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DNA repair in a chromatin environment

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Abstract. DNA mutations and aberrations are a problem for all forms of life. Eukaryotes specifically have developed ways of identifying and repairing various DNA mutations in a complex and refractory chromatin environment. The chromatin structure is much more than a packaging unit for DNA; it is dynamic. Cells utilize and manipulate chromatin for gene regulation, genome organization and maintenance of genome integrity. Once a DNA aberration has occurred, the various DNA repair machineries interact with chromatin proteins, such as the histone variant H2A.X, and chromatin remodeling machines of the SWI/SNF family to gain access and repair the lesion in a timely manner. Recent studies have thus begun to address the roles of chromatin proteins in DNA repair as well as to dissect the functions of DNA repair machinery in vitro on more physiological, nucleosomal templates.

Key words. Chromatin; histone modifications; DNA repair; transcription; H2A.X.

Introduction

A typical mammalian cell packages over a meter of DNA into a 10-μm nucleus through a highly specialized structure of DNA, histones and non-histone proteins known as chromatin. While this intimate structure of DNA and proteins is necessary to manage the size constraints of the cell, it is generally inhibitory to molecular processes, including transcription, recombination, replication and DNA repair, imposing a significant problem of accessibility for the cellular machinery. Thus, the chromatin structure must be dynamic, allowing the interconversion of structures not just between interphase and mitotic chromosome states during replication but also between chromosome domains within the interphase chromosomes in response to cellular signals. This includes responding to gene regulatory signals for transcription activation or repression as well as signaling the DNA repair machinery that a lesion has occurred in the genome. To accomplish this local chromatin reorganization, cells utilize large multi-subunit protein complexes to manipulate the chromatin structure, making it either more accessible or amenable to molecular processes (euchromatic) or more constrained and refractory (heterochromatic) as the case may require. Thus, in addition to packaging the DNA, the chromatin structure, organizes the nucleus and provides an additional level of genome regulation not available to naked DNA templates.

As with all DNA-centric mechanisms in a cell, DNA repair must function within varying chromatin environments. The DNA repair machinery performs this task in part through interactions with chromatin remodeling machinery, identification of specialized histones modified in response to DNA damage and coordination with transcription. This review is divided into two sections, with the first section intended to provide a broad overview of chromatin and our current understanding of how a cell's chromatin structure can be regulated, while the second section focuses on several recent examples of the interplay between DNA repair pathways and the dynamic chromatin structure. This is by no means an exhaustive survey of the literature.

Chromatin structure and histone modifications

The nucleosome

The basic building block of chromatin is the nucleosome core particle, composed of an octamer of core histones (two each of histones H2A, H2B, H3 and H4) wrapped

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~1.7 times with 146 bp of DNA (nucleosome structure is reviewed in detail in [1, 2]). Each core histone has a highly structured C-terminal core domain involved in intranucleosomal histone-histone interactions and an unstructured N-terminal tail, extending outside of the nucleosomal core, involved in internucleosomal interactions as well as with non-histone chromatin proteins (reviewed in [2, 3]). Multiple adjacent nucleosomes, separated by 20–80 bp of linker DNA which is often bound by a linker histone, are organized into a solenoidal structure consisting of ~6 nucleosomes per turn. This structure, termed the 30-nm fiber, is postulated to be the in vivo form for the majority of nucleosomes [1]. Multiple fibers interact to organize and compact the chromatin into even higher-order structures. Thus on the surface chromatin could be described as merely a regularly repeating structure that efficiently packages the entire DNA into a required space. However, this description misses the intricate beauty of the chromatin design as a dynamic, fluid genome regulatory and stabilizing element, because not all chromatin in a nucleus is equal. In fact, there exists the capacity for numerous variations on the nucleosome through post-translational modifications of the core histones, incorporation of variant histones and covalent modification of the DNA. When taken into account, differing combinations of nucleosomes yield the potential for all of the chromatin to be different.

Core histone modifications

DNA sequence comparisons reveal that the core histones are highly conserved across eukaryotes, both in their structured C-terminal histone fold domains as well as their highly charged N-terminal tails, suggesting that these 'tails' may serve fundamental functions within a cell as well. In the late 1960s, core histones were determined to be post-translationally modified via methylation [4] and acetylation [5]. Momentum for studying these post-translational modifications gained tremendous force in 1996 when *Tetrahymena* HAT A was found to be a homolog to the yeast transcriptional activator Gcn5p [6]. Subsequently, numerous transcriptional activators have been found with intrinsic HAT activity, including TAF250, p300, CBP, SRC1 and ACTR [7–10]. In addition to acetylation of lysine on all core histones, other well-documented post-translational modifications of histones include methylation of lysine on H3 and H4 and arginine on H3, phosphorylation of serines 10 and 23 of H3 (reviewed in [11]), and sumoylation of H4 [12]. It is now well established that covalent modifications occurring on core histone N-terminal tails, often multiple times with multiple modifications on the same histone, play important roles in gene regulation.

The majority of attention regarding post-translational modifications of histones has focused on the amino-terminal tail; however, several recent studies in *Saccharomyces cerevisiae* have found unique modifications and sites in some of the structured domains of histones as well as identified new histone-modifying enzymes. Mutation of *RAD6* blocks cell cycle progression through both mitosis and meiosis [13]. Interestingly, Rad6p also catalyzes the ubiquitination of H2B at lysine123 in vivo. Genetic screens for effectors of silencing in yeast identified *DOT1* (disruptor of telomeric silencing 1), encoding a new class of histone methyltransferase that specifically methylates lysine 79 of H3 and is involved in formation of heterochromatin [14, 15]. An additional level of regulation becoming apparent from these studies is the crosstalk between different modifications on the same tail, such as H3 K9 methylation and phosphorylation [16], or on different histones, as is the case with H2B ubiquitination and H3 K4 and K79 methylation [17–19].

Thus, although most nucleosomes contain a similar octamer of core histones, the available interaction surfaces of each nucleosome can vary substantially or change in response to stimuli, presenting a type of histone code to be interpreted by the cellular machinery [20]. This histone code hypothesis postulates that covalent modifications of the histones affect the binding of specific factors to the chromatin, which in turn potentially affects other histone modifications, chromatin structure and even DNA methylation.

Chromatin structure

Variation in the composition and structure of chromatin within an interphase chromosome is evident cytologically and biochemically, being grossly categorized into euchromatin and heterochromatin. Euchromatin decondenses after mitosis, contains gene-rich sequences that are transcriptionally active, consists of hyperacetylated histones and generally lacks linker histones or highly methylated DNA. Heterochromatin is highly condensed throughout the cell cycle, is gene poor, late replicating and consists of hypoacetylated core histones. In higher eukaryotes, heterochromatin contains densely methylated DNA sequences, linker histones and the repressor HP1 (heterochromatin protein 1). Heterochromatin is further divided into facultative heterochromatin that is developmentally regulated and constitutive heterochromatin, encompassing satellite DNAs (families of DNA repeats), the pericentromeric heterochromatin and the telomeric heterochromatin [21, 22]. Molecular probes such as nucleases and hydroxyl radicals indicate that DNA in the hyperacetylated euchromatic regions is much more accessible to cleavage than the condensed hypoacetylated heterochromatic DNA. Considering that many transcriptional regulators contain HAT (activators) or HDAC (repressors) activity [23], the acetylation data supports a histone code for affecting chromatin structure and gene regulation.

Chromatin remodeling

While it is clear that specific post-translational modifications of the core histones show strong correlations with gene regulation, often more changes are required. The DNA tightly bound to the octamer in a competitive manner does not make it easy for many DNA-interacting proteins to perform their function, and they require the nucleosome to be shifted (remodeled) away from the specific DNA substrate before they can be effective. Thus, cells contain a second type of chromatin-modifying proteins, the (Switch/Sucrose non-fermenting) SWI/SNF family of remodeling complexes [24, 25]. SWI/SNF complexes utilize ATP to alter the path of DNA on a nucleosome, effectively repositioning or moving the nucleosome and thus making DNA more accessible to other proteins [26, 27]. Currently there are three distinct families of complexes based on their ATPase subunit, SWI/SNF2, ISW1 and Mi-2. These proteins function in large, macromolecular complexes and function in both the repression and activation of transcription, DNA replication, recombination and DNA repair [28–31].

DNA repair and chromatin

Life has dealt with alterations and mutations to DNA since its beginning, utilizing limited mutagenesis as an evolutionary driving force. However, too many mutations or deleterious mutations must be identified and repaired. Thus, organisms have evolved multiple DNA repair pathways to deal with different types of genome lesions. There are three major types of mutations which occur within DNA; a base mismatch, the formation of a bulky dimer of two bases adjacent to each other and a double-stranded break (DSB). In eukaryotes, the different repair pathways for each of these mutations must be designed to function in the stifling chromatin environment. Recent data indicates that these pathways interact with the histones, non-histone chromatin proteins and chromatin-remodeling complexes to manipulate and utilize the chromatin structure to their advantage. Finally, some histone-modifying enzymes are known to act on transcription factors as well as histone substrates. It is possible that these chromatin modifiers may also function by post-translationally altering components of the DNA repair machinery.

DSB

DSBs, brought on by ionizing radiation (IR) and some chemicals, are potentially the most damaging lesions in the genome if not properly repaired. However, while they are the easiest mutation for the cell to detect, these lesions are the most difficult mutation to repair and are fixed through one of two distinct pathways: non-homologous end joining (NHEJ) or homologous recombination (HR). Not surprisingly, an increasing body of evidence supports an important role for chromatin modification in both the detection and repair of DSBs.

Histone modifications are clearly important for gene regulation; however, several lines of evidence from *S. cerevisiae* show that the acetylation of histones H4 and H3 are involved in DSB repair as well. A mutant strain of yeast (*hhf1-10*) in which all four acetylatable lysines of H4 were replaced with glutamines resulted in a pronounced loss of genome integrity and hypersensitivity to DSB-inducing agents, suggesting a role for either the lysine residue per se or lysine acetylation [32, 33]. Interestingly, mutants in *ESA1*, an H4-specific HAT and component of the NuA4 HAT complex, but not in other HATs (*GCN5*, *HAT1* or *SAS2*), had a similar hypersensitivity to DSB [33]. Further evidence implicates the NuA4 complex and H4 acetylation in DNA repair; NuA4 preferentially acetylates nucleosome arrays with linear ends, mutants of the Yng2p subunit of NuA4 are hypersensitive to DNA damage, the Arp4p histone tail-binding component of NuA4 is recruited to sites of DSBs and the binding of Arp4p to histones is sensitive to H4 K→Q mutations [33–35]. Acetylation of H3 has also been implicated in DSB repair. Yeast strains containing H3 K14, 23→R substitutions or mutations in *HAT1*, which acetylates newly synthesized H3 and H4 in the cytoplasm, are sensitive to DSBs induced by methyl methanesulfonate (MMS) [36]. The major effect is on the HR repair pathway with a minor reduction in NHEJ, suggesting a role for the H3 tails in DSB repair.

DSB repair and H2AX

In addition to post-translational modifications of core histones, nucleosomes can be altered by the incorporation of one of several histone variants [37]. H2AX constitutes ~10% of the total H2A in the cells of higher organisms, and it seems to be randomly incorporated into the genome. H2AX has an unusual tail on the C-terminus which projects out toward the linker histone position. There is a strong correlation between rapid phosphorylation of histone H2A species and DSB in all eukaryotes [37]. In yeast, this phosphorylation occurs on its only form of histone H2A surrounding the DSB. In the mammalian cell, the histone variant H2AX becomes phosphorylated (termed g-H2AX), and in *Drosophila* the substrate is H2Av [38–41]. Immediately following DSB formation due to ionizing radiation, meiotic recombination, immune cell rearrangements or during DNA replication, the H2AX molecules flanking the lesion are phosphorylated by the DNA-dependent protein kinase (DNA-PK) of the PI3 family of protein kinases [42]. DNA-PK binds the nucleosomal DNA ends via its Ku domain and phosphorylates nearby H2AX. This phosphorylation event occurs

preferentially in the presence of hyperacetylated histones, and it is known that acetylation activity is critical to successful DSB repair function, again suggesting a role for HATs in DSB repair [42].

To further investigate the role of g-H2AX, mice either deficient in H2AX or completely lacking H2AX were generated in WT and $p53^{-/-}$ backgrounds [43, 44]. In the absence of H2AX, the mice developed no more tumors then controls; however, $H2AX^{-/-}$ $p53^{-/-}$ mice developed lymphomas more quickly and in greater numbers then the control $p53^{-/-}$. Previous work in mouse cells lacking H2AX suggests that repair by homologous recombination is impaired but that NHEJ repair does not seem to be affected [45, 46]. However, the most recent evidence suggests that NHEJ is at least disrupted in H2AX-deficient cells [43, 44]. NHEJ is involved in B and T cell immune gene rearrangements involved in the creation of receptor and immunoglobulin diversity for the immune system. Analysis of the $H2AX^{-/-}$ $p53^{-/-}$ mice B cell cancers showed the cells had undergone abnormal rearrangements in the immunoglobulin genes; these faulty rearrangements were not found in a $p53^{-/-}$ background [43, 44]. Finally, mice $p53^{-/-}$ $H2AX^{-/+}$ still exhibited tumor formations and improper rearrangements, indicating that H2AX functions in a dose-dependent manner [43, 44]. Thus, both HR and NHEJ repair pathways for DSBs are somewhat disrupted by H2AX deficiency, and H2AX is involved in genome stability.

As evidence has shown, H2AX is important for genome stability and for the prevention of cancer; however, the exact role of g-H2AX has yet to be shown. While g-H2AX does not constitute the primary signal for DSB recognition, it may be involved in stabilization of the DSB area for (NHEJ occurring in S and G2 phases or homologous recombination in G1 [47]. Another attractive model is that g-H2AX may act as an anchored recruitment factor to bring the appropriate machinery to the area in need of repair or, as visualized recently, to cluster DSB chromosome domains to repair centers after breakage has occurred [48, 49].

Nucleotide excision repair

Ultraviolet (UV)-radiation induces the formation of cyclobutane pyrimidine dimers (CPD) or pyrimidine (6-4) pyrimidone photoproducts (6-4PP) that are excised via one of the two nucleotide excision repair (NER) pathways, depending upon where the lesion lies [50, 51]. The transcription-coupled DNA repair (TCR) pathway removes dimers that reside in transcribed DNA, while global genome repair (GGR) pathway removes dimers from all other DNA [52]. In NER, chromatin not only plays a role in the repair of a lesion, but it also affects damage formation. CPD distribution is mainly found in the minor groove facing away from the histone surface and 6-4PP will be preferentially formed in linker DNA, but will also form without preference throughout the histone core region as well. Regardless, both mutations result in an abnormal DNA structural bend that is used to help recognize the damaged region.

Briefly, the NER repair process involves the recognition of a lesion, a repair bubble formed by XPB and XPD helicases, excision by XPF and XPG endonucleases of about 24–32 nucleotides, nucleotide replacement by DNA polymerase and finally ligation of the nick [53]. This process must take place in a chromatin environment and the NER complexes required are very large, creating a problem that the cell must circumvent prior to repair. The solution is recruitment of HATS and chromatin-remodeling complexes. In vivo, histones are acetylated following UV irradiation, which helps to loosen up the nucleosomes hold on the DNA, a conclusion supported by the fact that the addition of HDAC inhibitors greatly increases the efficiency of NER. In vitro, using DNA lesions incorporated into mononucleosomes, the nucleosome structure was found to preferentially inhibit excision of CPDs (10-fold reduction) and to a lesser extent 6-4PPs (5-fold reduction) and acetylaminofluorene-guanine (AAF-G) adducts (6.6-fold reduction) [54, 55]. However, addition of SWI/SNF complex stimulated excision with the 6-4PPs and AAF-Gs but not the CPDs from the mononucleosomes, providing the first experimental evidence linking chromatin remodelers and NER.

Recently it was shown that p53 may act as a global relaxer of chromatin via recruitment of p300, leading to hyperacetylation of histones. This hyperacetylation of histones may be one of the initial steps in repair by GG-NER [56]. Using localized subnuclear UV irradiation, which induced global relaxation of chromatin, it was determined that the process is dependent upon p53. Rubbi et al. went on to suggest that a possible mechanism for repair after UV irradiation begins with detection by the arrest of RNA polymerase II at a lesion in a transcribed strand, resulting in the recruitment of TC-NER and activation of p53, which leads to genome-wide chromatin relaxation and thus accessibility for the GG-NER complexes.

Base excision repair

Base excision repair (BER) proteins deal with over 10,000 lesions in every human cell generated on a daily basis [57, 58]. The lesions do not create significant helical distortion and they do not stop transcription elongation, making recognition somewhat difficult. Once the problem is recognized, there are likely nucleosomes that must be dealt with before repair can proceed uninhibited. For example, the spontaneous deamination of cytosine results in a guanine-uracil (G-U) mismatch [59]. This common mismatch has been well studied on naked DNA templates, but only recently have nucleosomal templates

been investigated [60]. Using rotationally positioned nucleosomal G-U base pairs, the initial enzymes uracil DNA glycosylase and apyrimidinic/apurinic endonuclease exhibit 90% reduction in activity versus naked DNA templates on uracils rotationally positioned closer to the nucleosome. These enzymes were also found to have a two- to threefold difference in activity for uracils facing away from the nucleosome versus those facing toward the nucleosome. In both cases, the finishing step DNA polymerase b is completely inhibited by the nucleosome. In addition, nucleosomes reconstituted with tailless histones that mimic the highly acetylated histone state are also inhibitory, suggesting that acetylation is not sufficient for repair, and chromatin-remodeling factors are likely required for BER in vivo.

Conclusions and future directions

In vivo, DNA repair mechanisms must overcome chromatin architecture to function. Consequently, much of the research in DNA repair is now focusing on histone modifications, chromatin-remodeling events and interactions within a nucleosomal context. Of particular interest will be the evolving roles of the SWI/SNF chromatin-remodeling machines in NER and the function of histone variants such as g-H2AX in DSB repair and genome integrity.

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