Nucleotide excision repair: from molecular mechanisms to patient phenotypes

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Chapter 6

Discussion

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The DNA contains all the information required to build and develop an organism. Due to the exposure to endogenous and exogenous DNA damaging-agents, the DNA can be damaged which can have deleterious effects. To repair such DNA damages, a variety of repair mechanisms have evolved to protect the genome. The research described in this thesis focuses on nucleotide excision repair (NER), which recognizes and repairs bulky lesions in the DNA. In NER the damage recognition is subdivided into two sub-pathways. Whereas the transcription-coupled repair (TCR) repairs DNA lesions in actively transcribed DNA, global genome repair (GGR) recognizes lesions in the rest of the genome. Whilst the core factors required for NER are well-known, the precise role of its regulatory factors that fine-tune the function of the core factors is only lately receiving more attention. One group of regulatory factors are the modifiers and erasers of post-translational modifications (PTMs). In chapter 1 we describe several proteins that are involved in NER-mediated PTM such as PARylation and acetylation. In regard to this, PTM (e.g., PARylation) and chromatin remodelers (e.g., ALC1) are known for their ability to increase the binding affinity of core factors to the lesion, as well as for their capacity to make the lesion more accessible. Also during later phases of the repair mechanism, it is crucial that NER core factors all function well. This research shows that a tight and well-functioning regulation of the NER-core factors during the damage recognition phase is of crucial importance for the efficiency in repairing DNA lesions. The research described in this thesis provides new insights into the complex network of regulatory factors in NER and the importance of PTM to fine-tune repair. These new insights raise additional questions which are discussed in this chapter.

PARP and ALC1 in NER

The essential core factors required for the repair of UV lesions on naked DNA *in vitro* have been described before (Aboussekhra et al., 1995). The NER mechanism is organized as a network of core factors that function together to regulate the different repair steps, from the initial phases of damage detection and DNA unwinding, to the latter phases of lesion verification and lesion excision. While these core proteins face no difficulties in repairing DNA lesions under *in vitro* conditions, within *in vivo* settings additional regulatory factors are important to fine-tune the repair. In global genome repair more than twenty regulatory factors have been described that facilitate repair. While some assist in the recruitment of

core repair factors, others prime the area around the lesion aimed for repair, or stimulate the activity or binding of core factors (chapter 1, table 1-3). Such regulatory factors include classes of chromatin modulators, chromatin remodelers, posttranslational modifiers and erasers. Since ideal repair conditions are rarely found *in vivo*, due to differences in damage load, availability of core proteins and lesion accessibility, fine-tuning of the repair mechanism through its regulatory factors is crucial. So far, the majority of studies on regulatory factors have only highlighted the role of specific regulatory factors in the repair mechanism, without considering any possible interdependence and interaction with other regulatory factors in the overall repair network. To get a better understanding of the complete system of regulatory factors, their specific roles and mutual interaction, this fascinating network should be studied further.

The in global genome repair (GGR) described regulatory factors are mainly linked to the damage-recognition factor DDB2, rather than XPC. DDB2 is an important factor (Luijsterburg et al., 2012) that links ATP-dependent chromatin remodelling, as well as histone modifications, such as the recruitment of histone acetyltransferases (p300, HBO1) to GGR (Datta et al., 2001; Niida et al., 2017; Rapic-Otrin et al., 2002). While DDB2 is known to recruit a number of regulatory factors, little is known about the regulatory factors that are recruited by XPC to the lesion.

In Chapter 2, we identified an XPC-dependent network of regulatory factors in GGR. We showed that XPC forms a tight network with the regulatory factors PARP1, PARP2 and ALC1 to stimulate the repair of UV lesions. While PARP1 has been linked to NER in previous studies (Pines et al., 2012; Robu et al., 2017), this is the first time that PARP2 is linked to NER. As PARP2-deficient cells are sensitive to UV irradiation, but do not contribute to UV-induced PARylation (chapter 2), PARP2 might have another role. Besides functioning as a binding platform for other repair proteins, PARP2 could be involved in increasing the branching of the PAR chains, like previously described (Chen et al., 2018). It could also be responsible for modifying serine residues, like PARP1 (Prokhorova et al., 2021). So far, we only know that PARP2 is involved in NER, but its exact role and effects are still unclear. PARP1 and PARP2 are DNA-dependent PARP proteins, together with PARP3. So far, PARP3 has not been linked to NER, but to double-strand break repair (Boehler et al., 2011). Like PARP1 and PARP2, PARP3 becomes catalytically activated upon DNA binding (Langelier et al., 2012; Langelier et al., 2014). Getting a better understanding of all DNA-dependent PARP proteins would contribute to our understanding of their interaction and interdependence.

An interesting point in chapter 2 is the strong interaction of PARP2 with ALC1. ALC1 is well-described as an ATP-dependent chromatin

remodeller that loosens the chromatin structure upon DNA damage (Sellou et al., 2016). Aside from this strong protein-protein interaction, PARP2 could also stimulate the activity of ALC1, either directly or indirectly. ALC1 contains an autoinhibitory domain that gets inactivated upon PARylation (Singh et al., 2017), while ALC1's interaction with the H2A-H2B acidic pocket of the nucleosome prevents such inactivation (Wang et al., 2021). It is precisely this regulatory mechanism that might be affected by PARP2. In chapter 2 we provided evidence that the ATP-domain of ALC1 is important for the repair of UV lesions, indicating that chromatin remodelling activity of ALC1 is important for NER. Even when ALC1 uses its chromatin remodelling activity in NER, the exact nature of this activity should be further studied. Future research could address the nature of the chromatin remodelling activity, to study whether this is due to nucleosome sliding or histone eviction. To distinguish between these two aforementioned mechanisms, different experiments could be performed. While nucleosome sliding can be studied by monitoring the change of the position between the DNA and the nucleosome (Gottschalk et al., 2009), histone eviction is highlighted by labelling the histone subunits and observing any change of localization at damaged sites (Lan et al., 2012).

The link between high mobility group (HMG) proteins and NER

The HMG family consists of the three classes of proteins HMGA, HMGB, and HMGN. In turn, each class consists of multiple members and isoforms. Each of the HMGA, HMGB and HMGN-families contains a unique DNA-binding domain, which recognizes specific DNA features. The HMG proteins are the most abundant non-histone proteins in the nucleus of eukaryotic cells. As architectural proteins the HMG proteins can modulate chromatin, affecting several DNA-related cellular mechanisms, such as replication, transcription and DNA repair. In chapter 3 and chapter 4, we described whether the different members of the HMG family are recruited to UV lesions. While we provided a first impression of the different behavior of the HMG proteins, their role in response to UV irradiation remains unclear however.

The role of HMGN in mice is not the same as in humans

The HMGN family belongs to the group of high mobility proteins that can modulate chromatin. In particular upon DNA damage, when a whole orchestra of repair proteins is recruited, modulating chromatin is a way to increase the accessibility of these repair proteins. Initially, HMGN1 was linked to DNA damage repair through findings in mice that established the requirement of this protein for the repair of UV lesions in actively transcribed genes (Birger et al., 2003). However, our findings point at a

mice-specific role of HMGN1 in NER, as we showed that these findings could not be extrapolated to human cells, thereby excluding any role of HMGN1 in human NER. Thus, the homology of 83% between mouse and human HMGN1 (Apelt et al., 2020) does not guarantee for a conserved function between species. Our gathered data showed that neither HMGN1, nor HMGN2 are recruited to UV lesions. This was irrespective of cell-type, siRNAs, or knock-out conditions (chapter 3). Rather, the difference between human and mice HMGN could be explained by a species-specific difference. While in human cells repair of CPDs relies on the presence of GGR-specific DDB2 proteins, mouse cells lack this repair protein DDB2, instead relying on TCR for their repair of CPDs.

What stimulates the dissociation of HMGN and HMGA from DNA lesions?

Some DNA repair proteins are rapidly recruited to DNA lesions, while others dissociate or remain bound to DNA. It has been suggested that there is an exchange at DNA damage sites between repair proteins and proteins involved in biological processes, such as transcription (Polo and Jackson, 2011). Interestingly, we observed a clear dissociation of HMGN and HMGA proteins from sites of UV lesions, indicating that HMGA and HMGN are no repair factors. Rather, they are involved in other biological cell processes, by associating with active genes that are involved in transcription (reviewed: (Zhu and Hansen, 2010). In this regard, UV-induced dissociation of HMGN from DNA would provide space for the DNA repair machinery. In addition, the association of HMGN with active genes could also have a negative effect on the transcription of NER-related proteins. For example, it was described that HMGA1 proteins can repress the transcription of the NER-core factor XPA when overexpressed (Adair et al., 2007). Upon UV irradiation, repression of XPA transcription would obstruct NER. Therefore, dissociation of HMGN would prevent the transcription repression of XPA, helping to maintain sufficient levels of XPA for the repair mechanism.

What exactly drives the dissociation of HMGN and HMGA from local UV damage is not clear yet. A possible explanation for the dissociation would be DDB2-mediated chromatin unfolding, or damage-induced post-translational modification (PTM) on HMGN, resulting in a decreased DNA binding affinity.

One example of the role of PTM on protein dissociation is the histone chaperon FACT, which dissociates from DNA upon PARylation of its Spt16 subunit (Heo et al., 2008; Huang et al., 2006). As HMGN is subject to phosphorylation (Prymakowska-Bosak et al., 2001; Soloaga et al., 2003; Thomson et al., 1999), as well as acetylation (Bergel et al.,

2000; Herrera et al., 1999; Luhrs et al., 2002), which are both negatively charged PTMs, this could be a potential mechanism to repel HMGN from the negatively charged DNA. In line with this idea, *in vitro* studies showed that phosphorylation of serine residues within HMGN2 leads to a negatively charged and repelled HMGN2 from the negatively charged acidic patch of the nucleosome (Kato et al., 2011). Thus, PTMs affect the binding affinity of HMGN proteins.

Whether the same residues also play a role in the dissociation upon UV irradiation has not been studied yet. So far, the release of HMGN from the DNA has only been witnessed during mitosis. This release is caused by the phosphorylation of specific serine residues in the nucleosome-binding domain within HMGN1 and HMGN2 (Prymakowska-Bosak et al., 2001). Whether this releasing mechanism also happens upon damage induction is not clear yet. Therefore, future studies could focus on identifying residues that are modified in response to UV irradiation. Next, identification of UV-specific modifiers that target these residues in HMGN and determination of how these modifiers are activated and recruited into the proximity of HMGN would provide insights into the events that take place upon UV irradiation.

How does HMGB bind to NER-lesions?

In contrast to other HMG family members the variants of the HMGB family associate with UV-irradiated chromatin and are recruited to UV lesions. This might be partially explained by the distinct DNA-binding domains of the different HMG proteins, each specialized in recognizing a specific sequence of DNA. Whereas HMGA contains an A-T hook domain and HMGN a nucleosome-binding domain, HMGB is known for its two DNA-binding boxes. This so-called b-boxes recognize unstructured DNA. Interestingly, box A and box B only have a sequence similarity of 29%, implicating that each box has different binding substrates and a distinct DNA binding affinity. In order to obtain more insights into the role of HMGB proteins at UV irradiated chromatin, it would be relevant to study which of the two boxes, and more specifically which residues, are required to bind to the UV lesions. It is known that HMGB binds to different DNA damages, including UV lesions (Lanuszewska and Widlak, 2000; Pasheva et al., 1998), but it is not clear yet whether this is a direct or indirect interaction. The direct interaction with the GGR factor XPC-RAD23 (Lange et al., 2009), suggests that the association with DNA lesions might be indirect, as HMGB is possibly recruited to UV lesions via XPC-RAD23. Another possible mechanism for HMGB association with UV lesions is through DDB2-induced chromatin changes. DDB2 is known to be important for the recruitment of different chromatin modulators (chapter 1). Therefore, it

would be interesting to test whether the recruitment of HMGB is dependent on DDB2.

What is the function of HMGB at UV lesions?

The quick accumulation of HMGB at UV lesions shows that HMGB is regulated by UV irradiation, but for what purpose remains unclear. To explore the role of HMGB as a repair factor in NER, functional assays lacking HMGB need to be performed. Commonly used methods that measure the repair ability indirectly, such as clonogenic survivals after UV-C irradiation and unscheduled DNA synthesis, would be appropriate assays to test this. In addition, performing direct repair assays - where UV lesions are labelled by immunostaining and followed over time - would provide an answer to the question whether HMGB contributes to the repair of UV lesions.

Hypothesizing that HMGB has a role in NER, the follow-up question would be what precise role it has. As we know that HMGB is an architectural protein, it can bind to DNA through its DNA-binding motif, but it can also modulate chromatin. With its ability to bend DNA (McCauley et al., 2007) and to loosen up nucleosomes (Nalabothula et al., 2014), HMGB could facilitate an environment that allows repair proteins to better reach the DNA lesions. Earlier studies already showed that chromatin changes, specifically ATP-dependent ones, are an essential step in the damage recognition in NER (Jiang et al., 2010; Luijsterburg et al., 2012; Niida et al., 2017). Although HMGB itself does not possess ATP-dependent chromatin remodelling activity, it could still recruit or stimulate the activity of such chromatin remodelers. So far, only *in vitro* studies showed that HMGB stimulates the chromatin remodeler complexes ACF/CHRAC (Bonaldi et al., 2002), but whether this occurs also under *in vivo* conditions or even in response to DNA damage is not known. Still, chromatin modulation executed by HMGB would be one possible mechanism of HMGB to be involved in NER.

Another role of HMGB could be to facilitate the recruitment of repair proteins to the lesions. Mapping the interactome of HMGB upon UV irradiation would give a first idea about the network of proteins that associate or dissociate from HMGB after UV damage. A potential group of proteins that dissociate from HMGB upon UV irradiation could be transcription-linked proteins, as HMGB is also involved in transcription (Boonyaratanakornkit et al., 1998; Sutrias-Grau et al., 1999). As transcription is blocked upon UV irradiation, transcription-related proteins would likely dissociate from HMGB.

Potential UV-dependent interactors of HMGB could be NER proteins or proteins that stimulate NER. The interactome of HMGB has

not been mapped yet. Whereas it already has been described that HMGB interacts with several NER factors, ranging from the damage recognition-proteins XPC and RAD23 to the pre-incision complex proteins (XPA), this has only been observed at triplex-forming oligonucleotides (TFO)-directed psoralen crosslinks (Lange et al., 2009; Reddy et al., 2005) and not at UV lesions. TFO-directed psoralen crosslink formation is a specific method to induce crosslinks by binding psoralen to sites where TFOs are integrated into the DNA. As the repair of TFO-directed psoralen crosslinks relies on several repair mechanisms (NER and mismatch repair), it is still possible that HMGB interacts with NER factors (Zhao et al., 2009). In this respect the lesion can be recognized by NER when the crosslink is unhooked. However, TFO-induced NER might differ from canonical NER. These interaction studies on HMGB and NER proteins should be repeated in response to UV for verification.

While the majority of studies have focused on the role of HMGB1, so far only few studies focus on the role of the other three HMGB variants (HMGB2-HMGB4). In chapter 4 we observed that all four HMGB isoforms (HMGB1, HMGB2, HMGB3 and HMGB4) associate with UV lesions. To get a better understanding of the role of HMGB proteins in NER, a first step would be to perform an unscheduled DNA synthesis assay to measure NER after knocking down HMGB isoforms using specific siRNAs. Using siRNAs against individual HMGB isoforms, or a combination of isoforms, would help to understand whether all four variants have a different function or whether they are redundant. Since the four HMGB variants differ in the amino acid sequence, it cannot be ruled out that they have different functions.

New ERCC1 mutations cause a unique phenotype

In chapter 5 we describe two patients with ERCC1 mutations that display a distinct phenotype from previously described ERCC1 patients (Apelt et al., 2021). Whereas the ERCC1 patients in chapter 5 largely suffer from liver failure and kidney defects, the previously described ERCC1 patients displayed a different phenotype including skeletal abnormalities and an early childhood death (Jaspers et al., 2007; Kashiyama et al., 2013). Interestingly, the liver and kidney defects have not been described before in ERCC1 patients. As ERCC1 is an important endonuclease in NER and ICL repair, it is easy to assume that a defect in these repair pathways causes the liver and kidney problems. However, mice deficient in both NER and ICL repair did not show any liver or kidney defects (Mulderrig and Garaycoechea, 2020). Only in mice that lack ERCC1 liver and kidney abnormalities were observed (Kirschner et al., 2007; Weeda et al., 1997). This strengthens the hypothesis that the liver and kidney defects in the

patients are caused by a role of ERCC1 outside of the canonical repair pathways. A role of ERCC1 in early-stage liver or kidney development seems unlikely, since the organs develop and function normally. However, after early childhood the organ function decreased, leading to liver failure and eventually organ transplantation. This indicates a possible chronic accumulation of endogenous DNA damage in the organs of the ERCC1 patients.

A wide range of endogenous damages has been generally measured in the liver, ranging from ethano-adducts to products of lipid peroxidation and others (De Bont and van Larebeke, 2004). To get a better understanding of the role of ERCC1, liver cells that lack ERCC1 should be exposed to these different substances to mimic endogenous damage accumulation. One possible substance is toxic air pollutant PM2.5 (Xu et al., 2019) that induces inflammation and oxidative stress in liver cells. Since the liver is a complex organ that consists of different cell types, a model system should be used that takes this into account. Over the recent years, a few methods have been developed to study the effect of substances on organs. By using pluripotent stem cells, human mini livers can be made (Mun et al., 2019). These so-called liver organoids provide a perfect opportunity to study the consequences of DNA lesions in the complex liver environment. Another useful method would be the so called organ-on-a-chip, which combines a liver-specific cell model with actual blood flow (Beckwitt et al., 2018). Both methods mimic the human physiology of the liver more closely than a 2D cell model. By studying the role of ERCC1 in the liver and the kidney, we would not only get a better understanding of the complex environment of the organs, moreover it would provide insight into the causes of the ERCC1 defect in the patients.

Addressing the protein instability of ERCC1

The two patients in chapter 5 have a mutation in the ERCC1 gene that leads to reduced protein levels. When we generated recombinant ERCC1 R156W protein, a fraction of the protein aggregated, indicating that protein aggregation might be at least partially the cause of the lower protein levels of the patients. Another explanation for the reduced protein levels would be improper protein folding, which leads to protein degradation. Based on available structures of ERCC1 together with XPA (Jones et al., 2020; Tsodikov et al., 2007), we hypothesize that the R156W mutation which resides in the XPA-binding pocket of ERCC1 leads to the destabilization of the salt bridge with its opposing amino acid. To get a better understanding of the structural effects of the R156W mutation, a first step would be to perform cryo-EM on the recombinant mutant ERCC1-XPF complex (Jones et al., 2020). After solving the structure of the mutated ERCC1 protein,

we could formulate approaches to stabilize the ERCC1 R156W protein. So far, the use of protein-stabilizing drugs in the clinical environment is not very common. In particular, the identification of potential binding sites challenge the use of protein-stabilizing drugs, as these bindings sites should not be located within the functional domains of the protein. In the case of the ERCC1 R156W mutation, where the mutation lies in the XPA-binding pocket, finding a potential binding site that increases protein stability, but that not disrupts the XPA-binding is challenging.

So far stabilizing compounds have been used in the field of cancer research and more specifically in the p53 reactivation (Wiman, 2010). The p53 protein is an important tumor-suppressor, which becomes inactivated or destabilized in tumors (Bullock and Fersht, 2001). Through screening a wide variety of known chemical structures, compounds were identified that bind to a specific point mutation and increase the protein stability (Basse et al., 2010). By repeating these screens and combining them with *in vitro* methods that measure protein stabilization, a potential protein candidate could be found. This screenings could be repeated to identify compounds that interact with the ERCC1 R156W mutation. A challenging aspect of finding a compound could be the fact that in ERCC1 R156 forms a salt bridge with the opposing amino acid. To which extent the salt bridge needs to be restored to stabilize the ERCC1 protein has not been studied yet. Maybe in the future a compound is identified that binds to the missense mutation and that stabilizes the ERCC1 R156W protein. This compound could be used to prevent the ERCC1 R156W-mediated liver and kidney defects by local drug administration.

Until recently, we only identified two siblings with a deletion and the R156W missense mutation. Meanwhile, a third patient was identified with the same mutation and phenotype. With this publication, we created more awareness for ERCC1 mutations and their unique phenotype.

General conclusion

In general, NER is an important DNA repair mechanism that incises bulky lesions from the DNA, including UV lesions. The repair of these DNA lesions ensures that the lesions that block transcription and replication are removed. It also prevents that DNA lesions are turned into mutations. The research described in this thesis shows that in addition to the NER core factors, regulatory proteins also play an important role in the repair mechanism. Often, each regulatory protein is studied separately. By studying the role of several regulatory proteins simultaneously, a better understanding of the complex network of regulatory proteins around the NER core factors is created. Another finding of the thesis is that regulatory factors, and also core factors, do not always have the same role in different species. The roles of regulatory proteins have evolved over years and have adapted to the species-specific environmental factors and living habits. Before implementing research findings into the clinic, they should be validated in a human-like model. Lastly, this thesis points out that mutations in a specific NER core-factor can cause different phenotypes depending on the site of the mutation. It is important to study the different regulatory factors and patient mutations in NER to be able to develop mutation-specific treatment for the patients.

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