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CHROMATIN DYNAMICS AND DNA REPAIR

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1. ABSTRACT

Packing of the eukaryotic genome into chromatin poses an accessibility problem for the DNA repair machinery. Chromatin structure has to be changed for the repair to occur, and we are beginning to discover how different chromatin modifying mechanisms facilitate DNA repair in the chromatin context. On the other hand, the repair-related changes in chromatin should be transient, and a particular chromatin state should be able to survive the repair process. Defects in the proper maintenance of chromatin states after repair could be a factor in the aging process, as well as in other pathologies.

2. INTRODUCTION

DNA damage, caused by exposure to intracellular or external mutagens, presents a major threat for a living cell. In higher eukaryotes, accumulation of genomic changes is one of the leading causes of oncogenesis and aging (1). Accordingly, cells have developed diverse mechanisms to recognize defects in DNA structure and then respond by either repairing the lesion or undergoing apoptosis.

Although the mechanisms of cellular response to DNA damage were first elucidated in prokaryotes, later studies revealed many similarities between prokaryotes and eukaryotes in this regard (2,3). The most obvious difference, however, is the tight packing of the eukaryotic genome into chromatin, a hierarchically organized complex of DNA and histone and nonhistone proteins. This packing represents a common obstacle for most of the DNA functions. Concerning transcription, covalent modifications of core histone N-termini and ATP-dependent nucleosome remodeling play a role in regulation of gene expression in the chromatin context (4,5,6). On the other hand, the role of these chromatin modifications in other aspects of DNA metabolism, and in particular, in the cellular response to DNA damage, remains largely unexplored.

In addition to the accessibility problem that the tight packaging of DNA into chromatin poses for the repair machinery, another function of chromatin has relevance in the context of the chromatin - DNA damage interface. It is the phenomenon of chromatin memory, that is, the ability of alternative chromatin states to be maintained through many rounds of cell divisions. This phenomenon is believed to be involved in the mechanisms of epigenetic inheritance (7), an important concept of developmental biology. In light of the chromatin memory phenomena, chromatin instead of DNA can be considered to be the actual substance of inheritance in eukaryotes. Consequently, how the alternative chromatin states are properly maintained during DNA replication (8,9), repair and recombination becomes an important issue.

In this review we will discuss several issues related to the role of chromatin structure and dynamics in the cellular response to DNA damage. First we will outline the complexity of this response, since one might expect it to depend on the particular chromatin context and the kind of DNA lesion. We will describe the problem that chromatin presents for the recognition and repair of damaged DNA, by decreasing DNA accessibility. We will review some recent data indicative of the role of chromatin dynamics in repair. Finally, we will pose the question of the long lasting effects on chromatin after the lesion has been repaired, and what consequences these effects could have for the cell's physiology.

3. COMPLEXITY OF THE CELLULAR RESPONSE TO DNA DAMAGE

DNA can be damaged in a variety of ways, consequently, living cells have developed complex networks of multiple enzymatic systems to repair different kinds of DNA lesions. In particular, UV damage is mostly dealt with by photoreactivation and nucleotide excision repair (NER), double strand breaks (DSB) are repaired by homologous recombination (HR) and non-homologous end joining mechanisms (NHEJ), and a special enzymatic system targets nucleotide mismatches (10).

A unique feature of the eukaryotic genome is its packaging into chromatin, which exists in different higher order structures, varying in the degree of DNA condensation and nuclear compartmentalization. One might expect that the differences in lesion accessibility and localization, dependent on a particular chromatin context, could affect the cellular response to DNA damage. In a yeast cell, most of the genome is represented by active genes that are organized into relatively open and accessible euchromatin, whereas comparatively little of it (less than 10%) is more tightly packed into heterochromatin located on the nuclear periphery (10, 11). Compared to yeast, in higher eukaryotes the situation is more complex. In drosophila, two kinds of heterochromatin-like structures exist, responsible for the phenomena of Position Effect Variegation (PEV) and Polycomb Group repression (Pc(G)), respectively (12). They are represented by the biochemically and genetically distinct HP1 and Polycomb complexes, and one might expect differences in the response to DNA damage between these two types of heterochromatin as well. In mammals the number of different heterochromatin types is even higher, as there are three different HP1 homologues and several polycomb homologues.

Different kinds of DNA damage can occur in the different chromatin contexts, and the cellular response could depend on both kinds of differences. Therefore, from a combinatorial point of view, the challenge to study the DNA repair in the chromatin context is more complex than that of the study of transcription in the chromatin context, as all combinatorial variants of kinds of DNA damage and chromatin variations have to be explored. In fact, one could imagine two separate questions in this respect. First, what has to happen with the particular kind of chromatin in order for the particular DNA lesion to be efficiently repaired; essentially this is a question of DNA accessibility. Second is the question of chromatin maintenance: how a particular chromatin state is restored afterwards, in spite of the perturbations caused by the repair process.

Not much is known yet about the combinatorics of DNA repair and chromatin structure. So far, mostly the basic, nucleosomal level of chromatin organization has been explored in its relation to the DNA repair process. As expected, wrapping of DNA into the nucleosome presents an obstacle for repair of DNA lesions.

4. PACKING INTO CHROMATIN PRESENTS AN OBSTACLE FOR DNA REPAIR

In a typical mammalian interphase nucleus, genomic DNA is incorporated into a 10-nm-diameter nucleosomal fiber, with each nucleosome containing a core histone octamer (consisting of H2A, H2B, H3 and H4) and one linker histone H1 or H5 (13). A typical nucleosome contains 146 bp of DNA wrapped 1.65 times, in a toroidal supercoil, around the histone octamer. The 10-nm fiber is further packed into a higher-order structure, the so called 30-nm filament. The final packing ratio is determined by the third level of organization, which is the packing of the fiber itself.

Most of what is known about the effect of chromatin structure on the repair process concerns the most basic nucleosomal level of chromatin organization.

In early *in vitro* studies, it was demonstrated that nucleotide excision repair is inhibited by packing DNA into nucleosomes (14). More recent work extends these original findings in a more detailed setting. For example, nucleosomes can be reconstituted on DNA substrate that includes a single UV radiation photoproduct, and the effect of nucleosome organization on the excision nuclease and damage recognition can be investigated. These studies have confirmed the inhibition of excision and damage recognition by nucleosome (15, 15a ,16, 17).

Consistent with the above data, studies in living yeast cells of photolyase-dependent repair show that nucleosome packing inhibits DNA repair. The removal of CPD (cyclobutane-pyrimidine dimers) in the linker DNA and nuclease-sensitive regions is much faster compared to that of CPDs in nucleosomal DNA (15-30 min versus 2 hr) (18).

Another example of the negative effect of nucleosome structure on the repair process comes from *in vitro* studies of the migration of the Holliday junction, an important intermediate in recombination-mediated repair (19). This kind of repair is involved in the case of DSB. The work of Grigoriev *et al.* elegantly demonstrated that a histone octamer blocks branch migration of a Holliday Junction (20) and, therefore, should present an obstacle for DSB repair.

The role of higher level chromatin organization in DNA repair has not been yet addressed in precisely defined *in vitro* experiments. Its relevance can be inferred from *in vivo* studies. It was shown, for example, that heterochromatic DNA is repaired by NER with less efficiency than is the euchromatic DNA, which could be accounted for by the differences in packing (18). However, the higher efficiency of NER on euchromatic DNA might also be explained by the phenomenon of TCR (Transcription Coupled Repair), that preferentially repairs the transcribed strand of DNA.

To summarize, the organization of eukaryotic DNA into chromatin limits the accessibility of damaged

DNA for recognition and subsequent repair. Recent studies, reviewed in the next section, shed light on how the cell could deal with this problem.

5. CHROMATIN DYNAMICS AND THE DNA DAMAGE RESPONSE

The structure of chromatin has evolved to make the tight packaging of the eukaryotic genome compatible with its dynamic nature. Over the last several decades, a large volume of knowledge has been accumulated concerning the changes in chromatin that accompany gene regulation. These changes include postranslational modifications of chromatin proteins (most notably, of core histone N-termini), changes in interactions between chromatin proteins and DNA (e.g., nucleosome remodeling) and changes in chromatin composition (e.g, specialized histone variants).

The role of different types of chromatin dynamics (such as histone modifications and ATP-dependent nucleosome remodeling) in transcription has been firmly established (5). Several recent studies provide biochemical evidence for the role of chromatin modifications and remodeling in the cellular response to DNA damage.

5.1. Histone modifications

The group of Dr. Nakatani has recently provided an evidence that links histone acetylation to DNA repair by analyzing TIP60 histone acetyltransferase (HAT) and the proteins associated with it in the TIP60 complex (21, 22). TIP60 is a member of the MYST family of HATs, that also includes MOZ, Ybf2/Sas3, Sas2, ESA1, MOF and MOZ related factor MORF (23). Two TIP60 interacting proteins, named TAP54a and TAP54b, turned out to be the human homologues of the bacterial ATPase/helicase RuvB. RuvB is involved in recombination and recombination-dependent repair in E.coli. It acts as a motor protein that catalyzes migration of the Holliday junction during recombination and repair. Both TAP54a and TAP54b are also ATPases. As expected, the TIP60 complex has also a helicase activity, most probably, attributable to the TAP54a and TAP54b. However, neither subunit alone or in a complex with each other is sufficient for this activity. Importantly, ectopic expression of a dominant negative mutant of TIP60 lacking histone acetylase activity results in impaired double-strand DNA break repair. Surprisingly, these cells also become less sensitive to DNA damage due to a less pronounced apoptotic response to DNA irradiation. These results indicate that the TIP60 complex plays a role in DNA repair and apoptosis (21, 22, 23). Lately evidence for a role of HAT activity in repair of DSB was strengthened by demonstration that acetylation of H4 tails by histone acetyltransferase ESA1, the yeast counterpart of the human TIP60, is essential for DSB repair (24).

Another TIP60 interacting protein is PAF400/TRRAP - a large protein that is also a component of the PCAF/GCN5 histone acetyltransferase complex (24a). PAF400/TRRAP belongs to the ATP family of kinases (but it is not a kinase by itself (25)). Some members of this family, such as ATM, ATR and DNA-PK are involved in the cellular response to DNA damage (26). Considering the evidence that p53 is acetylated by PCAF and p300/CBP in a DNA damage dependent manner (27; 22), PAF400 might be involved in the control of acetylation responding to DNA damage. Thus far it remains unknown how the TIP60 complex is involved in the decision to repair the damaged DNA or undergo apoptosis. As a possibility, the TIP60 complex acetylates histones that will be further recognized by the repair machinery. The TIP60 complex itself may be directly involved in DNA repair via the RuvB homologues. It might also acetylate proteins other than histones, for example p53, known to be involved in apoptosis.

PCAF, first identified as a p300/CBP-associated factor that competes with the adenoviral oncoprotein E1A (28), might also be involved in the cellular response to DNA damage, via its acetylation of p53 and association with the ATM-like p400. Interestingly, most of the components of the PCAF/GCN5 multiprotein complex, including the histone-like subunits (28a, 22), are different from that of the TIP60 complex. Therefore, these two complexes might be involved in the cellular response to DNA damage in different ways. In line with this, studies from Dr. Tora's group on the TFTC complex (closely related to the PCAF/GCN5 complex), have provided evidence of its role in the transcription-coupled repair of UV damaged DNA. Two components of TFTC turned out to be the PCAF-related HAT GCN5 and the SAP130 subunit which has homology with UV-damaged DNA-binding factor DDB1. Moreover, they demonstrated that the TFTC complex preferentially binds UV-irradiated DNA and also acetylates histone H3 on the nucleosomes assembled on UV-damaged DNA. These results indicate that TFTC complex could have a function in the repair of UV damaged DNA (29). Comparing the data available for the two histone acetyltransferases PCAF/GCN5 and TIP60, one can hypothesize that they are involved in repair of different kinds of DNA damage: UV damage and DSB, respectively.

Another well known HAT is p300 (30, 22), which is a transcriptional co-activator with many biological functions. Interestingly, several reports point to involvement of p300 in the DNA damage response as well. p300 interacts with Proliferating Cell Nuclear Antigen (PCNA) and associate with freshly synthesized DNA after UV irradiation (31). Consistently, it has been found to interact with the p48 component of the XPE-related complex DDB (32, 33). Also, it has been shown to acetylate a FEN1 endonuclease, implicated in DNA repair, and to regulate its function (34). It has also been reported to associate with thymine DNA glycosylase (TDG), involved in repair of G/T and G/U mismatches, and to regulate repair by acetylation of TDG (35). Finally, it has been shown to associate in vivo with BRCA1, a tumor suppressor with properties of a transcription factor involved in DNA repair (36).

Among the enzymes with activity opposite to that of the HATs, the NAD dependent histone deacetylase Sir2 has the most links to DNA repair. Its nuclear localization changes in response to DNA damage, and yeast Sir2 mutants show increased sensitivity to DSB (37, 38). Interestingly, inactivation of the Sir2 homologue in mammals makes cells more sensitive to DNA damage as well (39, 40). However, in this case the effect is attributed to the increased levels of p53 acetylation that direct the injured cells towards apoptosis. It is intriguing that the

effect of the dominant negative mutants of the Sir2 deacetylase in mammalian cells mirrors the effect of the dominant negative mutant of the histone acetylase TIP60: whereas the former increases cell sensitivity to DNA damage, the latter makes them more resistant (21), consistent with the opposing enzymatic activities of these proteins.

5.2. Chromatin remodeling

A second class of chromatin changes is provided by various ATP-dependent nucleosome remodeling complexes (5). Studies of the involvement of these activities in transcription regulation demonstrate their role in facilitating the accessibility of DNA for the transcriptional machinery in the chromatin context. The evidence for a similar role of nucleosome remodeling in repair are more scarce (18); however, they include the following examples:

1. Cockayne syndrome B protein (CSB) is known to be involved in transcription coupled repair (TCR). It belongs to the SWI2/SNF2 family of DNA-dependent ATPases and recently was shown to be capable of remodeling chromatin *in vitro* (41).

2. Remodeling complex INO80, which contains an ISWI-like ATPase, contains RuvB like proteins, similarly to the TIP60 complex (42). Ino80 mutants are hypersensitive to DNA damaging agents (42).

3. Chromatin remodeling factor ACF, (43) was shown to facilitate nucleotide excision repair of internucleosomal linker regions *in vitro* (16) and was implicated in the DNA repair as well.

4. The breast cancer suppressor BRCA1 gene product, which plays a role in repair of DSB by homologous recombination, was indicated to be involved in chromatin remodeling via its c-terminal BRST domain (36).

5.3. Specialized histone variants

Finally, a third class of changes in chromatin, implicated in the control of DNA repair, is represented by the histone H2AX, a version of an H2A which contains a phosphorylatable C-terminus. Phosphorylation of Serine 139 in the unique carboxy-terminal tail of H2AX is one of the first cellular responses to double strand breaks in DNA (DSB), as it occurs within 1 to 3 minutes after DNA damage (44, 44a). Interestingly, DSB induce this response, whereas other types of damage, such as UV irradiation, do not. Immunohistochemical analysis indicates that phosphorylated H2AX is recruited to the damage induced foci and colocalizes with Rad50, Rad51 and BRCA1 (44). Although the significance of these foci remains unknown, phosphorylated H2AX might promote DNA damage signaling by recruiting repair related factors to damage sites or, as another possibility, phosphorylated H2AX could trigger changes in the local chromatin structure around the break.

The case of H2AX is an example of how different variations in chromatin (in this case, alternative histone variants and histone phosphorylation) are cooperatively required to control a genome function (in this case, the DSB repair). There is increasing evidence for similar cooperation in many other cases. Different histone modifications, such as acetylation and phosphorylation have been shown to be linked (45), as well as chromatin remodeling and histone acetylation (46). Thus, concerning DNA repair, one might expect that various kinds of histone modifications, for example acetylation, phosphorylation and ribosylation, as well as chromatin remodeling events, might act in concert and control distinct repair processes on DNA.

6. LONG-LASTING EFFECTS OF DNA REPAIR ON CHROMATIN

So far, we have reviewed what has to happen with chromatin in order for efficient DNA damage recognition and repair to take place. In other words, we were concerned with the chromatin dynamics before the actual repair proceeds. Given the variety of different kinds of chromatin, the question that naturally follows is, how does a particular chromatin state survive the perturbations caused by the repair of DNA damage? Differently put, what happens with chromatin after the lesion has been successfully repaired?

Chromatin dynamics after DNA repair has been studied on nucleosomal level in human fibroblasts using the micrococcal nuclease (MNase) sensitivity assay. Linker regions between nucleosomes are more sensitive to MNase compared to the DNA wrapped around the histone octamer. Moreover, disruption of chromatin structure makes DNA more sensitive to MNase. Interestingly, repair patches are MNase-sensitive immediately after DNA repair synthesis, but become MNase-resistant 24 later *in vitro* (47, 48, 18). These data indicate that the nucleosome might be disrupted immediately after DNA repair synthesis, and that chromatin is regenerated and reorganized slowly after DNA repair synthesis (49, 18).

The above data pertain to the nucleosomal level of chromatin organization. Concerning the effect of the DNA repair process on higher order chromatin structure, does the cell have a mechanism that monitors and ensures proper maintenance of alternative chromatin states after the repair process? Obviously, the absence of (or any defects in) this kind of system could have long lasting epigenetic effects profoundly influencing the cell fate. In particular, it may result in apoptosis or senescence. In fact, some factors or mutations that increase the sensitivity of cells to DNA damage might not be directly involved in DNA repair per se, but rather be responsible for the maintenance of the alternative states of chromatin during repair.

One example of such a factor might be CAF-1 (Chromatin Assembly Factor) (50, 51). It has been reported to have a role in chromatin assembly in UV damaged regions tested in an *in vitro* assay using Xenopus eggs extracts (52, 18), and to be recruited in the repair of DNA breaks and gaps (53, 54). Importantly, yeast strains lacking

chromatin assembly factor I (CAC) show increased sensitivity to UV light (55). One might hypothesize that this sensitivity reflects the requirement of CAF-1 for the proper maintenance of the appropriate chromatin state after the repair has occurred. According to this idea, the absence of CAF-1 activity would activate cellular checkpoint mechanisms that monitor proper chromatin reassembly, and the fate of the cell would then be directed towards apoptosis.

An existence of cellular checkpoint mechanisms that monitor the proper maintenance of heterochromatin domains during cell proliferation has been proposed by B.H. Howard's group (Ogryzko *et al.*1996; Howard 1996). In particular, it was suggested that defects in these mechanisms might contribute to the phenomenon of replicative senescence. DNA replication, however, is not the only way to perturb chromatin structure. Here, we propose that a contribution to the process of aging can come from similar defects in chromatin reassembly during DNA repair, instead of replication. This suggestion has an intriguing consequence with respect to alternative models of aging phenomena. In particular, according to the free radical theory of aging, DNA damage due to accumulation of reactive oxygen species (ROS) is the major factor in the aging process (56). One can speculate that the improper maintenance of chromatin states during repair of ROS induced damage contributes to shortening of the life span of the organism. Thus, our proposal has the potential to view different and competing modes of aging from a unified perspective. Further research efforts will be required to test the validity of this hypothesis.

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