' steps as described by the ARR model, with chromatin modifying enzymes displaying an affinity for damaged DNA and damaged DNA-recognising proteins interacting directly with histone acetylases.

5.3 Non-chromatin remodellers assisting NER in vivo

Gadd45

The *GADD* genes form a group of genes that are specifically induced after cells are growth-arrested or exposed to DNA damaging agents (Fornace et al., 1989). The product of the *GADD45* gene, Gadd45, has been linked to NER via several observations. The Gadd45 protein displays a specific affinity for UV-damaged and hyperacetylated nucleosomal DNA and can modulate the accessibility of such DNA-nucleosome complexes (Carrier et al., 1999). Human tumour cells in which the Gadd45 levels were knocked down by Gadd45 antisense expression showed reduced repair of UV-damaged DNA (Smith et al., 1996). Gadd45-/- MEFs have reduced UDS following exposure to UV, coinciding with a reduced rate of CPD and 6-4PP removal (Smith et al., 2000). Finally, Gadd45-/- murine keratinocytes show a strong defect in the repair of CPD compared to wild type murine keratinocytes after irradiation with low doses of UVB (Maeda et al., 2002). Interestingly, p53 regulates *GADD45* (reviewed in Zhan, 2005) which might lead to responses of p53-/- cells to DNA damage being erroneously attributed to a direct effect of p53-deficiency (see also below).

HMGN1

HMGN (high-mobility group N) proteins are not classical chromatin-remodelling factors, but are capable of destabilising higher-order chromatin structures by targeting two main elements known to compact chromatin, histone H1 and the N-terminal tail of histone H3 (reviewed in Bustin, 1999; Bustin, 2001). In doing so, they increase the rate of transcription and replication (Crippa et al., 1993; Trieschmann et al., 1995; Vestner et al., 1998). HMGN1-/- mice show decreased rates of CPD removal from the transcribed strand of active genes (Birger et al., 2003). Whether this effect is correlated to overall lower transcription rates in the absence of HMGN1 and hence, lower TCR rates, or whether the more relaxed chromatin in HMGN1+/+ cells allows the TCR machinery to be more efficiently targeted to RNA pol II stalled on lesions is not known.

p53

p53 has been known for a long time to play an important role in NER, most notably by regulating the expression levels of DDB2 and XPC (discussed in chapter 3.4). More directly, p53 has been reported to associate with TFIIH modulating its activity in transcription and NER (Leveillard et al., 1996; Wang et al., 1995), although there has been no follow-up to these initial observations.

Surprisingly however, recently p53 has been implicated in NER as a global chromatin accessibility factor (Allison and Milner, 2004; Rubbi and Milner, 2003). Rubbi and Milner reported that chromatin relaxation following UV occurs in normal, XP-A, -C or -E but not in p53-null human fibroblasts, because p53-deficient cells were specifically defective in acetylation of histone H3 after UV irradiation (Rubbi and Milner, 2003). The authors also reported that this relaxation of chromatin occurs in the entire nucleus even if only part is UV-irradiated (Rubbi and Milner, 2003). Furthermore, they found p53 and p300 to colocalise with sites of NER using immunofluorescent labelling of p53 or p300 and detection of transient ssDNA to visualise patches of NER, followed by image analysis (Rubbi and Milner, 2001; Rubbi and Milner, 2003). However, using more conventional methods such as subnuclear UV irradiation followed by indirect immunofluorescent labelling of p53, p300 and CPD and 6-4PP, no such colocalisation has been observed (Fitch et al., 2003a; M. Volker, M. Vrouwe, unpublished observations).

Furthermore, since Gadd45 is under control of p53 (reviewed in Zhan, 2005) the cells used by Rubbi and Milner (2003) could also be deficient in a Gadd45-dependent process that only indirectly depends on p53.

5.4 Post-repair chromatin restoration

CAF-1 and Asf1

In contrast to the pre-repair ('access') chromatin remodelling, post-repair ('restore') chromatin remodelling has not been extensively studied. The best-studied factor in the restoration of the chromatin structure is CAF-1, a histone chaperone that is involved in depositing nucleosomes on newly synthesised DNA during replication (reviewed in Mello and Almouzni, 2001). Additionally, *in vitro* CAF-1 is capable of specifically assembling nucleosomes onto damaged DNA that has been repaired by NER (Gaillard et al., 1996), and CAF-1 is recruited to UV-damaged DNA both *in vitro* (Moggs et al., 2000) and *in vivo* (Green and Almouzni, 2003). This recruitment depends on functional NER (Green and Almouzni, 2003) and crucially depends on PCNA (Green and Almouzni, 2003) which is involved in the resynthesis stage of NER (chapter 3.10). It therefore seems plausible that CAF-1 is responsible for the local restoration of the chromatin structure directly following repair. Its association with PCNA could imply that CAF-1 is also involved in the restoration of chromatin following other repair pathways that utilise PCNA in their DNA resynthesis stages, such as long patch BER or homologous recombination.

Recently it was found that *in vitro*, the histone chaperone Asf1 can synergistically facilitate the nucleosome assembly by CAF-1 during NER (Mello et al., 2002). In contrast to CAF-1, Asf1 does not associate specifically with damaged DNA nor is it recruited to damaged DNA during repair (Mello et al., 2002). It is therefore thought that Asf1 acts upstream of CAF-1 by supplying CAF-1 with histones so that CAF-1 can efficiently execute its function (Mello et al., 2002).

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