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Review

The Domino Effect: Nucleosome Dynamics and the Regulation of Base Excision Repair Enzymes

Julia C. Cook and Sarah Delaney *

Department of Chemistry, Brown University, Providence, RI 02912, USA
* Correspondence: sarah_delaney@brown.edu

Abstract: DNA damage is induced by exogenous and endogenous sources, creating a variety of lesions. However, the cellular repair machinery that addresses and corrects this damage must contend with the fact that genomic DNA is sequestered in the nucleoprotein complex of chromatin. As the minimal unit of DNA compaction, the nucleosome core particle (NCP) is a major determinant of repair and poses unique barriers to DNA accessibility. This review outlines how the base excision repair (BER) pathway is modulated by the NCP and describes the structural and dynamic factors that influence the ability of BER enzymes to find and repair damage. Structural characteristics of the NCP such as nucleobase positioning and occupancy will be explored along with factors that impact the dynamic nature of NCPs to increase mobilization of nucleosomal DNA. We will discuss how altering the dynamics of NCPs initiates a domino effect that results in the regulation of BER enzymes.

Keywords: base-excision repair; nucleosome core particle; nucleosome dynamics; DNA damage repair

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1. Introduction

Genomic integrity is continuously threatened by a variety of DNA-damaging events. Damaging agents, such as the reactive oxygen species that are byproducts of metabolic processes or environmental agents such as ultraviolet light, cigarette smoke, or industrial chemicals, can be generated within the cell [1–3]. These agents account for a variety of damage types including single- and double-strand breaks, inter- and intra-strand crosslinks, mismatched nucleobases, and modification of the nucleobases.

When considering modification of the nucleobases, oxidation, alkylation, deamination, and hydrolysis reactions are the most common. In this review, modified nucleobases will be referred to as lesions. Approximately 100 lesions have been identified in vitro and many of these have been detected in cellular DNA [2]. Replication of lesions can have serious consequences for an organism [3]. Lesions can be mutagenic, meaning they are mispaired by a DNA polymerase during replication. They can also be cytotoxic, meaning that they cause a DNA polymerase to stall replication, leading to apoptosis. Genetic stability is essential for cell viability and the mutagenicity and cytotoxicity derived from nucleobase lesions can impact human health with outcomes ranging from neurodegenerative diseases to immune disorders, cancer, and aging [4–10].

Fortunately, organisms have robust DNA repair processes to assure the quality of further genetic advancement. These include direct reversal repair (DRR), mismatch repair (MMR), homologous recombination (HR), non-homologous end joining (NHEJ), single-strand break repair (SSBR), nucleotide excision repair (NER), and base excision repair (BER). Each of these processes plays an important role in maintaining genomic stability. In this review, we focus on the BER pathway, which functions to correct non-bulky nucleobase lesions that generally do not significantly distort the helical structure of DNA.

2. Base Excision Repair

BER is accomplished by a series of enzymes and can be considered to occur in two parts: excision of the lesion from the sugar–phosphate backbone and filling of the resulting "hole" with the appropriate canonical nucleobase [11–14]. Initiation of BER is determined by recognition of a lesion by a DNA glycosylase enzyme. There are 11 known human DNA glycosylases each with a specific target lesion(s) [15]. For an in-depth description of the substrate specificity of DNA glycosylases, we refer the reader to a comprehensive review article from the Eichman group [15]. DNA glycosylases use similar catalytic mechanisms for lesion excision [16], however, details of the methods used to search the genome and differentiate lesions from canonical nucleobases are not fully understood. Current data support that DNA glycosylases utilize a combination of short-range sliding and hopping techniques. Through these motions, DNA glycosylases are able to survey ~70,000 base pairs (bp) of DNA [17] in the search for the rare instance of a lesion—a needle in a haystack. Recent work has shown that UV-damaged DNA binding protein (UV-DDB), which serves as a damage sensor in global genomic NER, stimulates DNA glycosylase activity in vitro raising the intriguing possibility that it may contribute to the searching process [18,19].

DNA glycosylases have been described to interrogate a region of DNA and some have been shown use exosite pockets in the enzyme to inspect each nucleobase [17]. Structural and dynamic properties of base pairs are used to differentiate between canonical and damaged bases, collapsing canonical bases back into place in the DNA helix and shifting target lesions into the active site for excision. The nonspecific interactions that control these transfers allow the DNA glycosylase to quickly differentiate damaged from undamaged nucleobases, preventing competitive inhibition of the enzyme by canonical bases which can exist in 30,000-fold excess over the target lesion(s) [17].

When a lesion enters the active site, a DNA glycosylase catalyzes its excision by cleaving the glycosidic bond that attaches the lesion to the sugar–phosphate backbone [11,16,20]. A DNA glycosylase may fall into one of two classifications: monofunctional or bifunctional (Figure 1). A monofunctional DNA glycosylase catalyzes glycosidic bond cleavage through a substitution reaction using an activated water molecule as the nucleophile (Step 1). The resulting abasic (AP) site is further acted upon by apurinic/apyrimidinic endonuclease 1 (APE1) to form a nick in the backbone with 3′-OH and 5′-deoxyribose phosphate (5′-dRP) termini (Step 2). The subsequent enzyme in the pathway, DNA polymerase β (Pol β), has two roles. It catalyzes removal of the 5′-dRP group (Step 3a) and incorporates a canonical deoxynucleotide at the 3′-OH (Step 3b). A DNA ligase seals the resulting nick to complete the repair event (Step 4).

A bifunctional DNA glycosylase initiates glycosidic bond cleavage using an amino group in the enzyme active site as the nucleophile. In addition to glycosidic bond cleavage, bifunctional DNA glycosylases can catalyze β-elimination of the DNA backbone by formation of a Schiff base, leading to a break in the backbone with 3′-α,β-unsaturated aldehyde (PUA) and 5′-phosphate termini (Step 1). Some bifunctional glycosylases also catalyze δ-elimination to yield a 3′-phosphate. APE1 can act on the elimination product to form a 3′-OH terminus (Step 2) used by Pol β for deoxynucleotide incorporation (Step 3), and DNA ligase seals the nick and completes the repair (Step 4). In some instances, the β-elimination activity of a bifunctional DNA glycosylase may be bypassed with APE1 acting directly on the abasic site [21,22]. Interestingly, it was recently demonstrated that a small-molecule activator of 8-oxo-7,8-dihydroguanine glycosylase 1 (OGG1), a bifunctional DNA glycosylase, alters the repair process in cells to no longer require APE1 but rather depend on polynucleotide kinase phosphatase activity [23]. XRCC1 is a scaffold protein that plays a role in BER by interacting with Pol β and DNA ligase [24].

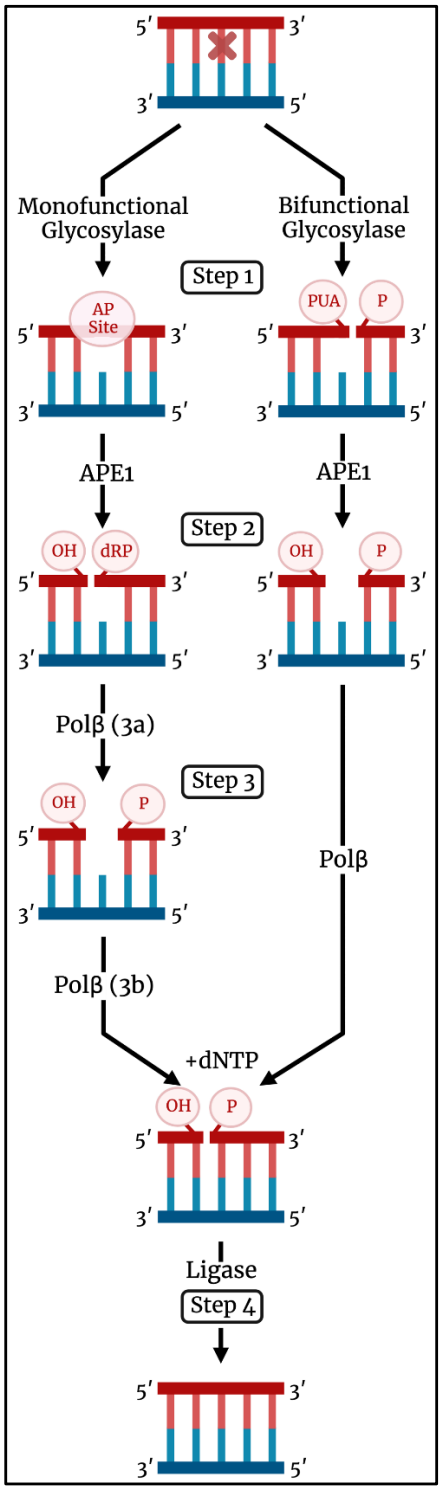

Figure 1. Schematic illustration of the BER pathway initiated by a monofunctional (**left**) and bifunctional (**right**) DNA glycosylase. A lesion is recognized and excised by a DNA glycosylase (Step 1). APE1 processes the product of glycosylase activity by incising the AP site (for a monofunctional glycosylase) or removing the 3′-PUA (for a bifunctional glycosylase) (Step 2). Pol β removes the 5′-dRP (for a monofunctional glycosylase) and incorporates a canonical nucleotide at the 3′-OH (Step 3). A DNA ligase/XRCC1 complex seals the nick to complete the repair. Image created using BioRender (biorender.com (accessed on 29 September 2022)).

The above-described process of recognition, removal, and replacement of a lesion is known as short-patch BER (SP-BER) and is the predominant form of BER. In an instance when chemical modification of the 5′-dRP blocks the dRP lyase activity of Pol β, for example under conditions of oxidative or alkylative stress, a process known as long-patch BER (LP-BER) is used [25,26]. The polymerase performs strand-displacement synthesis incorporating multiple (between two and six) deoxynucleotides at the nick. Flap endonuclease 1 (FEN1) removes the displaced single-stranded flap of DNA, which contains the modified dRP at the 5′-terminus, and the resulting nick is sealed by DNA ligase.

While working to maintain the integrity of the three billion base pairs in the human genome, the above-described BER enzymes function to complete highly complex and vital roles. It is known that these BER enzymes are clinically important, and that deficiencies or inactivity can have detrimental consequences for human health [27–32]. However, successful completion of the repair process requires that the repair enzymes can physically access the site of DNA damage, which is not always the case.

3. The Nucleosome Core Particle

To manage the vast amount of genetic material, eukaryotic systems utilize dense packaging known as chromatin, which is organized into arrays of nucleosomes. Nucleosomes were first observed via electron microscopy (EM) and were described as "linear arrays of spherical chromatin particles" [33]. Each of the spherical particles is now known to represent the simplest unit of packaged DNA, the nucleosome core particle (NCP). The first crystallographic analysis of an NCP revealed the wrapping of DNA around a protein core [34]. Subsequent and higher-resolution crystallography structures provided near atomic-level detail of how DNA is bound to and organized by the protein core [35]. In an NCP, 145–147 bp of DNA wrap tightly in a left-handed orientation making 1.65 rotations around a protein core comprised of the four histones H2A, H2B, H3, and H4 (Figure 2). Each histone has a central folded domain, called the histone fold, flanked by disordered N- and C-terminal tail regions. The histone core is organized and formed by two H2A/H2B dimers and an H3/H4 tetramer. A two-fold axis of symmetry runs through the histone core and is referred to as the dyad axis [35].

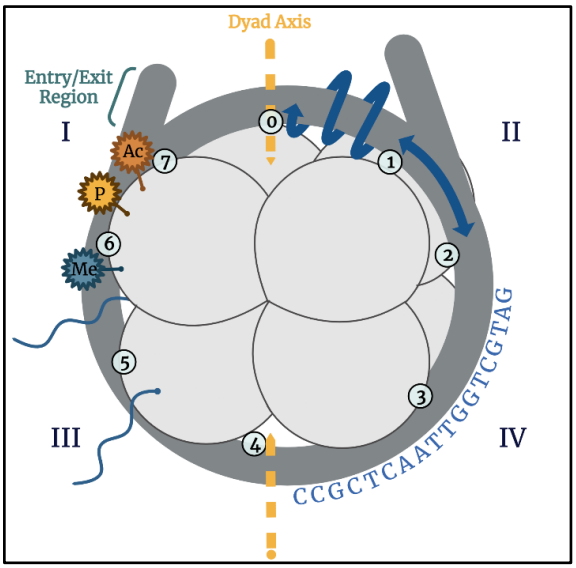

Figure 2. Representation of a nucleosome core particle (NCP) showing the histone core (light gray) and DNA (dark gray). The dyad axis, entry/exit regions, and seven SHLs (circles numbered 1–7) are labeled. For simplicity, the NCP is divided into four quadrants to depict factors that will be discussed in this review: post translational modifications (region I), rotational and translational nucleobase positioning (region II, blue arrows), unstructured N-terminal histone tails (region III), and DNA-sequence-dependent factors (region IV). Image created using BioRender.

Throughout the nucleoprotein complex of an NCP are various energetically important points of contact. Seven locations of major groove–histone contacts known as super-helical locations (SHLs) are located between each end of histone-bound DNA, referred to as the entry/exit regions, and the dyad axis [35]. These contacts represent landmarks which are used as references to translationally label base pairs throughout the NCP. Similarly, the histone core serves as a reference to rotationally label each DNA nucleobase depending on whether it faces inward towards the histones, outward towards solution, or somewhere in between (Figure 2, II, blue arrows). These translational and rotational positions are commonly identified using chemical and enzymatic footprinting techniques. Defining these geometric and positional relationships provides key information to understand how BER at specific lesion locations may be impacted by structural limitations such as steric hindrance by the histone core and solvent accessibility.

Moving from the NCP to a higher level of packaging, in a nucleosome array, a string of NCPs are spaced at intervals of 200 ± 40 bp and are stabilized by the linker histone H1. Electron cryo-microscopy (cryo-EM) and crystal structures of a 197 bp nucleosome with two linker DNA arms, revealed that H1 binds both linkers, draws the two arms together, and induces a more compact and rigid conformation [36]. Cryo-EM analysis of arrays of multiple nucleosomes has provided mechanistic details of how nucleosomes assemble into even-higher-order chromatin structures [37–44].

The ubiquitous sequestration of DNA presents a conundrum for BER enzymes, which must interact intimately with DNA. Therefore, understanding the physicochemical properties of packaged DNA may unlock information relevant to the methods cells use to regulate DNA access and provide insight on the biological limitations of repair in a genomic context. The next sections of this review will describe the structural and dynamics of NCPs and how these factors may initiate a domino effect to modulate and influence BER.

4. Structural Characteristics Dictate Accessibility of Nucleosomal DNA

Incorporation of DNA into nucleosomes can be described in terms of nucleosome positioning and occupancy. While positioning refers to the location of NCPs on genomic DNA, occupancy reflects how likely a region of genomic DNA is to be bound in an NCP (i.e., density). Neither positioning nor occupancy are random but rather sequences are deliberately included or excluded from nucleosomes [45–47].

Chemical footprinting and crystallographic analyses of NCPs have revealed that the wrapping of DNA around the histone core distorts the DNA structure. For example, the periodicity of DNA in an NCP averages 10.2 bp/turn compared to 10.5 bp/turn in the unpackaged duplex [35,43,48], causing an energetic strain which is compensated for by electrostatic interactions between the positively charged histones and the negatively charged DNA [49]. In turn, the flexibility of a DNA sequence has been identified as a major determinant of its ability to incorporate into a nucleosome (Figure 2, IV) [40,45–47,49,50].

The Widom 601 DNA sequence provides an example of how sequence determines positioning [50]. This sequence was selected from a library of 5×10^{12} chemically synthetic random DNA molecules as having the highest affinity for the histone octamer [50]. Further analysis revealed that the 601 DNA also has strong positioning ability. The presence of a TA/TT/AA dinucleotide every ~10 bp allows the DNA to be compressed and bend into the minor groove [50]. This periodic distribution of dinucleotides was also observed in nucleosomes isolated from biological sources and is now known to be hallmark of nucleosome positioning. An experimental advantage of using a strong positioning sequence such as 601 DNA is that it has specific, predictable binding to histones and provides a homogeneous population of structurally well-defined NCPs [51,52]. However, data obtained using a strong positioning sequence are likely not broadly reflective of the behavior of all regions of the genome which include strongly-positioning sequences, sequences that excluded NCPs, and everything in between.

In contrast to strong positioning sequences, weak positioning sequences with low flexibility have been observed in arrays with low nucleosome occupancy, in regions of nucleosome depletion, and in regions important for promotor accessibility, transcriptional activity, and other genomic processes. Some polymeric sequences, in particular poly(A:T) tracts, disfavor interaction with the histone core due to their limited flexibility [53] and prevent formation of nucleosomes in the promoter regions of eukaryotic genomes [47,54]. Notably, however, computational analysis was correct in predicting nucleosome positioning only half of the time based on sequence alone, reflecting the complexity of positioning [45]. Though these weaker positioning sequences do not create defined nucleosome populations like 601 DNA, which can complicate interpretation of the results, their biologically-relevant sequence patterns are vital for understanding how sequence alone may influence native systems.

Analysis of genome-wide mutational spectra revealed that nucleosome positioning and occupancy influence mutational patterns [55]. Some mutation types are biased towards nucleotides that are bound in a nucleosome compared to those in linker DNA [55,56]. In turn, these reinforced lesion patterns vary across the genome to modulate DNA accessibility, forming a dependent relationship between sequence and accessibility. This relationship has also been seen to directly impact both the formation and repair of DNA lesions [55,56].

5. Structural Components of the Nucleosome Core Particle Impact BER

Using a number of biochemical strategies and model systems, a variety of research groups have reported that the physical location of a lesion in an NCP impacts how well it can be repaired by BER [13,57–62]. These experiments typically exploit the fact that BER enzymes break (or the product can be chemically converted to a break) or make bonds in the sugar–phosphate backbone. Therefore, enzyme activity can be monitored by changes in the size of DNA fragments using sequencing gel electrophoresis. Many of these biochemical experiments were made possible by the use of strong positioning sequences such as Widom 601 DNA. Other positioning sequences such as 5s rDNA sequence, a naturally occurring sequence derived from the 5s ribosomal RNA gene, and α-satellite DNA found at centromeres, have also been used [35]. The use of a positioning sequence allows for the creation of a homogenous population of NCPs with lesions in well-defined rotational and translational positions [50].

The initiation of BER on NCPs by DNA glycosylases has been extensively studied in reconstituted mononucleosomes and it is generally accepted that lesions that face outward from the histone core are more readily excised than those that are sterically occluded by facing inward towards histones [13,24,57–62]. An exception is near the dyad axis where several DNA glycosylases have been shown to have suppressed activity regardless of the rotational positioning of the lesion, which may arise from the underwinding of DNA near SHL 0. Due to transient unwrapping, DNA in the entry–exit regions can, at times, be repaired similarly to unpackaged DNA. Notably, these biochemical observations are consistent with genome-wide patterns of DNA damage accumulation and mutational density; lesions and mutations accumulate near the dyad axis of positioned nucleosomes and at regions of the DNA facing the histone core [63–65].

Histone variants are proteins that can substitute for the core histones and have distinct amino acid sequences [66]. These variants confer different structural properties on nucleosomes, influence positioning, affect gene expression and DNA repair, and contribute to disease [66]. Several histone variants have been shown to facilitate DNA glycosylase activity by increasing access to otherwise occluded lesion sites [67–69].

Notably, histone N-terminal tails can participate in DNA damage repair by reacting with the AP site product formed by DNA glycosylases. AP sites are known to be chemically labile, and they can be further destabilized in NCPs. Lysine residues in the N-terminal tail regions can form DNA–protein crosslinks with AP sites, which are susceptible to strand cleavage via an elimination reaction [70–73]. Furthermore, in a process enhanced by histones, the bifunctional DNA glycosylase OGG1 was found to crosslink the 3′-PUA

product and hinder the subsequent steps of BER. However, in the presence of APE1 the formation of these crosslinks is suppressed [62].

Enzymes acting downstream of DNA glycosylases can also be impacted by the packaging of DNA into nucleosomes. The ability of APE1 to incise DNA is dependent on the rotational positioning of the AP site [74–77]. A cryo-EM structure of APE1 bound to an NCP revealed that the enzyme uses a "sculpting mechanism" to bend the nucleosomal DNA and catalyze incision at a solution-accessible AP site [74]. Reports of BER on twelve-nucleosome arrays demonstrated that DNA glycosylase and APE1 activity are inhibited or accelerated in this higher-order packaging depending on the rotational and translational position of the lesion [78,79].

The nucleotide incorporation activity of Pol β on NCPs and nucleosome arrays is decreased on an NCP relative to unpackaged DNA, with the amount of suppression depending on the solution-accessibility of the gap [58,78,80–83]. In contrast, the dRP lyase activity of Pol β is comparable in unpackaged DNA and an NCP and is not hindered by the presence of the histone core [81]. Interestingly, even the absence of modification of the 5′-dRP, LP-BER can occur on the linker DNA between nucleosomes but was not observed for DNA bound to the histone octamer [84]. The two activities of Pol β are catalyzed by separate domains and the observation that one is hindered in an NCP while the other is not may derive from distinct binding modes and/or interactions with nucleosomes.

The BER enzymes have been shown to work cooperatively and, in some cases, to stimulate each other. Indeed, Pol β nucleotide incorporation activity is enhanced on NCPs in the presence of DNA ligase IIIα-XRCC1 (LigIIIα-XRCC1) [85]. Similarly, Pol β nucleotide incorporation activity is enhanced by the chromatin remodeler SWI/SNF [67,78] and the architectural factor HMGB1 [83]. For the final step of BER, LigIIIα-XRCC1 [85] may require transient unwrapping from the histones to seal a nick [85] whereas DNA ligase I may not [86–88].

BER enzymes may also use other unique physical characteristics or be modulated by interactions with proteins from other pathways. Single-strand selective monofunctional uracil DNA glycosylase 1 (SMUG1) uses a helical wedge to distort DNA to recognize and access lesion sites [89]. Alkyladenine DNA glycosylase (AAG) has been shown to interact with transcription machinery such as transcriptional receptors, estrogen receptor α, the transcription elongation complex, and RNA polymerase II. These relationships have been seen to stimulate DNA glycosylase activity, promoting both repair and transcription and developing a dependent relationship between BER and transcription [90–97]. More research is needed regarding the interplay between BER and related processes to understand how DNA glycosylases as well as downstream BER enzymes may be capable of overcoming nucleosomal obstacles.

6. Dynamics of Nucleosome Core Particles

Of the ~146 bp of nucleosomal DNA, ~120 bp are in direct contact with the histone fold domains while the other ~13 bp at each entry/exit region are more loosely bound by alpha-helices unique to H2 [35]. These loosely bound ends undergo spontaneous and transient unwrapping and rewrapping from the histones, often referred to as DNA breathing [98–100]. Much of this breathing is controlled by the disordered N-terminal histone tail regions which aid in keeping the nucleosome closed via interactions with one another and with nucleosomal DNA (Figure 2, III). Indeed, studies on NCPs with and without N-terminal histone tails have shown that the lack of histone tails increases DNA breathing by influencing nucleosome opening in a largely sequence-dependent manner [98,99]. These actions enable exposure of regions of DNA that are otherwise inaccessible to protein binding.

Ensemble and single-molecule fluorescence resonance energy transfer (FRET) experiments have shown that nucleosomes unwrap asymmetrically and exist in a partially unwrapped state 2–10% of the time [100]. Spontaneous sliding has also been observed in which the nucleosome repositions itself by altering the translational position of the DNA. This mobility is mainly limited to the entry/exit regions and is significantly reduced by the presence of linker histones [101]. Protein binding to nucleosomal DNA during these windows of partial destabilization further facilitates increased DNA mobility by shifting the unwrapping equilibrium. This observation supports that spontaneous site exposure via DNA breathing may modulate site accessibility for protein binding in locations that may otherwise be translationally or rotationally hindered [102,103].

When considering the mechanism of nucleosome sliding, loop and twist defects have been proposed [101]. The loop method uses a histone core "scooting" technique where an entry/exit region spontaneously unwraps, and while it most often rewraps in the same location, occasionally the DNA is pulled in and binds to the histone core forming a DNA bulge. Through a series of these bulge-intermediate structures, small translational changes can account for a larger positioning change [101].

Structural changes to a nucleosome can also occur through a twist defect, in which a bulge is formed by either an additional or a missing base pair [101]. This twist defect can then translate through the nucleosome promoting a series of either over- or under-twisted intermediate structures. These defects have also been thought to recruit chromatin remodelers which may use these stepwise twist or loop defects to displace previously stabilized nucleosomes [101,104]. Though the loop and twist defects can cause larger changes in nucleosome positioning, they rarely occur across the genome and, more commonly, smaller spontaneous changes are the cause of slight unwrapping [101,104].

In addition to DNA unwrapping, the histone protein core is dynamic with histone exchange and deposition of histone variants [105,106]. Single-molecule FRET experiments have also demonstrated that nucleosomes experience spontaneous gaping, where the two gyres of an NCP separate from each other like the hinged motion of a clam shell [107]. Interestingly, a DNA glycosylase has also been shown to alter inter-nucleosomal interactions by decompacting chromatin fibers and condensing nucleosome arrays, demonstrating that binding of BER enzymes also impacts chromatin structure [108].

7. Energetic Environment Dictates Accessibility of Nucleosomal DNA

One factor that affects the energetic landscape of the NCP is the existence of post-translational modifications (PTMs) (Figure 2, I) [98]. These modifications occur after protein biosynthesis by either enzymatic or non-enzymatic additions to amino acids, creating a diverse population of histones which differ in their chemical makeup. Modification of histones is extensive and commonly known PTMs include acetylation, methylation, phosphorylation, ubiquitylation, ADP-ribosylation, crotonylation, succinylation, and malonylation [109]. Although PTMs occur commonly on N-terminal histone tails, these modifications are known to influence internucleosomal interactions in higher order structures, but do not significantly impact stability at the mononucleosome level. PTMs on the globular histone core, however, have been seen to affect mononucleosomal structure in a variety of ways depending on the electrostatic charge and bulkiness of the PTM [109]. A single PTM can reduce the free energy for nucleosome formation by 2 kcal/mol, increasing the structure's stability and increasing the probability of an altered structure by a factor of 25 [109–111].

Histone PTMs can have a range of structural and dynamic impacts on DNA–histone and histone–histone interactions. To describe the effects of PTMs, one can broadly consider the interactions between the histone tails and nucleosomal DNA, the DNA–histone interactions in the entry/exit regions and near the dyad axis, and the histone–histone interfaces. PTMs have been shown to alter these interactions, often reducing DNA–protein affinity, and destabilizing the nucleosome at large. Electrostatic interactions are very important as their balance plays a major role in maintaining a stable complex between DNA and the histone core [109–112].

Decreased DNA–protein affinity can weaken structural regulation, stabilization, and compaction [109–112]. Crystallography and biochemical experiments on nucleosomes containing histones modified with a single acetylation site, which neutralizes the positive charge on a lysine side chain, have demonstrated increased disassembly specifically in the dyad region [110]. Acetylation of lysines 115 and 122 of histone H3 enhances the efficiency of ATP-dependent disassembly of nucleosomes mediated by chromatin remodelers [110]. These observations have been further supported by FRET studies that captured structural distortion of the nucleosome resulting in destabilization to expose target binding sites buried in the nucleosome with key locations at sites of transcription-factor binding located near the dyad axis and entry/exit regions [45,113]. Establishing this dependent relationship between PTMs and nucleosome unwrapping supported the previous hypothesis that structural factors influence NCP dynamics and reduce DNA–histone association [98,109–118].

8. Dynamics of the Nucleosome Core Particle Impact DNA Repair

Structural and energetic effects of PTMs can be thought of as a chemical code: providing instructions for cellular components in order to stimulate activity and signal interactors to histone binding sites [109]. In addition to the increased mobility caused by DNA breathing, PTMs that affect the nucleosome's dynamic environment can further shift the unwrapping equilibrium as a mean of improving DNA accessibility [62,117,119,120]. Some ways in which PTMs influence mobility include unwrapping, rewrapping, sliding, assembly, and disassembly (Figure 3) [109]. Nucleosomes containing histone variants have also been shown to have similar effects on the nucleosome by increasing mobility [50,109].

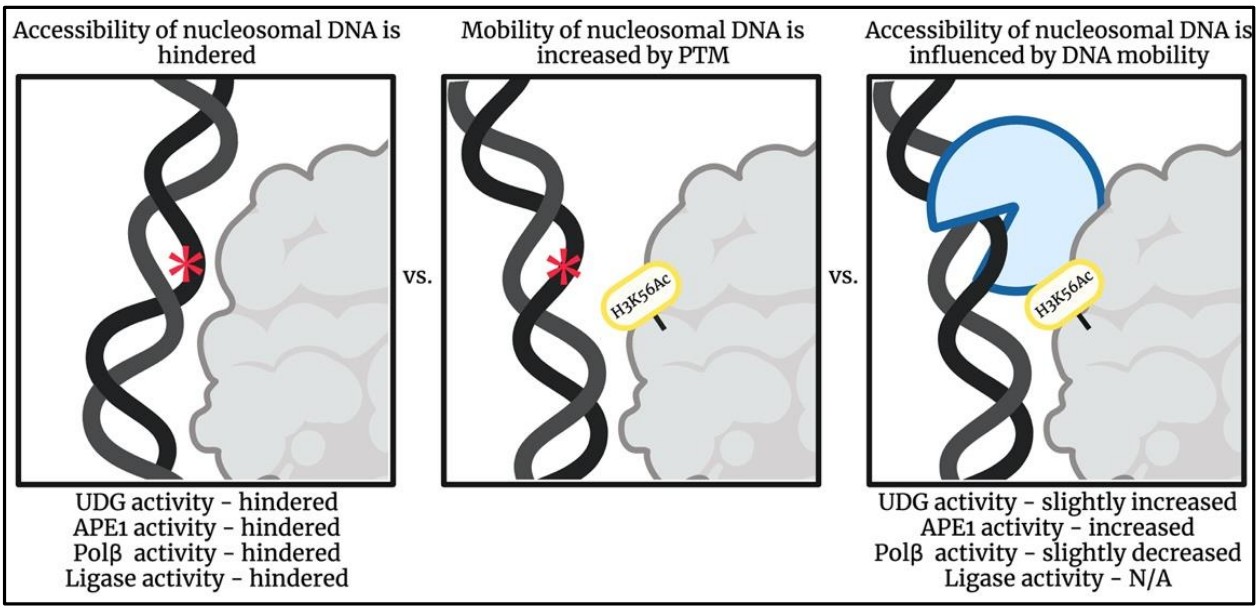

Figure 3. Schematic illustrating how a post-translational modification, H3K56Ac, can increase DNA mobility allowing for altered binding patterns of BER enzymes in regions otherwise hindered [117,118,121–131]. Impact of H3K56Ac on DNA ligase activity has not been reported. DNA lesion represented by red asterisk symbol. Image created using BioRender.

Many studies utilizing single-site histone modifications have reported that PTMs influence nucleosome dynamics, and eukaryotic systems may exploit these changes to regulate access to DNA. For example, an acetylation site located in the dyad region [110,118] as well as at several locations throughout the nucleosome [117] has been shown to contribute to increased nucleosome disassembly. Increased mobilization affects the binding properties of chaperones, remodelers, and other proteins known to aid in DNA wrapping that impacts nucleosomal processes that are otherwise thermodynamically and/or physiologically unfavored (Figure 3) [109].

Experimental results of destabilization and expansion by charged PTMs have supported a connection between PTMs on the NCP's histone core and their effects on nucleosomal DNA accessibility [110,117,118]. PTMs that influence nucleosome repositioning, assembly, and disassembly increase site exposure and occur in areas of the nucleosome where repair in the nucleosome may be otherwise hindered. Examples of these modifications include the acetylation of lysine 56 on histone H3 (H3K56) [118,121–126], acetylation of lysine 91 on histone H4 [132], and phosphorylation of serine 28 on histone H3 [133].

Acetylation of H3K56 enhances APE1 activity [127] whereas acetylation of H3K56 and H3K14 has been shown to decrease Pol β nucleotide-incorporation activity near the dyad region of a mononucleosome [80]. H3K56 is acetylated during S phase by CBP/p300 once the histone is incorporated into an NCP [128]. In the absence of DNA damage, the deacetylases Hst3 and Hst4 remove the PTM during G2 [129,130]. It is known that defects in this regulation of H3K56 acetylation render cells sensitive to alkylating agents [125], which are known to generate lesions that are repaired by BER. At the molecular level, H3K56 interacts with a phosphate in the DNA backbone [131], and charge neutralization via acetylation likely causes increased dynamics. While H3 is located near the dyad axis it has been reported that acetylation of H3K56 influences DNA dynamics throughout the NCP and its effects are not localized to the dyad axis [117]. The differing impacts of this PTM on APE1 and Pol β may reflect different bind modes of these enzymes.

In studies on twelve-nucleosome arrays, the combined activity of a DNA glycosylase and APE1 were examined with acetylation of H3K18 and H3K27 [134]. Modification of H3K18 resulted in an increase in the incised DNA product while modification of H3K27 had the opposite effect. Given that CBP/p300 is responsible for installing both of these PTMs, this acetyltransferase may play a direct role in modulating the BER pathway in chromatin.

9. Future Outlooks

Genetic compaction into chromatin poses a unique barrier for cellular machinery, including those involved with processes of DNA repair. Understanding the complex dynamics of the NCP will provide vital information to elucidate the physical accessibility of genomic DNA. Appreciating that PTMs are capable of altering the ways that DNA interacts with histones, it is of interest to examine how PTMs alter overall nucleosome dynamics. Data on this subject is often collected using techniques of structural mapping and chemical reactivity in vitro. Although these techniques have allowed for the analysis of nucleosomal interactions in a controlled setting, many currently used systems lack global aspects of native nucleosomes.

To account for these limitations, future studies will benefit from model systems of increased complexity. For example, in vitro systems involving global damage and PTMs as well as those consisting of higher-order structures will allow for a deeper interpretation of processes that occur in nature. In vivo studies will fill major knowledge gaps to identify on a genome-wide scale how the amount and location of lesions are modulated by PTM. Exploring the relationships between BER and other processes such as transcription will also be important to identify any crosstalk or collaboration. These future directions will bypass limitations of current in vitro approaches aimed at exploring complex nucleosome relationships involving PTMs to provide further insight on how histone modifications and other nucleosomal factors, both structural and energetic, may function as teammates to create a domino effect between nucleosome dynamics and the regulation of BER enzymes.

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