Free Radical Biology and Medicine 107 (2017) 159–169

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Review Article

Chromatin associated mechanisms in base excision repair - nucleosome remodeling and DNA transcription, two key players☆

Hervé Menoni[a,d,*], Paolo Di Mascio[b], Jean Cadet[c], Stefan Dimitrov[d], Dimitar Angelov[a,**]

[a] Laboratoire de Biologie et Modélisation de la Cellule (LBMC) CNRS/ENSL/UCBL UMR 5239 and Institut NeuroMyoGène – INMG CNRS/UCBL UMR 5310, Université de Lyon, Ecole Normale Supérieure de Lyon, 69007 Lyon, France
[b] Departamento de Bioquímica, Instituto de Química, Universidade de Sao Paulo, CP 26077, CEP 05508-000 Sao Paulo, SP, Brazil
[c] Département de Médecine Nucléaire et de Radiobiologie, Université de Sherbrooke, Sherbrooke, Québec, Canada J1H 5N4
[d] Université de Grenoble Alpes/INSERM U1209/CNRS UMR 5309, 38042 Grenoble Cedex 9, France

ARTICLE INFO

Keywords:
DNA oxidative damage
Base excision repair
OGG1
8-oxoG
Transcription coupled repair
Nucleosome
Chromatin
Chromatin remodeling

ABSTRACT

Genomic DNA is prone to a large number of insults by a myriad of endogenous and exogenous agents. The base excision repair (BER) is the major mechanism used by cells for the removal of various DNA lesions spontaneously or environmentally induced and the maintenance of genome integrity. The presence of persistent DNA damage is not compatible with life, since abrogation of BER leads to early embryonic lethality in mice. There are several lines of evidences showing existence of a link between deficient BER, cancer proneness and ageing, thus illustrating the importance of this DNA repair pathway in human health. Although the enzymology of BER mechanisms has been largely elucidated using chemically defined DNA damage substrates and purified proteins, the complex interplay of BER with another vital process like transcription or when DNA is in its natural state (*i.e.* wrapped in nucleosome and assembled in chromatin fiber is largely unexplored. Cells use chromatin remodeling factors to overcome the general repression associated with the nucleosomal organization. It is broadly accepted that energy-dependent nucleosome remodeling factors disrupt histones-DNA interactions at the expense of ATP hydrolysis to favor transcription as well as DNA repair. Importantly, unlike transcription, BER is not part of a regulated developmental process but represents a maintenance system that should be efficient anytime and anywhere in the genome. In this review we will discuss how BER can deal with chromatin organization to maintain genetic information. Emphasis will be placed on the following challenging question: how BER is initiated within chromatin?

1. Introduction

Constant formation of DNA lesions resulting from aerobic metabolism, environmental conditions or spontaneous hydrolysis of weak chemical bounds are major challenges to the maintenance of genome stability in mammalian cells [1]. Several reactive oxygen species (ROS) including the highly reactive hydroxyl radical (•OH) that are formed as byproducts of cellular metabolic processes can modify the bases and 2-deoxyribose moieties of the DNA [2–5]. Oxidation of proteins or lipids, which can be submitted to the same kinds of radical attack, can be discarded and replaced by non-damaged ones. In contrast, DNA damage jeopardizes the integrity of the genetic information, an essential element for the stability of the genome and cell viability [6].

Suitable repair pathways for numerous kinds of DNA lesions have been described. Within the vast majority of DNA damage events, the information coded by the undamaged complementary strand can be utilized to maintain genome integrity. Cells have selected sophisticated mechanisms to detect and excise the damaged base, or a patch of nucleotides surrounding the lesion. The base excision repair (BER) and the nucleotide excision repair (NER) are the major excision repair pathways described in mammals. Strikingly, a complete elimination of the BER system is not compatible with life and leads to an early embryonic lethality [6,7]. For historical reasons NER deficiencies have been linked to a broad spectrum of clinical outcomes from mild sun

☆ This article is one of a series of papers on the subject of oxidative DNA damage & repair that have been published as a special issue of Free Radical Biology & Medicine to commemorate the Nobel Prize won by Prof. Tomas Lindahl. A detailed introduction and synopsis of all the articles in the special issue can be found in the following paper by Cadet & Davies [181].

* Corresponding author at: Laboratoire de Biologie et Modélisation de la Cellule (LBMC) CNRS/ENSL/UCBL UMR 5239 and Institut NeuroMyoGène – INMG CNRS/UCBL UMR 5310, Université de Lyon, Ecole Normale Supérieure de Lyon, 69007 Lyon, France.
** Corresponding author.
E-mail addresses: herve.menoni@ens-lyon.fr (H. Menoni), dimitar.anguelov@ens-lyon.fr (D. Angelov).

http://dx.doi.org/10.1016/j.freeradbiomed.2016.12.026
Received 27 September 2016; Received in revised form 13 December 2016; Accepted 19 December 2016
Available online 20 December 2016

sensitivity to premature death and various neurodegenerative diseases, segmental premature ageing syndromes or cancer proneness. A link of BER and human diseases is not so extensively characterized but BER is a DNA repair pathway involved in cancer and ageing [8].

This review focuses on BER mechanisms with some reference to other DNA repair pathways for which further information could be found [9–11]. BER is the main pathway for the repair of most small DNA base lesions caused by oxidation, deamination and alkylation. These modifications are in general not helix-distorting and they do not strongly interfere with transcription [12]. BER is initiated when a specific DNA glycosylase recognizes a modified base. In a subsequent step the glycosylase cleaves the *N*-glycosylic bond between the damaged base and the 2-deoxyribose moiety of the nucleotide. This creates an abasic site called either apurinic or apyrimidinic site (AP-site). There are at least 11 mammalian glycosylases that can detect in a more or less specific way different types of damaged bases, making BER a widely usable repair pathway that can deal with a wide variety of modified bases. DNA glycosylases are small monomeric enzymes, grouped according to motifs conserved from prokaryotes to humans [13]. Glycosylases can be classified as bi- or mono-functional depending on their capacity to cleave DNA or only the *N*- glycosidic bond of a damaged base. In metazoans, AP sites are processed by the AP endonuclease APE1, which generates a single strand break (SSB) in the DNA [12]. The resulting gap is filled by DNA polymerase β, which uses the undamaged strand as a template. The final step of BER is ligation of the nicked DNA strand, by DNA ligase III that forms a complex with XRCC1. XRCC1 plays a major role in SSB repair and the completion of BER by interacting with various partners either by increasing (*e.g.* PNK) or reducing (*e.g.* PARP-1) their activities (reviewed in [14]. A redundancy with other ligases present in the nucleus may be possible suggesting that XRCC1 complexed with ligase III is not required for BER to proceed [15]. A very wide plasticity exists in cells for the requirement of ligase in nucleus as well as in mitochondria [16]. In the same way, it has been speculated since many years that glycosylases may have redundant function with their overlapping activities on some DNA lesions [17]. This could explain the small increase of the steady state level of specific modified bases in various knockout mice for single DNA glycosylases.

The amount of DNA lesions and their location can vary a lot from cell to cell according to changes in physiological or environmental conditions (*e.g.* exposure to chemicals, agents generating ROS, sunlight and other processes including spontaneous chemical bond breakage, activation-induced deaminase during B-cell maturation *etc.*) [18,19]. The steady-state level of DNA damage that is observed results from their continuous formation and removal dynamic by the repair machinery present in the cell. The accumulation of DNA lesions, when failure in repair occurs, can have various outcomes depending on the intrinsic properties of the lesions: i) mutagenesis in the case of 8-oxo-7,8-dihydroguanine (8-oxoG) [20] or uracil [21], ii) replication block for 5,6-dihydroxy-5,6-dihydrothymine also called “thymine glycols” (Tg) [22] and complete transcription block for various helix-distorting DNA lesions such as ultraviolet light (UV)–induced cyclobutane pyrimidine dimers (CPDs) [23,24]. Therefore, DNA damage can trigger a complex response with various consequences on cellular physiology. This enlightens the importance for cells to accurately handle DNA repair together with transcription (and other cellular processes) in order to avoid more deleterious effects [25]. Even though, transcription through DNA lesions (*e.g.* 8-oxoG) can induce transcriptional mutagenesis [18,26], uncontrolled BER initiation can be more dangerous by triggering cell death and cellular sensitivity to DNA damaging agents [27,28]. Imbalances in the execution of normally regulated repair steps may be at origin of harmful effects observed on cells upon over-expression of proteins involved in repair pathways (*e.g.* glycosylases) [29]. Whereas 8-oxoG is not a strong block for transcription [30], the OGG1 glycosylase induced nick that are generated upon the lesion processing can cause transcription blockage [31]. Strikingly, elongation by RNA Pol II in a purified reconstituted transcription system can be blocked to different extents, illustrating that depending on the type of DNA lesion a complex spectrum of transcription impediment can occur in the nucleus [32]. Certainly, *in vivo* many other parameters such as chromatin context, promoter strength, or simply “who is first” on the lesion create wide options for the type of DNA Damage Response (DDR) generated by a same DNA insulting agent.

The basic subunit of chromatin, the nucleosome, 147 bp of DNA, wrapped in a left-handed toroidal helix around a histone octamer is a barrier to most of the factors interacting with DNA [33,34]. The next level of packaging of DNA into chromatin or the so-called 30 nm fiber and its higher level compaction forms represent other levels of obstruction.

In this review we will focus on the repair of non-helix-distorting lesions which are primarily substrates for the BER and discuss how chromatin associated mechanisms such as transcription and chromatin remodeling could play a role in the repair of such modified bases. First, we will describe *in vitro* studies on nucleosomal substrates. In the second part we will discuss the mechanisms that could favor access of BER factors to chromatin with a special mention to histone variant. Thirdly, results from live cell experiments will shed light on the connection between BER, transcription and chromatin remodeling. Finally we will give a more speculative view on BER initiation *in vivo* and conclude with some of the future challenges to address in the field.

2. BER *in vitro* on chromatin substrate

Most of the enzymes involved in BER have been extensively characterized (for structural targeted reviews, see [35,36]). Studies using short naked DNA substrates, in which a single modified base was site specifically inserted, gave insight in the repair substrates specificity of DNA glycosylases [37,38]. Interactions between various BER proteins have been described, especially with XRCC1, a scaffold protein with no catalytic activity, which is believed to favor optimal reaction [39]. However, much less is known on BER enzymes or scaffold proteins function in the context of chromatin. Here we will give a brief overview of the main findings and conclusions that can be drawn from relevant studies on three major BER lesions: uracil, Tg and 8-oxoG. For a more detailed information on various reconstituted systems used to study BER involving nucleosomal substrates we direct the reader to a recent review [40].

2.1. *Accessibility of various BER-lesions within* in-vitro *nucleosomal assemblies*

2.1.1. *Uracil*

Uracil in DNA results from either hydrolytic deamination of cytosine, creating a premutagenic U:G mispair, or misincorporation of dUMP instead of dTMP during replication, creating a U:A pair (reviewed in [13]). The mutagenic uracil base is recognized by a Uracil DNA Glycosylase (UDG) enzyme, which cleaves the *N*-glycosidic bond giving rise to a DNA abasic site. The removal of free uracil from *E. coli* DNA containing deaminated cytosine residues was the first glycosylase activity described by Lindahl [41]. The nucleosomal substrate reconstituted with the 5 S rRNA gene DNA (5 S), containing one single site-specific U:A base pairs, showed a rotational position independent 3- to 10-fold- decrease of SMUG1 and UNG2 efficiency compared to free DNA [42]. In disagreement with this initial study, a 10- to 30-fold rotational position dependent inhibition of UDG efficiency was reported [43,44]. These discrepancies might be due to the different DNA sequences used to position the nucleosome and also suggested that nucleosome was not such a strong barrier to BER initiation. However, another group using the same 5 S positioned nucleosomes reported a UDG activity inhibited 10^3–10^4-fold for inward facing sites, while for outward facing uracil reacted as efficiently as in free DNA [45]. Experimental difficulties in determining the initial rates

of cleavage, requiring high-quality and naked-DNA free nucleosomes, could explain these variations inherent to assays on nucleosomal templates.

Restriction enzymes show a ~10^4-fold decrease in the cleavage efficiency as the recognition site is moved from near the DNA entry−exit on the octamer toward the nucleosome dyad axis [46]. In contrast, the distribution of UDG reactive and unreactive uracil sites across the entire nucleosome core is not clearly related to the position relative to the nucleosome dyad. This is indicative that additional mechanisms beyond DNA unwrapping, such as local dynamic or conformations of individual sites, are likely to be involved in UNG reactivity [47]. Rotational exposure of the site towards the solution is the major but probably not the only condition for the reactivity of UNG [45,48].

2.1.2. 5,6-Dihydroxy-5,6-dihydrothymine

Generally, outward facing thymine glycols were more rapidly repaired than inward facing ones, and those located furthest away from the dyad were repaired the fastest by the NTH1 glycosylase. These findings are suggestive that steric accessibility coupled with unwrapping motions is an important factor for efficient repair [49–51]. NTH1 data support the idea of sterically occlusion from access in presence of histones; however, the level of activity inhibition between inward and outward orientations is modest compared to UNG.

2.1.3. 8-Oxo-7,8-dihydroguanine

8-oxoG, an ubiquitous lesion oxidatively generated by •OH, singlet oxygen or one-electron oxidants, is repaired by the BER pathway [52]. The glycosylase responsible for recognition of the common oxidatively induced lesion 8-oxoG is OGG1 [52]. The human DNA glycosylase OGG1, is the functional homologue of bacterial Fpg and is capable of recognizing and removing 8-oxoG opposite C, but not opposite A and also 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG) [53,54]. A potential redundancy thanks to other glycosylases remains hypothetical (and probably marginal) since nuclear extract from cell OGG1-deficient does not excise efficiently 8-oxoG *in vitro*[17]. OGG1 is a bifunctional enzyme, displaying glycosylase and apurinic/apyrimidinic (AP)-lyase activities [54–56]. With its “rather slow” AP-lyase activity OGG1 nicks the backbone 3′ to the AP-site according to a β-elimination mechanism, resulting in a 3′-dRP end group [57]. The DNA nicked by OGG1 at the site of the lesion (3′ to the lesion) is then processed by APE1, which creates a free 3′-hydroxyl group that is required for the gap filling by DNA polymerase β. Finally, the 8-oxoG repair is completed by ligation of the nick by DNA ligase III present in complex with the scaffold protein XRCC1.

The mechanism of BER within reconstituted positioned nucleosomes has been studied by introducing a single 8-oxoG lesion in the DNA fragment located at 10 bp distance from the dyad [58]. It was reported that OGG1, APE1 and DNA Pol β activities were strongly reduced in nucleosome core DNA. The chromatin remodeler SWI/SNF (SWItch/Sucrose Non-Fermentable) stimulated each one of the three BER repair steps with efficiency close to those observed for naked DNA. Interestingly, SWI/SNF-induced remodeling without nucleosome mobilization was sufficient to achieve this effect (see Section 3.4). Notably, SWI/SNF was also able to assist NER, but its effect on NER of UV-lesions was found to be very modest (a 1.5- to 2-fold increase of NER efficiency was reported in the presence of SWI/SNF [59,60]. These data demonstrate a qualitatively different effect of SWI/SNF on BER compared to NER and suggest that *in vivo* chromatin remodelers of the SWI/SNF family may be required for efficient BER of 8-oxoG. Unfortunately, no data on rotational position dependence of OGG1 activity were reported. However, as mentioned, OGG1 recognizes rather the base pairing than the molecular structure of the lesion. Thus, we may expect a lower influence of the nucleosome rotational position compared to uracil since the base complementary to 8-oxoG is in opposite orientation regarding the histone octamer surface.

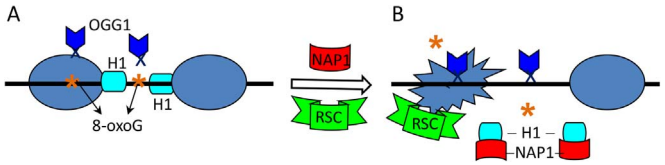

Fig. 1. Model of the NAP-1 and RSC assisted initiation of BER within H1-complexed dinucleosomes based on *in vitro* studies. (A) OGG1 is unable to excise 8-oxoG (denoted by Asterisk) in dinucleosomal templates. (B) Eviction of H1 by NAP1 is sufficient for 8-oxoG excision in the linker DNA, while both H1 eviction and nucleosome remodeling are required for the excision of 8-oxoG located within nucleosome core DNA. For details see [61].

The efficiency of OGG1 to remove 8-oxoG and cleave the DNA within *in vitro* reconstituted positioned dinucleosomal templates was recently reported [61]. OGG1 activity was measured on a single 8-oxoG located either in the vicinity of the dyad of one nucleosome or in the center of the 20- or 75-bp linker DNA. H1 containing dinucleosomes assembled with help of the H1 chaperone NAP-1 (Nucleosome Assembly Protein 1) were used to understand how this linker histone affects BER initiation (Fig. 1). As expected, 8-oxoG within the nucleosome core DNA was inaccessible to OGG1. In absence of H1, 8-oxoG located in the linker DNA was processed as efficiently as in naked DNA independently on the linker length. This completes and confirms experiments carried out with UDG in oligo-nucleosome substrates [62]. In contrast, a 10-fold inhibition of OGG1 was observed within H1 complexed dinucleosomes which is however abrogated upon NAP-1-mediated H1 removal. The presence of RSC (Remodel the Structure of Chromatin), a SWI/SNF family remodeler, and excess of H1 chaperone NAP-1 were sufficient for allowing 8-oxoG processing independently on its position within dinucleosome. Briefly, both histone H1 removal and dinucleosome remodeling are necessary and sufficient for efficient repair initiation of nucleosomal 8-oxoG (Fig. 1).

3. Mechanisms of accessibility of BER enzymes to chromatin

While nucleosomes were once thought to strictly inhibit access of DNA-dependent factors, it is accepted that at least some BER components can use nucleosomal DNA as substrate for their enzymatic processes [40]. However, BER initiation and completion of a large proportion of DNA lesions (or repair-intermediates) remain refractory within chromatin. Dynamic behaviors intrinsic to nucleosomes, such as transient, partial unwrapping of DNA from the histone octamer, may favor DNA scanning by BER glycosylases. Yet, cells have several other ways to provide transient access of proteins to their DNA target sites within chromatin, namely by the action of ATP-dependent chromatin remodeling complexes [63–65], by histone tails post-translational modifications and by incorporation of histone variants [66]. We will briefly present these different strategies.

3.1. Post-translational modifications of histone tails

Considerable amount of results have connected histone tails modifications with chromatin dependent DNA-related cellular processes. One should recognize the confusion regarding the causalities relationships between the effects observed that have essentially correlative values [67]. Whereas, the role of histone tails modifications in recruitment of non-histone proteins to chromatin is satisfactory well characterized, flabby evidence on direct structure/organization changes has been reported so far. It has been shown both *in vitro* and *in vivo* that hyperacetylation of histone tails does not abolish their interactions with linker DNA [68–70] as it was initially thought. One possible exception is acetylation of H4K16 that seems to weaken interactions between adjacent nucleosomes [71], thus interfering with the 30 nm fiber stability [72,73]. Similarly, phosphorylation, that may have important consequences for chromatin compaction *via* electric

charge modification, has no reported effect on mono-nucleosome/chromatin structure *in vitro* although its involvement in mitosis, apoptosis and gametogenesis is well documented [74].

To date, no solid data are available on a significant role of histone tails modifications in BER. In contrast, correlation between histone modifications and either NER or double strand break repair (DSBR) (*e.g.* γH2AX) has been reported in hundreds of papers, even though mechanisms of their occurrence in respect to DNA lesion and their functional roles are still on a speculative level [75–80]. Finally, it is noteworthy that due to the biased nature of current methods to measure changes in chromatin accessibility *in vivo*, it is largely unclear whether higher order chromatin condensation is associated with important changes in DNA accessibility. In support to this marginal effect of higher level of chromatin compaction (*i.e.* above the dinucleosomal level) little methylase accessibility difference at domains marked with repressive and active histone modifications regions has been observed [66].

3.2. Histone variants

Canonical histone genes are present in clusters throughout the genome and are expressed in S phase and replication-coupled deposited. In contrast, histone variant genes are non-allelic, often contain introns, and are expressed at most times during the cell cycle in a replication-independent manner thus allowing their specific chromatin deposition [81]. Histone variants have emerged as important contributors to the regulation of chromatin structure and therefore of almost all DNA-based processes [82]. Incorporation of histones variants can affect nucleosome stability, DNA wrapping, post-translational modifications, and generate specialized chromatin domains (*e.g.* centrosome) [83]. Hence, these specialized histones play important roles in transcriptional regulation, cell cycle progression, DNA repair and chromatin stability [84]. The precise regulatory mechanisms are fulfilled thanks to accurate chromatin deposition, eviction and exchange of histone variants with their corresponding conventional analogs through the involvement of specialized histone chaperones/remodelers complexes [85–87]. Mutations or improper regulation of histone variants and/or the dedicated deposition/eviction/exchange chaperone complex members can lead to important pathologies and diseases including tumor development. However, the molecular mechanisms are poorly understood so far [88,89].

Although support for correlations between histone variants including tail covalent modifications and DNA damage response has been provided experimentally, the molecular mechanisms of these links are largely unknown [90]. Prominent examples are the well-known phosphorylation of the H2A variant, H2A.X, as one of the earliest events in response to the formation of DNA double strand breaks [91] and the incorporation of H3 variants into the site of UVC damage [92]. Zeitlin et al. reported the accumulation of the centromeric H3 variant CENP-A at DNA DSB sites induced by laser micro-irradiation or endonuclease in mammalian cells [93]. However considering that mislocalized CENP-A may lead to aberrant centromere formation the functional relevance of its accumulation at damage sites remains unclear.

Importantly, no direct links between histone variants and BER have been reported so far although some indirect clues exist. The macrodomain of macroH2A has been shown to bind the catalytic and zinc finger domains of PARP1 inhibiting its enzymatic activity *in vitro* [94]. Although PARP1 appears to be integral to single strand break repair (SSBR), recent observations suggest that RNAi-mediated depletion of PARP1 has no effect on BER, whereas treatment of cells with an agent that blocks the cyclic binding of PARP1 to SSBs interfered with BER [95]. Besides, one can anticipate a link between BER and histones variants on the basis of the modified accessibility of variant nucleosomes (chromatin). As an example it has been shown that macroH2A plays an important role in gene silencing by interfering with transcription factor binding and nucleosome remodeling [96]. In addition, it exhibits greater than canonical nucleosomes salt-dependent stability and excludes the binding of H1 [97]. These features are indicative of a reduced accessibility of BER components to macroH2A nucleosomes. In contrast, a naturally enhanced accessibility of BER enzymes to lesions located on H2A.Bbd, H2AL2, CENP-A containing nucleosomes is expected. This is due to a more open conformation, a lower stability and an inability to stably associate with linker histone H1 hence to fold into compact 30 nm fiber [58,98–102]. However, in the case of H2A.Bbd (the only histone variant tested in DNA repair assays so far), despite an initial better accessibility, the inactive SWI/SNF remodeling on these nucleosome leads to an impaired BER in comparison with remodeled conventional nucleosomes [58].

3.3. Site-exposure model of Widom – thermodynamic fluctuations induced DNA unwrapping from nucleosome ends

Studies from many laboratories reveal that nucleosomal DNA is partially accessible to several DNA-binding proteins, even in the absence of exogenous factors, despite the fact that the crystallographic structure of the nucleosome [34] shows that the binding sites would be occluded. In earlier studies [103,104] the “site exposure model” was proposed to explain this behavior of nucleosomes *in vitro*. This would explain findings of widely disparate experiments, including the equilibrium binding of a protein to a nucleosomal DNA target site, the kinetics of digestion of nucleosomal DNA at internal sites by restriction enzymes or at the ends of nucleosomal DNA by exonucleases. According to this hypothesis, the equilibrium constants describing this dynamic site exposure decrease progressively from either the ends of the nucleosomal DNA toward the middle or the dyad of the nucleosome. The transient DNA release from the octamer surface, starting from one end of the nucleosomal DNA would be responsible for the observed differences in accessibility. However, it should be noted that more recent and refined experiments unambiguously showed that Widom's data on thermodynamic fluctuation opening and accessibility to restriction enzymes are strongly overestimated, and in reality restricted to the first ~10–12 bps from the nucleosome ends [100,105,106]. Importantly, thermodynamic fluctuations induced nucleosome opening should be reduced in folded chromatin, in the presence of linker histones and/or divalent cations such as magnesium. These agents generate the so-called stem structure of linker DNA “closing” the nucleosome and hence preventing its transient “opening”, DNA loop injection and mobility [107–110]. Besides, heat-induced repositioning experiments have mostly been performed on mono- or dinucleosomal substrates. On longer chromatinized substrates no evidence for a long-range nucleosome repositioning has been found [111].

A currently shared view is that spontaneous partial unwrapping of DNA from the underlying histone octamer enables BER enzymes to bind to oxidatively generated lesions that would otherwise be sterically inaccessible [40,50]. Although DNA unwrapping-mediated exposure of a lesion ~10 bps from a mononucleosome edge occurred ~7–8 times per minute, exposure rates fell dramatically for lesions located 10 or more bps further in from the nucleosome edge [50]. The rates are likely too low to account for the observed rates of BER in cells. Thus, ATP-dependent chromatin remodeling, either BER-specific or when associated with transcription, replication, or other DNA related processes, probably contributes to efficient BER *in vivo*.

3.4. ATP-dependent chromatin remodeling

Chromatin remodeling factors consist of one dedicated ATPases of the SNF2 super-family associated with variable numbers of additional subunits [112] to form large multi-proteic stable structures. Prominent examples of such complexes are the families SWI2/SNF2, ISWI, CHD and INO80 [113,114]. These four groups of remodelers can be distinguished by their biochemical properties and the peculiarities of their nucleosome remodeling [115]. All families of remodeling ATPases

can facilitate nucleosome sliding, namely, the relocation of intact histone octamers on DNA, without displacement to other DNA segments [116–121]. In addition, at very high concentrations SWI/SNF-related remodeling factors seem able *in vitro* to disrupt histone-DNA interactions more extensively leading to histone dimer or octamer eviction from DNA [116,122]. Noteworthy, *in vivo* such high remodelers/nucleosome (~stoichiometric) ratios can be realized only locally by targeted recruitment. Interestingly, the isolation of the Swr1 remodeling complex (belonging to the INO80 family) has demonstrated another function of the chromatin remodeling machines, namely, histone variant exchange [123,124].

The crucial role of remodeling factors in chromatin plasticity has been highlighted not only *in vitro*, but also *in vivo* using genetic experiments in yeast, *Drosophila*, *C. elegans* and higher eukaryotes [125–128]. DNA-related nuclear activities such as transcription, replication, repair, and recombination are occurring thanks to numerous changes in the local chromatin structure. Chromatin remodeling is a vital process within eukaryotic cells. It is involved in controlling gene expression, DNA replication and repair, epigenetic phenomena, and also in several human pathologies [129]. The nucleosomes are continuously substrates to ATP-dependent nucleosome remodeling complexes that dissociate interactions between histone and DNA facilitating nucleosome relocation and histone eviction/exchange. At the same time, nucleosomal DNA is continuously "scanned" by DNA repair factors present in the cell. A requirement for ATP-dependent nucleosome remodeling has been documented within the first three steps of BER of otherwise inaccessible 8-oxoG within the nucleosome core DNA, and appears to depend on the type of nucleosomes [58].

Interestingly, the activity of ATP-dependent chromatin remodeling complexes is reduced within nucleosomes bound to H1 [130,131] but not abolished [132,133]. These results suggest that remodeling complexes (alone or in cooperation with linker histone chaperones) can be involved in linker histones eviction contributing to the fast dynamic exchange of H1 observed *in vivo* with FRAP techniques [134,135]. A reversible dramatic reduction of H1 exchange rate upon transient inhibition of ATP synthesis in Tetrahymena cells supports a major role for ATP-dependent chromatin remodelers to affect chromatin dynamic by facilitating eviction of H1 [136]. Nevertheless, the action of chromatin remodelers on H1 mobility *in vivo* seems more complex than previously anticipated. A competition between various remodelers may lead both to assembly and removal of H1 [137,138].

At least two models for nucleosome remodeling have been suggested based on biochemical data [139]. According to the first model, proposed for the SWI/SNF remodeler, DNA is peeled from the surface of the histone octamer, forming a large DNA loop, which then propagates around the nucleosome surface. The second model, originally proposed for RSC, suggests that DNA moves in 1 bp rotational waves on the histone octamer surface, driven by the tracking domain of the ATPase subunit of RSC. Single molecule experiments indicate that both RSC and SWI/SNF are able to generate loops with an average size of about 110 bp at the dyad axis of the nucleosome, which then allows the nucleosome to slide [119,140].

The two models described above implicitly assume that nucleosome mobilization is a continuous event, proceeding without dissociation of the remodeler from the nucleosome. Recent experimental data have however showed that this is not the case, at least for RSC [141]. The mechanism of RSC nucleosome mobilization has been studied by a combination of high-resolution atomic force microscopy (AFM), electron cryo-microscopy (ECM) and biochemistry techniques on mononucleosome substrates [141]. Two types of products were generated during the RSC remodeling of centrally positioned 255 bp nucleosomes, i) mobilized particles located at the DNA ends and ii) non-mobilized nucleosome-like particles, named "remosomes", which contain 180–190 bp of DNA associated with the histone octamer. Importantly, the latter RSC released metastable particles exhibited distinct and highly irregular DNA shapes and increased restriction enzyme and DNase I accessibility within the core DNA. In other words, the remosomes consist in a heterogeneous population of over-complexed particles with strongly perturbed histone-DNA interactions. These data strongly suggest that remosomes are a set of particles containing a relatively randomly (with a slight preference for the dyad) distributed metastable loop of 20–40 bp DNA stretches dissociated from the octamer surface. A recent mathematical model using all atom simulation and the highly optimized molecular dynamics code Gromacs (5.0) at a 0.5 μs time scale is illustrating in Fig. 2 how a remosome could look like [142].

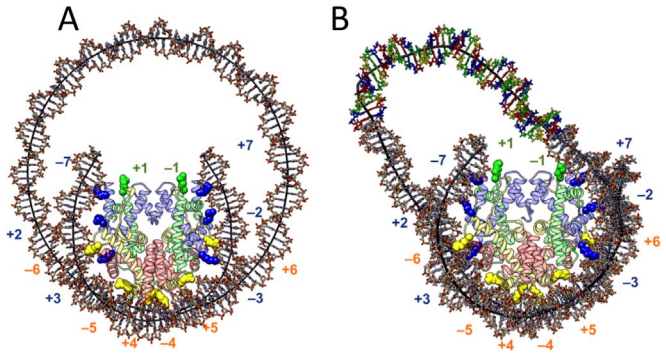

Fig. 2. Mathematical model of the "remosomes". A) Initial model of a modified nucleosome with 42 extra base pairs, leading to an "epicyclic" DNA loop located above the pseudodyad position of the nucleosome. B) The conformation adopted after 480 ns of MD simulation where local DNA kinks and average DNA bending allow more extensive histone-DNA contacts to form. For details see [142]. *This model was kindly provided by Richard Lavery.*

4. BER *in vivo* and the link with transcription, chromatin remodeling and NER factors

Structural studies, providing mechanistic insights at a molecular level, were confined to purified proteins and/or synthetic DNA substrates. In conjunction with previously quoted studies, such as repair in the presence of nucleosomes, the way BER can deal with cellular environment starts to be better understood. The study of BER *in vivo* has been hampered by the difficulty to introduce DNA damage repaired primarily by this pathway without other DNA lesions that could lead to misleading interpretation of the results [143]. This explains the scarcity of studies where attempts were made to delineate BER function in living cells. In contrast, study of NER or DSB repair thanks to UV-light or specific endonucleases have favored the assessment of these pathways in living cells. We will focus in this section on the link of BER with transcription, ATP-dependent chromatin remodeling and NER factors.

The characterization of tight connections between transcription and DNA repair has been the subject of intense research since the first discoveries of a faster repair of DNA in transcribed region. A well described mechanism called Transcription-Coupled-NER (TC-NER) explained how cells could repair preferentially the transcribed strand of DNA to restore rapidly transcription and recovery of RNA synthesis upon UV damage infliction (for a review see [10]). However, most of the non-bulky DNA lesions (*e.g.* 8-oxoG, uracil or AP-site) can be bypassed by RNA polymerase II during transcriptional elongation without initiating that repair pathway [144–146]. Some of these lesions (*e.g.* 8-oxoG) may subtly alter transcription activities compared to the complete stalling observed for bulky CPDs. In a reconstituted transcription system or with cellular extracts a weak block was observed at 8-oxoG sites during transcription [30]. More recently, it was shown that elongation factors, such as CSB, TFIIS or elongin could increase the efficiency of RNA pol II to read through oxidatively induced lesions, and therefore contribute to transcriptional mutagenesis [32]. In addition to this direct influence on transcription, transcriptional inactivation of damaged DNA can occur at non-bulky DNA lesions after BER-

initiation and subsequent formation of a SSB [144]. For this reason, BER must be highly coordinated in order to avoid interference with transcription.

Interestingly, a factor involved in transcription, FACT (FAcilitates Chromatin Transcription), has been recently shown to be likely implicated in BER within living cells [105]. FACT is a vital protein which displays a histone chaperone activity with multiple roles including one in TC-NER of UVC damaged DNA [147]. Newly, Tap-Tag pull down of FACT complexes and MS analysis showed that upon H_2O_2 treatment induced oxidative stress in HeLa cells FACT is released from transcription protein complexes to get associated with repair proteins and chromatin remodelers from the SWI/SNF family [105]. Upon local generation of oxidized DNA by low-intensity 405 nm laser micro-irradiation of HeLa cells, in presence of the non DNA interacting type II (singlet oxygen) photosensitizer Ro-198022, that generates essentially 8-oxoG but non DSB and UV-lesions, FACT is rapidly recruited at the sites of damage that co-localize with glycosylase OGG1. Interestingly, FACT facilitates glycosylase action in the removal of uracil from nucleosomal DNA thanks to an enhancement in the remodeling activity of the ATP-dependent chromatin remodeler RSC. Altogether, the data suggests that FACT may act in concert with RSC to facilitate excision of DNA lesions during the initial step of BER. Further studies are necessary to assess whether FACT is required to promote a coordination of BER and therefore to avoid persistence of BER-intermediates such as SSBs that are strong blocks of transcription.

Another protein, as well involved both in transcription and TC-NER, Cockayne Syndrome group B (CSB), seems to be able to interfere with BER of oxidatively damaged DNA lesions in multiple ways. A variety of mutations in CSB cause Cockayne Syndrome (CS), a rare inherited recessive disease leading to a progressive multisystem degeneration resembling a premature ageing [148]. In biochemical assays, CSB has been shown to influence incision at 8-oxoG sites by the OGG1 DNA glycosylase, but another work [149] suggested that CSB could be important for repair even if this glycosylase is absent. We will briefly describe these different facets of CSB in the BER pathway.

The ability of CSB to influence the incision of the DNA backbone in synthetic oligonucleotides strands containing a single 8-oxoG lesion has been noted in a number of *in vitro* studies that used whole cell or nuclear extracts of normal and CSB-deficient cells [150–152]. While this is indicative of a potential role of CSB in the BER pathway, it remained unclear whether CSB increased OGG1 expression or had a more direct function in the BER pathway. It has been shown that CSB could increase expression of OGG1 [150] and it was proved that a reduced amount of OGG1 could be responsible for the reduced incision observed at 8-oxoG sites in repair assays. However extracts of normal cells (*i.e.* containing the same levels of OGG1), from which CSB was depleted still showed reduction in incision at 8-oxoG sites [152]. In addition, even if CSB was not found to directly interact with OGG1, its presence may influence the binding of proteins from cell extracts to 8-oxoG *in vitro*. It was shown that CSB co-localizes with OGG1 in cells in response to damage induction by γ-radiation [152]. This led these authors to propose the existence of a protein complex in which CSB and OGG1 together with other factors would influence OGG1 incision activity. In agreement with this hypothesis, CSB was found to physically interact with APE1 and stimulate this enzyme [153]. All these results suggested that CSB could influence incision at 8-oxoG both by regulating OGG1 expression and by functioning according to a hypothetical "BER complex" bearing this glycosylase.

The role of CSB in BER when OGG1 is absent supposes that CSB could improve the activity of other glycosylases or influence the efficiency of BER by chromatin remodeling activities at the site of DNA damage [149,154]. Thus, CSB favors incision at FapyG and FapyA lesions by the DNA glycosylase NEIL1 [155] and stimulates NEIL2 DNA glycosylase activity [156]. In addition, CSB belongs to the SWI/SNF ATP-dependent chromatin remodeler family and might influence BER by chromatin remodeling activities. While chromatin remodeling has been shown to be required to initiate repair of BER-lesions embedded in nucleosome (see chapter 2) and considering that CSB is able to change the conformation of the DNA upon binding to it [157], it remains to be proven that CSB is able to favor glycosylase accessibility and specifically at sites of DNA damage. Recently CSB was proposed to interact with NAP-1L-histone chaperone for efficient TC-NER [158]. According to this study, chromatin remodeling and repair protein recruitment mediated by CSB are separable activities. So, such complex mechanisms require further studies to better assess the role of in BER.

If CSB is indeed able to modulate BER by making DNA better accessible to repair proteins, this would probably influence both the removal of 8-oxoG *via* incision by OGG1 and the back-up repair that has been observed in the absence of OGG1. The latter effect could be due to interaction with NEIL1 or NEIL2. Interestingly, NEILs are functionally distinct from OGG1/NTH1 *in vivo*. NEIL2 shows a unique preference for excising lesions from a DNA bubble, whereas NTH1 and OGG1 are only active with duplex DNA. NEIL1 was also found to efficiently excise 5-hydroxyuracil, a minor oxidation product of cytosine, from the bubble and single-stranded DNA but does not have strong activity toward 8-oxoG in the bubble [159]. The observed OGG1/NTH1-independent repair of oxidized bases in the transcribed sequences would support the possibility that NEILs are preferentially involved in the repair of lesions in DNA bubbles that are generated during transcription and/or replication. In support of this possibility, it was found that Neil2-null mice accumulate oxidized DNA bases in the transcriptionally active sequences of the genome [160]. It was also shown that NEIL2 associates with RNA polymerase II and the transcriptional regulator heterogeneous nuclear ribonucleoprotein-U (hnRNP-U), both *in vitro* and in cells. NEIL2 immunocomplexes from cell extracts preferentially repaired the mutagenic 5-hydroxyuracil in the transcribed strand. [161].

In the absence of CSB the pronounced inactivation of a reporter gene carrying a single 8-oxoG is strongly attenuated by an additional OGG1 deficiency. This is indicative that the processing of the lesion by OGG1 can mediate host cell inactivation rather than reactivation and that other glycosylases if involved are not leading to the same inactivation as for OGG1 [144]. CSB deficiency leads to a significant decrease of a reporter gene in spontaneously transformed mouse embryonic fibroblasts (MEFs) compared to the corresponding CSB-proficient MEFs [162]. A stronger decrease of expression is observed for a defined SSB located in the non-transcribed DNA strand, than in the transcribed strand. These indirect observations sound to be consistent with recent data suggesting the existence of a novel chromatin-specific mechanism allowing the detection of NT-SSBs by the transcribing enzyme [163]. SSBs in the non-transcribed DNA strand can be more harmful for transcription than those located in the transcribed strand due to a relief of unconstrained DNA supercoiling accumulated during transcription through chromatin by NT-SSBs. Repair of NT-SSBs seems to require the activity of CSB [162], suggesting that it could be involved in repair of NT-SSBs even though a Pol II arrest on NT-SSBs during transcription of histone-free DNA *in vitro* was not detected [163,164]. The chromatin structure could enable detection of NT-SSBs by inducing the arrest of transcribing Pol II through formation of small intranucleosomal DNA loops. A tempting model, where CSB together with RNA polymerases could favor repair remains to be further tested. A strong implication of CSB in the repair of BER lesions (*i.e.* 8-oxo-G) involving a DNA transcription connection was inferred from a live-cell imaging that revealed a strong, very rapid and transcription (at least partly) dependent recruitment of CSB to sites of oxidatively generated DNA lesions [165]. In this study no downstream NER factors like XPA were visibly co-recruited indicating that BER was the activated transcription coupled repair pathway and not a canonical TC-NER.

A controversy remains in the TCR field due to one retracted publication proposing the existence of a TCR of 8-oxoG involving NER factors including XPG, TFIIH and CSB. Further work is required to address the crucial question of whether either a full TC-NER or only initiators of TC-NER is (are) involved in TCR of BER lesions. A recent

study suggesting that additional mechanisms and factors can be involved in 8-oxoG repair showed hSSB1 (NABP2/ OBFC2B) to be required for the repair of 8-oxoG by the hOGG1-mediated base excision repair pathway [166]. It was reported in a few studies (reviewed in [167]) that the transcription independent NER-initiator XPC is involved in the protection of cells against the effects of oxidatively induced DNA damage. Even though indication that XPC can be specifically recruited to oxidatively induced lesions in living cells, further studies are needed to further clarify to which extent XPC is involved and what could be the mechanisms implicated [165].

5. Concluding remarks and future directions

Major progresses have been made towards a better understanding how DNA repair operates on chromatin since pioneer work in the late 70′. Several models, including the “access-repair-restore” (ARR) one model were proposed to explain the mechanisms of NER on bulky dipyrimidine UVC lesions (for a recent review see [87]). However, in contrast to NER, how does BER function on chromatin remains still elusive? This is obviously associated with both the complexity of chromatin templates and the difficulty to inflict only non-bulky DNA damage detected by glycosylases. The absence of strong chromatin related signals such as phosphorylation of H2AX as in DSB repair or transcription arrest as for UVC-lesions intuitively suggest that BER could neither require nor lead to substantial changes to chromatin and transcription. *In vitro* studies have shown however, that BER is partly inhibited within nucleosomal DNA and at least half of the base modifications are inaccessible to the initiating enzymes (*i.e.* glycosylases). In addition, CSB-deficiency connect transcription as well as “CAG-triplet expansion” to oxidatively induced DNA lesions [144,162,168,169]. So, how BER is initiated within chromatin without disturbing epigenetic information remains an intriguing question.

Here, we analyzed both the mechanisms and factors that may assist BER to operate in chromatin, such as chromatin remodeling or transcription associated factors. However, how these factors are “pre-targeted” to the lesions before any glycosylase can sense the DNA damage is still an open question. Does an untargeted ATP-dependent chromatin remodeling, DNA transcription or replication mediated disturbance/disruption of nucleosomes are helping BER to initiate in a “stochastic” manner? If this is the case, a significant proportion of lesions might simply remain unrepaired until exposed by “chance” to factors that help nucleosomal DNA accessibility.

Several studies support the notion that binding of a “pioneering” factor to chromatin organized DNA constitutes the primary event in DNA-templated reactions, such as transcription, which leads to chromatin changes and exposure to other proteins [170–174]. This model implies the existence of pioneering factors that can interact with DNA sequences, even when they are wrapped into nucleosomes. Access for these factors might be facilitated by an opportunistic interaction during spontaneous nucleosome unwrapping. On the other hand, ATP-dependent chromatin remodeling enzymes are highly abundant in the cell, with about one remodeling complex per ten nucleosomes. The majority of them can generate metastable remosomes that provide a versatile access to any nucleosomal sequence position. The generation of remosomes could help the probabilistic (random) access enhancement of repair (and transcription) initiating enzymes to DNA. As the glycosylases “scan” sites, they can recognize and stably bind to the respective lesions that are located on transiently exposed free DNA loop within the “remosomes”. Beside the recognition and the first step of lesion processing, the glycosylase can further participate in establishing competence for subsequent repair proteins, through recruitment of other chromatin-associated factors.

It is also tempting to speculate that pervasive transcription might be used by cells to monitor DNA integrity through facilitating DNA repair and activating DNA damage signaling. Indeed, the quasi-stochastic RNA Pol II “scanning” of the genomic DNA, results in the synthesis of RNA copies containing the majority of genomic DNA sequences from both euchromatin and heterochromatin regions, known as non-coding RNAs (ncRNAs) [175–177]. This non-promoter regulated pervasive (intergenic) transcription could play a role of perfect DNA damage sensor through the induction of local nucleosome/chromatin structural perturbation, throughout the entire genome, thus facilitating access of BER initiating enzymes. When RNA Pol II complexes are blocked (or slowed down) at sites of DNA lesions, they would be able to promote recruitment of BER proteins to perform transcription coupled repair (TCR) in an evocative way as TC-NER. This hypothesis is fully in accordance with the observations of FACT recruitment on sites of NER [147] and BER [105] as well as with CSB accumulation [165] to oxidatively generated DNA micro-damage [165]. An illustration of these hypotheses is presented in Fig. 3.

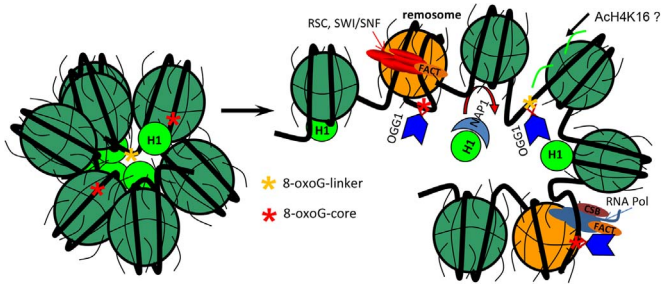

Fig. 3. Working model BER initiation, involving quasi-stochastic generation of remosomes linker histone eviction mediated by the SWI/SNF family of ATP-dependent chromatin remodeler, histone chaperones.

It is reasonable to question whether intergenic transcription induced chromatin disruption plays a role in priming the repair or its initiation is dependent on other preceding chromatin-related events. By analogy with promoter regulated gene transcription, which requires ATP-dependent nucleosome remodeling, one can speculate that remosomes play a role in intergenic transcription initiation. Whereas major interest is placed on the biological role of remodelers as targeted species, one can imagine that the quasi-randomly generated remosomes throughout the entire genome could have a role in pervasive transcription and DNA repair. An important consequence would be that the distinction between transcription coupled and global genome repair has to be reconsidered and generalized in terms of chromatin-related effects. Noteworthy, these considerations apply not only to BER, but also to some aspects of NER initiation too.

Although the majority of key factors that promote access of BER initiation enzymes at damage sites within chromatin have been identified, the underlying molecular mechanisms are not completely characterized and understood. In particular, the role of chromatin remodeling factors and transcription in chromatin dynamics would deserve further investigation. Some key points to address are whether RNA polymerases are initiators of repair, by detecting DNA lesions and recruiting factors helping chromatin remodeling such as CSB and FACT or random nucleosomes remodeling favors repair without requirement of transcription. This can be done *in vitro* by using purified proteins or/ and cellular extracts and transcription/repair competent reconstituted chromatin arrays of positioned nucleosomes containing single BER lesions. The use of such systems would enable dynamic study of repair relatively closely to cellular conditions. *In vivo* experiments can be designed to locally generate “pure” BER-lesions by laser micro-photosensitization in cells stably expressing Killer Red [178] or miniSOG [179] tagged DNA-interacting proteins. For instance a recent use of Killer Red revealed differences in recruitment of repair proteins to heterochromatin and euchromatin [180]. In combination with live cell imaging fluorescent microscopy and protein depletion (RNAi KD, KO *etc.*) this would enable to carry out real time-resolved experiments on BER factors recruitment at defined chromatin locations in presence or absence of any protein of interest.

Acknowledgments

This work was supported by institutional funds from, the Université de Grenoble Alpes-UGA to SD, the Centre National de la Recherche Scientifique-CNRS to DA and SD, the Institut National de la Santé et de la Recherche Médicale-INSERM to SD and HM and by grants from: the Agence Nationale de la Recherche-ANR (ANR-12-BSV5-0017 « CHROME » to DA and SD), the Ligue Nationale contre le Cancer (Équipe labellisée to AH and SD, and post-doc support to HM), the European Union's Seventh Framework Programme FP7/2007–2013/ COST Action CM1201 “Biomimetic Radical Chemistry” to DA, the Fundação de Amparo à Pesquisa do Estado de São Paulo-FAPESP (No. 2012/12663-1, CEPID Redoxoma No. 2013/07937-8), (Conselho Nacional para o Desenvolvimento Científico e Tecnológico-CNPq (No. 301307/2013-0 and Pro-Reitoria de Pesquisa da Universidade de São Paulo-PRPUSP (NAP Redoxoma No. 2011.1.9352.1.8).

E. Ben Simon is acknowledged for the technical assistance as well as Richard Lavery for kindly providing the MD model of remosomes in Fig. 2.

References

[1] T. Lindahl, Instability and decay of the primary structure of DNA, Nature 362 (6422) (1993) 709–715.
[2] M.D. Evans, M. Dizdaroglu, M.S. Cooke, Oxidative DNA damage and disease: induction, repair and significance, Mutat. Res. 567 (1) (2004) 1–61.
[3] J. Cadet, J.L. Ravanat, M. TavernaPorro, H. Menoni, D. Angelov, Oxidatively generated complex DNA damage: tandem and clustered lesions, Cancer Lett. 327 (1–2) (2012) 5–15.
[4] J. Cadet, J.R. Wagner, DNA base damage by reactive oxygen species, oxidizing agents, and UV radiation, Cold Spring Harb. Perspect. Biol. 5 (2) (2013).
[5] J. Cadet, J.R. Wagner, V. Shafirovich, N.E. Geacintov, One-electron oxidation reactions of purine and pyrimidine bases in cellular DNA, Int. J. Radiat. Biol. 90 (6) (2014) 423–432.
[6] J.H. Hoeijmakers, DNA damage, aging, and cancer, N. Engl. J. Med. 361 (15) (2009) 1475–1485.
[7] S. Maynard, S.H. Schurman, C. Harboe, N.C. de Souza-Pinto, V.A. Bohr, Base excision repair of oxidative DNA damage and association with cancer and aging, Carcinogenesis 30 (1) (2009) 2–10.
[8] S.S. Wallace, D.L. Murphy, J.B. Sweasy, Base excision repair and cancer, Cancer Lett. 327 (1–2) (2012) 73–89.
[9] J. Lukas, C. Lukas, J. Bartek, More than just a focus: the chromatin response to DNA damage and its role in genome integrity maintenance, Nat. Cell Biol. 13 (10) (2011) 1161–1169.
[10] J.A. Marteijn, H. Lans, W. Vermeulen, J.H. Hoeijmakers, Understanding nucleotide excision repair and its roles in cancer and ageing, Nat. Rev. Mol. Cell Biol. 15 (7) (2014) 465–481.
[11] O.D. Scharer, Nucleotide excision repair in eukaryotes, Cold Spring Harb. Perspect. Biol. 5 (10) (2013) a012609.
[12] M.L. Hegde, T.K. Hazra, S. Mitra, Early steps in the DNA base excision/single-strand interruption repair pathway in mammalian cells, Cell Res. 18 (1) (2008) 27–47.
[13] H.E. Krokan, R. Standal, G. Slupphaug, DNA glycosylases in the base excision repair of DNA, Biochem. J. 325 (Pt 1) (1997) 1–16.
[14] K.W. Caldecott, XRCC1 and DNA strand break repair, DNA Repair 2 (9) (2003) 955–969.
[15] D. Simsek, A. Furda, Y. Gao, J. Artus, E. Brunet, A.K. Hadjantonakis, B. Van Houten, S. Shuman, P.J. McKinnon, M. Jasin, Crucial role for DNA ligase III in mitochondria but not in Xrcc1-dependent repair, Nature 471 (7337) (2011) 245–248.
[16] H. Arakawa, T. Bednar, M. Wang, K. Paul, E. Mladenov, A.A. Bencsik-Theilen, G. Iliakis, Functional redundancy between DNA ligases I and III in DNA replication in vertebrate cells, Nucleic Acids Res. 40 (6) (2012) 2599–2610.
[17] A. Klungland, I. Rosewell, S. Hollenbach, E. Larsen, G. Daly, B. Epe, E. Seeberg, T. Lindahl, D.E. Barnes, Accumulation of premutagenic DNA lesions in mice defective in removal of oxidative base damage, Proc. Natl. Acad. Sci. 96 (23) (1999) 13300–13305.
[18] J. Cadet, T. Douki, D. Gasparutto, J.L. Ravanat, Oxidative damage to DNA: formation, measurement and biochemical features, Mutat. Res. 531 (1–2) (2003) 5–23.
[19] R.W. Maul, H. Saribasak, S.A. Martomo, R.L. McClure, W. Yang, A. Vaisman, H.S. Gramlich, D.G. Schatz, R. Woodgate, D.M. Wilson 3rdP.J. Gearhart, Uracil residues dependent on the deaminase AID in immunoglobulin gene variable and switch regions, Nat. Immunol. 12 (1) (2011) 70–76.
[20] S. Shibutani, M. Takeshita, A.P. Grollman, Insertion of specific bases during DNA synthesis past the oxidation-damaged base 8-oxodG, Nature 349 (6308) (1991) 431–434.
[21] B. Kavli, O. Sundheim, M. Akbari, M. Otterlei, H. Nilsen, F. Skorpen, P.A. Aas, L. Hagen, H.E. Krokan, G. Slupphaug, hUNG2 is the major repair enzyme for removal of uracil from U:a matches, U:G mismatches, and U in single-stranded DNA, with hSMUG1 as a broad specificity backup, J. Biol. Chem. 277 (42) (2002) 39926–39936.
[22] P. Aller, M.A. Rould, M. Hogg, S.S. Wallace, S. Doublie, A structural rationale for stalling of a replicative DNA polymerase at the most common oxidative thymine lesion, thymine glycol, Proc. Natl. Acad. Sci. 104 (3) (2007) 814–818.
[23] F. Brueckner, U. Hennecke, T. Carell, P. Cramer, CPD damage recognition by transcribing RNA polymerase II, Science 315 (5813) (2007) 859–862.
[24] C. Walmacq, A.C. Cheung, M.L. Kireeva, L. Lubkowska, C. Ye, D. Gotte, J.N. Strathern, T. Carell, P. Cramer, M. Kashlev, Mechanism of translesion transcription by RNA polymerase II and its role in cellular resistance to DNA damage, Mol. Cell 46 (1) (2012) 18–29.
[25] A. Ciccia, S.J. Elledge, The DNA damage response: making it safe to play with knives, Mol. Cell 40 (2) (2010) 179–204.
[26] D. Bregeon, P.A. Peignon, A. Sarasin, Transcriptional mutagenesis induced by 8-oxoguanine in mammalian cells, PLoS Genet. 5 (7) (2009) e1000577.
[27] M.L. Rinne, Y. He, B.F. Pachkowski, J. Nakamura, M.R. Kelley, N-methylpurine DNA glycosylase overexpression increases alkylation sensitivity by rapidly removing non-toxic 7-methylguanine adducts, Nucleic Acids Res. 33 (9) (2005) 2859–2867.
[28] Y. Yoshikawa, A. Yamasaki, K. Takatori, M. Suzuki, J. Kobayashi, M. Takao, Q.M. Zhang-Akiyama, Excess processing of oxidative damaged bases causes hypersensitivity to oxidative stress and low dose rate irradiation, Free Radic. Res. 49 (10) (2015) 1239–1248.
[29] W.P. Roos, B. Kaina, DNA damage-induced cell death: from specific DNA lesions to the DNA damage response and apoptosis, Cancer Lett. 332 (2) (2013) 237–248.
[30] E. Larsen, K. Kwon, F. Coin, J.M. Egly, A. Klungland, Transcription activities at 8-oxoG lesions in DNA, DNA Repair 3 (11) (2004) 1457–1468.
[31] N. Kitsera, D. Stathis, B. Luhnsdorf, H. Muller, T. Carell, B. Epe, A. Khobta, 8-Oxo-7,8-dihydroguanine in DNA does not constitute a barrier to transcription, but is converted into transcription-blocking damage by OGG1, Nucleic Acids Res. 39 (14) (2011) 5926–5934.
[32] N. Charlet-Berguerand, S. Feuerhahn, S.E. Kong, H. Ziserman, J.W. Conaway, R. Conaway, J.M. Egly, RNA polymerase II bypass of oxidative DNA damage is regulated by transcription elongation factors, EMBO J. 25 (23) (2006) 5481–5491.
[33] A.R. Cutter, J.J. Hayes, A brief review of nucleosome structure, FEBS Lett. 589 (20 Pt A) (2015) 2914–2922.
[34] K. Luger, A.W. Mader, R.K. Richmond, D.F. Sargent, T.J. Richmond, Crystal structure of the nucleosome core particle at 2.8 A resolution, Nature 389 (6648) (1997) 251–260.
[35] J.C. Fromme, A. Banerjee, G.L. Verdine, DNA glycosylase recognition and catalysis, Curr. Opin. Struct. Biol. 14 (1) (2004) 43–49.
[36] K. Hitomi, S. Iwai, J.A. Tainer, The intricate structural chemistry of base excision repair machinery: implications for DNA damage recognition, removal, and repair, DNA Repair 6 (4) (2007) 410–428.
[37] G.L. Dianov, Monitoring base excision repair by in vitro assays, Toxicology 193 (1–2) (2003) 35–41.
[38] B. Pascucci, G. Maga, U. Hubscher, M. Bjoras, E. Seeberg, I.D. Hickson, G. Villani, C. Giordano, L. Cellai, E. Dogliotti, Reconstitution of the base excision repair pathway for 7,8-dihydro-8-oxoguanine with purified human proteins, Nucleic Acids Res. 30 (10) (2002) 2124–2130.
[39] Y. Kubota, R.A. Nash, A. Klungland, P. Schar, D.E. Barnes, T. Lindahl, Reconstitution of DNA base excision-repair with purified human proteins: interaction between DNA polymerase beta and the XRCC1 protein, EMBO J. 15 (23) (1996) 6662–6670.
[40] A.J. Balliano, J.J. Hayes, Base excision repair in chromatin: insights from reconstituted systems, DNA Repair 36 (2015) 77–85.
[41] T. Lindahl, An N-glycosidase from Escherichia coli that releases free uracil from DNA containing deaminated cytosine residues, Proc. Natl. Acad. Sci. 71 (9) (1974) 3649–3653.
[42] H. Nilsen, T. Lindahl, A. Verreault, DNA base excision repair of uracil residues in reconstituted nucleosome core particles, EMBO J. 21 (21) (2002) 5943–5952.
[43] B.C. Beard, J.J. Stevenson, S.H. Wilson, M.J. Smerdon, Base excision repair in nucleosomes lacking histone tails, DNA Repair 4 (2) (2005) 203–209.
[44] B.C. Beard, S.H. Wilson, M.J. Smerdon, Suppressed catalytic activity of base excision repair enzymes on rotationally positioned uracil in nucleosomes, Proc. Natl. Acad. Sci. 100 (13) (2003) 7465–7470.
[45] H.A. Cole, J.M. Tabor-Godwin, J.J. Hayes, Uracil DNA glycosylase activity on nucleosomal DNA depends on rotational orientation of targets, J. Biol. Chem. 285 (4) (2010) 2876–2885.
[46] J.D. Anderson, J. Widom, Sequence and position-dependence of the equilibrium accessibility of nucleosomal DNA target sites, J. Mol. Biol. 296 (4) (2000) 979–987.
[47] Y. Ye, M.R. Stahley, J. Xu, J.I. Friedman, Y. Sun, J.N. McKnight, J.J. Gray, G.D. Bowman, J.T. Stivers, Enzymatic excision of uracil residues in nucleosomes depends on the local DNA structure and dynamics, Biochemistry 51 (30) (2012) 6028–6038.
[48] J.M. Hinz, Y. Rodriguez, M.J. Smerdon, Rotational dynamics of DNA on the nucleosome surface markedly impact accessibility to a DNA repair enzyme, Proc. Natl. Acad. Sci. 107 (10) (2010) 4646–4651.
[49] I.D. Odell, S.S. Wallace, D.S. Pederson, Rules of engagement for base excision repair in chromatin, J. Cell Physiol. 228 (2) (2013) 258–266.
[50] R.L. Maher, A. Prasad, O. Rizvanova, S.S. Wallace, D.S. Pederson, Contribution of DNA unwrapping from histone octamers to the repair of oxidatively damaged DNA in nucleosomes, DNA Repair 12 (11) (2013) 964–971.
[51] A. Prasad, S.S. Wallace, D.S. Pederson, Initiation of base excision repair of

oxidative lesions in nucleosomes by the human, bifunctional DNA glycosylase NTH1, Mol. Cell Biol. 27 (24) (2007) 8442–8453.
[52] T. Lindahl, P. Karran, R.D. Wood, DNA excision repair pathways, Curr. Opin. Genet. Dev. 7 (2) (1997) 158–169.
[53] F. Dantzer, M. Bjoras, L. Luna, A. Klungland, E. Seeberg, Comparative analysis of 8-oxoG:C, 8-oxoG A:C and C:CDNA repair in extracts from wild type or 8-oxoG DNA glycosylase deficient mammalian and bacterial cells, DNA Repair 2 (6) (2003) 707–718.
[54] J.P. Radicella, C. Dherin, C. Desmaze, M.S. Fox, S. Boiteux, Cloning and characterization of hOGG1, a human homolog of the OGG1 gene of Saccharomyces cerevisiae, Proc. Natl. Acad. Sci. 94 (15) (1997) 8010–8015.
[55] T.A. Rosenquist, D.O. Zharkov, A.P. Grollman, Cloning and characterization of a mammalian 8-oxoguanine DNA glycosylase, Proc. Natl. Acad. Sci. 94 (14) (1997) 7429–7434.
[56] P.A. van der Kemp, D. Thomas, R. Barbey, R. de Oliveira, S. Boiteux, Cloning and expression in Escherichia coli of the OGG1 gene of Saccharomyces cerevisiae, which codes for a DNA glycosylase that excises 7,8-dihydro-8-oxoguanine and 2,6-diamino-4-hydroxy-5-N-methylformamidopyrimidine, Proc. Natl. Acad. Sci. 93 (11) (1996) 5197–5202.
[57] D.O. Zharkov, T.A. Rosenquist, S.E. Gerchman, A.P. Grollman, Substrate specificity and reaction mechanism of murine 8-oxoguanine-DNA glycosylase, J. Biol. Chem. 275 (37) (2000) 28607–28617.
[58] H. Menoni, D. Gasparutto, A. Hamiche, J. Cadet, S. Dimitrov, P. Bouvet, D. Angelov, ATP-dependent chromatin remodeling is required for base excision repair in conventional but not in variant H2A.Bbd nucleosomes, Mol. Cell Biol. 27 (17) (2007) 5949–5956.
[59] R. Hara, A. Sancar, The SWI/SNF chromatin-remodeling factor stimulates repair by human excision nuclease in the mononucleosome core particle, Mol. Cell Biol. 22 (19) (2002) 6779–6787.
[60] R. Hara, A. Sancar, Effect of damage type on stimulation of human excision nuclease by SWI/SNF chromatin remodeling factor, Mol. Cell Biol. 23 (12) (2003) 4121–4125.
[61] H. Menoni, M.S. Shukla, V. Gerson, S. Dimitrov, D. Angelov, Base excision repair of 8-oxoG in dinucleosomes, Nucleic Acids Res. 40 (2) (2012) 692–700.
[62] S. Nakanishi, R. Prasad, S.H. Wilson, M. Smerdon, Different structural states in oligonucleosomes are required for early versus late steps of base excision repair, Nucleic Acids Res. 35 (13) (2007) 4313–4321.
[63] W. Czaja, P. Mao, M.J. Smerdon, Chromatin remodelling complex RSC promotes base excision repair in chromatin of Saccharomyces cerevisiae, DNA Repair 16 (2014) 35–43.
[64] F. Gong, D. Fahy, H. Liu, W. Wang, M.J. Smerdon, Role of the mammalian SWI/SNF chromatin remodeling complex in the cellular response to UV damage, Cell Cycle 7 (8) (2008) 1067–1074.
[65] J.M. Hinz, W. Czaja, Facilitation of base excision repair by chromatin remodeling, DNA Repair 36 (2015) 91–97.
[66] O. Bell, V.K. Tiwari, N.H. Thoma, D. Schubeler, Determinants and dynamics of genome accessibility, Nat. Rev. Genet. 12 (8) (2011) 554–564.
[67] T. Kouzarides, Chromatin modifications and their function, Cell 128 (4) (2007) 693–705.
[68] V. Stefanovsky, S.I. Dimitrov, D. Angelov, I.G. Pashev, Interactions of acetylated histones with DNA as revealed by UV laser induced histone-DNA crosslinking, Biochem. Biophys. Res. Commun. 164 (1) (1989) 304–310.
[69] S.I. Dimitrov, V. Stefanovsky, L. Karagyozov, D. Angelov, I.G. Pashev, The enhancers and promoters of the Xenopus laevis ribosomal spacer are associated with histones upon active transcription of the ribosomal genes, Nucleic Acids Res. 18 (21) (1990) 6393–6397.
[70] V. Mutskov, D. Gerber, D. Angelov, J. Ausio, J. Workman, S. Dimitrov, Persistent interactions of core histone tails with nucleosomal DNA following acetylation and transcription factor binding, Mol. Cell Biol. 18 (11) (1998) 6293–6304.
[71] B. Dorigo, T. Schalch, A. Kulangara, S. Duda, R.R. Schroeder, T.J. Richmond, Nucleosome arrays reveal the two-start organization of the chromatin fiber, Science 306 (5701) (2004) 1571–1573.
[72] M. Shogren-Knaak, H. Ishii, J.M. Sun, M.J. Pazin, J.R. Davie, C.L. Peterson, Histone H4-K16 acetylation controls chromatin structure and protein interactions, Science 311 (5762) (2006) 844–847.
[73] D.J. Tremethick, Higher-order structures of chromatin: the elusive 30 nm fiber, Cell 128 (4) (2007) 651–654.
[74] D. Rossetto, N. Avvakumov, J. Cote, Histone phosphorylation: a chromatin modification involved in diverse nuclear events, Epigenetics 7 (10) (2012) 1098–1108.
[75] R. Waters, P. van Eijk, S. Reed, Histone modification and chromatin remodeling during NER, DNA Repair 36 (2015) 105–113.
[76] S. Li, Implication of posttranslational histone modifications in nucleotide excision repair, Int. J. Mol. Sci. 13 (10) (2012) 12461–12486.
[77] A. Gospodinov, Z. Herceg, Shaping chromatin for repair, Mutat. Res. 752 (1) (2013) 45–60.
[78] R. Waters, S.H. Reed, Y. Yu, Y. Teng, Chromatin modifications and nucleotide excision repair, SEB Exp. Biol. Ser. 59 (2008) 189–201.
[79] T. Clouaire, G. Legube, DNA double strand break repair pathway choice: a chromatin based decision? Nucleus 6 (2) (2015) 107–113.
[80] N.C. House, M.R. Koch, C.H. Freudenreich, Chromatin modifications and DNA repair: beyond double-strand breaks, Front. Genet. 5 (2014) 296.
[81] W.F. Marzluff, P. Gongidi, K.R. Woods, J. Jin, L.J. Maltais, The human and mouse replication-dependent histone genes, Genomics 80 (5) (2002) 487–498.
[82] M.S. Cheema, J. Ausio, The Structural Determinants behind the Epigenetic role of Histone variants, Genes 6 (3) (2015) 685–713.
[83] C. Volle, Y. Dalal, Histone variants: the tricksters of the chromatin world, Curr. Opin. Genet. Dev. 25 (2014) 8–14,138.
[84] S. Venkatesh, J.L. Workman, Histone exchange, chromatin structure and the regulation of transcription, Nat. Rev. Mol. Cell Biol. 16 (3) (2015) 178–189.
[85] Z.A. Gurard-Levin, J.P. Quivy, G. Almouzni, Histone chaperones: assisting histone traffic and nucleosome dynamics, Annu. Rev. Biochem. 83 (2014) 487–517.
[86] F. Mattiroli, S. D'Arcy, K. Luger, The right place at the right time: chaperoning core histone variants, EMBO Rep. 16 (11) (2015) 1454–1466.
[87] S.E. Polo, G. Almouzni, Chromatin dynamics after DNA damage: the legacy of the access-repair-restore model, DNA Repair 36 (2015) 114–121.
[88] P. Chen, J. Zhao, G. Li, Histone variants in development and diseases, J. Genet. Genom. 40 (7) (2013) 355–365.
[89] L.M. Zink, S.B. Hake, Histone variants: nuclear function and disease, Curr. Opin. Genet. Dev. 37 (2016) 82–89.
[90] G. Soria, S.E. Polo, G. Almouzni, Prime, repair, restore: the active role of chromatin in the DNA damage response, Mol. Cell 46 (6) (2012) 722–734.
[91] E.P. Rogakou, D.R. Pilch, A.H. Orr, V.S. Ivanova, W.M. Bonner, DNA double-stranded breaks induce histone H2AX phosphorylation on serine 139, J. Biol. Chem. 273 (10) (1998) 5858–5868.
[92] S.E. Polo, D. Roche, G. Almouzni, New histone incorporation marks sites of UV repair in human cells, Cell 127 (3) (2006) 481–493.
[93] S.G. Zeitlin, N.M. Baker, B.R. Chapados, E. Soutoglou, J.Y. Wang, M.W. Berns, D.W. Cleveland, Double-strand DNA breaks recruit the centromeric histone CENP-A, Proc. Natl. Acad. Sci. 106 (37) (2009) 15762–15767.
[94] D.A. Nusinow, I. Hernandez-Munoz, T.G. Fazzio, G.M. Shah, W.L. Kraus, B. Panning, Poly(ADP-ribose) polymerase 1 is inhibited by a histone H2A variant, MacroH2A, and contributes to silencing of the inactive X chromosome, J. Biol. Chem. 282 (17) (2007) 12851–12859.
[95] C.E. Strom, F. Johansson, M. Uhlen, C.A. Szigyarto, K. Erixon, T. Helleday, Poly (ADP-ribose) polymerase (PARP) is not involved in base excision repair but PARP inhibition traps a single-strand intermediate, Nucleic Acids Res. 39 (8) (2011) 3166–3175.
[96] D. Angelov, A. Molla, P.Y. Perche, F. Hans, J. Cote, S. Khochbin, P. Bouvet, S. Dimitrov, The histone variant macroH2A interferes with transcription factor binding and SWI/SNF nucleosome remodeling, Mol. Cell 11 (4) (2003) 1033–1041.
[97] D.W. Abbott, B.P. Chadwick, A.A. Thambirajah, J. Ausio, Beyond the Xi: macroH2A chromatin distribution and post-translational modification in an avian system, J. Biol. Chem. 280 (16) (2005) 16437–16445.
[98] C.M. Doyen, F. Montel, T. Gautier, H. Menoni, C. Claudet, M. Delacour-Larose, D. Angelov, A. Hamiche, J. Bednar, C. Faivre-Moskalenko, P. Bouvet, S. Dimitrov, Dissection of the unusual structural and functional properties of the variant H2A.Bbd nucleosome, EMBO J. 25 (18) (2006) 4234–4244.
[99] F. Montel, H. Menoni, M. Castelnovo, J. Bednar, S. Dimitrov, D. Angelov, C. Faivre-Moskalenko, The dynamics of individual nucleosomes controls the chromatin condensation pathway: direct atomic force microscopy visualization of variant chromatin, Biophys. J. 97 (2) (2009) 544–553.
[100] Y. Roulland, K. Ouararhni, M. Naidenov, L. Ramos, M. Shuaib, S.H. Syed, I.N. Lone, R. Boopathi, E. Fontaine, G. Papai, H. Tachiwana, T. Gautier, D. Skoufias, K. Padmanabhan, J. Bednar, H. Kurumizaka, P. Schultz, D. Angelov, A. Hamiche, S. Dimitrov, The flexible ends of CENP-A nucleosome are required for mitotic fidelity, Mol. Cell 63 (4) (2016) 674–685.
[101] M.S. Shukla, S.H. Syed, D. Goutte-Gattat, J.L. Richard, F. Montel, A. Hamiche, A. Travers, C. Faivre-Moskalenko, J. Bednar, J.J. Hayes, D. Angelov, S. Dimitrov, The docking domain of histone H2A is required for H1 binding and RSC-mediated nucleosome remodeling, Nucleic Acids Res. 39 (7) (2011) 2559–2570.
[102] S.H. Syed, M. Boulard, M.S. Shukla, T. Gautier, A. Travers, J. Bednar, C. Faivre-Moskalenko, S. Dimitrov, D. Angelov, The incorporation of the novel histone variant H2AL2 confers unusual structural and functional properties of the nucleosome, Nucleic Acids Res. 37 (14) (2009) 4684–4695.
[103] K.J. Polach, J. Widom, Mechanism of protein access to specific DNA sequences in chromatin: a dynamic equilibrium model for gene regulation, J. Mol. Biol. 254 (2) (1995) 130–149.
[104] K.J. Polach, J. Widom, A model for the cooperative binding of eukaryotic regulatory proteins to nucleosomal target sites, J. Mol. Biol. 258 (5) (1996) 800–812.
[105] J.L. Charles Richard, M.S. Shukla, H. Menoni, K. Ouararhni, I.N. Lone, Y. Roulland, C. Papin, E. Ben Simon, T. Kundu, A. Hamiche, D. Angelov, S. Dimitrov, FACT assists base excision repair by boosting the remodeling activity of RSC, PLoS Genet. 12 (7) (2016) e1006221.
[106] C. Wu, A. Travers, A 'one-pot' assay for the accessibility of DNA in a nucleosome core particle, Nucleic Acids Res. 32 (15) (2004) e122.
[107] S. Meyer, N.B. Becker, S.H. Syed, D. Goutte-Gattat, M.S. Shukla, J.J. Hayes, D. Angelov, J. Bednar, S. Dimitrov, R. Everaers, From crystal and NMR structures, footprints and cryo-electron-micrographs to large and soft structures: nanoscale modeling of the nucleosomal stem, Nucleic Acids Res. 39 (21) (2011) 9139–9154.
[108] S. Pennings, G. Meersseman, E.M. Bradbury, Linker histones H1 and H5 prevent the mobility of positioned nucleosomes, Proc. Natl. Acad. Sci. 91 (22) (1994) 10275–10279.
[109] S.H. Syed, D. Goutte-Gattat, N. Becker, S. Meyer, M.S. Shukla, J.J. Hayes, R. Everaers, D. Angelov, J. Bednar, S. Dimitrov, Single-base resolution mapping of H1–nucleosome interactions and 3D organization of the nucleosome, Proc. Natl. Acad. Sci. 107 (21) (2010) 9620.
[110] K. Ura, J.J. Hayes, A.P. Wolffe, A positive role for nucleosome mobility in the transcriptional activity of chromatin templates: restriction by linker histones, EMBO J. 14 (15) (1995) 3752–3765.

[111] G. Meersseman, S. Pennings, E.M. Bradbury, Mobile nucleosomes–a general behavior, EMBO J. 11 (8) (1992) 2951–2959.
[112] K. Havas, I. Whitehouse, T. Owen-Hughes, ATP-dependent chromatin remodeling activities, Cell Mol. Life Sci. 58 (5–6) (2001) 673–682.
[113] Y. Bao, X. Shen, SnapShot: chromatin remodeling complexes, Cell 129 (3) (2007) 632.
[114] G. Langst, P.B. Becker, Nucleosome mobilization and positioning by ISWI-containing chromatin-remodeling factors, J. Cell Sci. 114 (2001) 2561–2568.
[115] B.R. Cairns, Chromatin remodeling complexes: strength in diversity, precision through specialization, Curr. Opin. Genet. Dev. 15 (2) (2005) 185–190.
[116] C.R. Clapier, M.M. Kasten, T.J. Parnell, R. Viswanathan, H. Szerlong, G. Sirinakis, Y. Zhang, B.R. Cairns, Regulation of DNA Translocation Efficiency within the Chromatin Remodeler RSC/Sth1 Potentiates Nucleosome Sliding and Ejection, Mol. Cell 62 (3) (2016) 453–461.
[117] A. Hamiche, J.G. Kang, C. Dennis, H. Xiao, C. Wu, Histone tails modulate nucleosome mobility and regulate ATP-dependent nucleosome sliding by NURF, Proc. Natl. Acad. Sci. 98 (25) (2001) 14316–14321.
[118] G. Langst, E.J. Bonte, D.F. Corona, P.B. Becker, Nucleosome movement by CHRAC and ISWI without disruption or trans- displacement of the histone octamer, Cell 97 (7) (1999) 843–852.
[119] G. Lia, E. Praly, H. Ferreira, C. Stockdale, Y.C. Tse-Dinh, D. Dunlap, V. Croquette, D. Bensimon, T. Owen-Hughes, Direct observation of DNA distortion by the RSC complex, Mol. Cell 21 (3) (2006) 417–425.
[120] F. Montel, M. Castelnovo, H. Menoni, D. Angelov, S. Dimitrov, C. Faivre-Moskalenko, RSC remodeling of oligo-nucleosomes: an atomic force microscopy study, Nucleic Acids Res. 39 (7) (2011) 2571–2579.
[121] A. Saha, J. Wittmeyer, B.R. Cairns, Chromatin remodeling through directional DNA translocation from an internal nucleosomal site, Nat. Struct. Mol. Biol. 12 (9) (2005) 747–755.
[122] Y. Lorch, M. Zhang, R.D. Kornberg, Histone octamer transfer by a chromatin-remodeling complex, Cell 96 (3) (1999) 389–392.
[123] M.S. Kobor, S. Venkatasubrahmanyam, M.D. Meneghini, J.W. Gin, J.L. Jennings, A.J. Link, H.D. Madhani, J. Rine, A protein complex containing the conserved Swi2/Snf2-related ATPase Swr1p deposits histone variant H2A.Z into euchromatin, PLoS Biol. 2 (5) (2004) E131.
[124] G. Mizuguchi, X. Shen, J. Landry, W.-H. Wu, S. Sen, C. Wu, ATP-driven exchange of histone H2AZ variant catalyzed by SWR1 chromatin remodeling complex, Science 303 (5656) (2004) 343–348.
[125] B.R. Cairns, Y. Lorch, Y. Li, M. Zhang, L. Lacomis, H. Erdjument-Bromage, P. Tempst, J. Du, B. Laurent, R.D. Kornberg, RSC, an essential, abundant chromatin-remodeling complex, Cell 87 (7) (1996) 1249–1260.
[126] C. Muchardt, M. Yaniv, ATP-dependent chromatin remodelling: SWI/SNF and Co. are on the job, J. Mol. Biol. 293 (2) (1999) 187–198.
[127] P. Sudarsanam, F. Winston, The Swi/Snf family nucleosome-remodeling complexes and transcriptional control, Trends Genet. 16 (8) (2000) 345–351.
[128] T. Tsukiyama, J. Palmer, C.C. Landel, J. Shiloach, C. Wu, Characterization of the Imitation Switch subfamily of ATP-dependent chromatin-remodeling factors in Saccharomyces cerevisiae, Genes Dev. 13 (6) (1999) 686–697.
[129] G. Bennett, M. Papamichos-Chronakis, C.L. Peterson, DNA repair choice defines a common pathway for recruitment of chromatin regulators, Nat. Commun. 4 (2013) 2084.
[130] A. Ramachandran, M. Omar, P. Cheslock, G.R. Schnitzler, Linker histone H1 modulates nucleosome remodeling by human SWI/SNF, J. Biol. Chem. 278 (49) (2003) 48590–48601.
[131] D.A. Hill, A.N. Imbalzano, Human SWI/SNF nucleosome remodeling activity is partially inhibited by linker histone H1, Biochemistry 39 (38) (2000) 11649–11656.
[132] V.K. Maier, M. Chioda, D. Rhodes, P.B. Becker, ACF catalyses chromatosome movements in chromatin fibres, EMBO J. 27 (6) (2008) 817–826.
[133] J. Clausell, N. Happel, T.K. Hale, D. Doenecke, M. Beato, Histone H1 subtypes differentially modulate chromatin condensation without preventing ATP-dependent remodeling by SWI/SNF or NURF, PLoS One 4 (10) (2009) e0007243.
[134] M.A. Lever, J.P. Th'ng, X. Sun, M.J. Hendzel, Rapid exchange of histone H1.1 on chromatin in living human cells, Nature 408 (6814) (2000) 873–876.
[135] T. Misteli, A. Gunjan, R. Hock, M. Bustin, D.T. Brown, Dynamic binding of histone H1 to chromatin in living cells, Nature 408 (6814) (2000) 877–881.
[136] Y. Dou, J. Bowen, Y. Liu, M.A. Gorovsky, Phosphorylation and an ATP-dependent process increase the dynamic exchange of H1 in chromatin, J. Cell Biol. 158 (7) (2002) 1161–1170.
[137] J. Ocampo, R.V. Chereji, P.R. Eriksson, D.J. Clark, The ISW1 and CHD1 ATP-dependent chromatin remodelers compete to set nucleosome spacing in vivo, Nucleic Acids Res. 44 (10) (2016) 4625–4635.
[138] D.F. Corona, G. Siriaco, J.A. Armstrong, N. Snarskaya, S.A. McClymont, M.P. Scott, J.W. Tamkun, ISWI regulates higher-order chromatin structure and histone H1 assembly in vivo, PLoS Biol. 5 (9) (2007) e232.
[139] V.K. Gangaraju, B. Bartholomew, Mechanisms of ATP dependent chromatin remodeling, Mutat. Res. 618 (1–2) (2007) 3–17.
[140] B.R. Cairns, Chromatin remodeling: insights and intrigue from single-molecule studies, Nat. Struct. Mol. Biol. 14 (11) (2007) 989–996.
[141] M.S. Shukla, S.H. Syed, F. Montel, C. Faivre-Moskalenko, J. Bednar, A. Travers, D. Angelov, S. Dimitrov, Remosomes: RSC generated non-mobilized particles with approximately 180 bp DNA loosely associated with the histone octamer, Proc. Natl. Acad. Sci. 107 (5) (2010) 1936–1941.
[142] M. Pasi, R. Lavery, Structure and dynamics of DNA loops on nucleosomes studied with atomistic, microsecond-scale molecular dynamics, Nucleic Acids Res. 44 (11) (2016) 5450–5456.
[143] N.R. Gassman, S.H. Wilson, Micro-irradiation tools to visualize base excision repair and single-strand break repair, DNA Repair 31 (2015) 52–63.
[144] A. Khobta, N. Kitsera, B. Speckmann, B. Epe, 8-OxoguanineDNA glycosylase (Ogg1) causes a transcriptional inactivation of damaged DNA in the absence of functional Cockayne syndrome B (Csb) protein, DNA Repair 8 (3) (2009) 309–317.
[145] I. Kuraoka, M. Endou, Y. Yamaguchi, T. Wada, H. Handa, K. Tanaka, Effects of endogenous DNA base lesions on transcription elongation by mammalian RNA polymerase II. Implications for transcription-coupled DNA repair and transcriptional mutagenesis, J. Biol. Chem. 278 (9) (2003) 7294–7299.
[146] S.D. Kathe, G.P. Shen, S.S. Wallace, Single-stranded breaks in DNA but not oxidative DNA base damages block transcriptional elongation by RNA polymerase II in HeLa cell nuclear extracts, J. Biol. Chem. 279 (18) (2004) 18511–18520.
[147] C. Dinant, G. Ampatziadis-Michailidis, H. Lans, M. Tresini, A. Lagarou, M. Grosbart, A.F. Theil, W.A. van Cappellen, H. Kimura, J. Bartek, M. Fousteri, A.B. Houtsmuller, W. Vermeulen, J.A. Marteijn, Enhanced chromatin dynamics by FACT promotes transcriptional restart after UV-induced DNA damage, Mol. Cell 51 (4) (2013) 469–479.
[148] C.L. Licht, T. Stevnsner, V.A. Bohr, Cockayne syndrome group B cellular and biochemical functions, Am. J. Hum. Genet. 73 (6) (2003) 1217–1239.
[149] M. Osterod, E. Larsen, F. Le Page, J.G. Hengstler, G.T. Van Der Horst, S. Boiteux, A. Klungland, B. Epe, A global DNA repair mechanism involving the Cockayne syndrome B (CSB) gene product can prevent the in vivo accumulation of endogenous oxidative DNA base damage, Oncogene 21 (54) (2002) 8232–8239.
[150] G. Dianov, C. Bischoff, M. Sunesen, V.A. Bohr, Repair of 8-oxoguanine in DNA is deficient in Cockayne syndrome group B cells, Nucleic Acids Res. 27 (5) (1999) 1365–1368.
[151] R.R. Selzer, S. Nyaga, J. Tuo, A. May, M. Muftuoglu, M. Christiansen, E. Citterio, R.M. Brosh Jr.V.A. Bohr, Differential requirement for the ATPase domain of the Cockayne syndrome group B gene in the processing of UV-induced DNA damage and 8-oxoguanine lesions in human cells, Nucleic Acids Res. 30 (3) (2002) 782–793.
[152] J. Tuo, C. Chen, X. Zeng, M. Christiansen, V.A. Bohr, Functional crosstalk between hOgg1 and the helicase domain of Cockayne syndrome group B protein, DNA Repair 1 (11) (2002) 913–927.
[153] H.K. Wong, M. Muftuoglu, G. Beck, S.Z. Imam, V.A. Bohr, D.M. Wilson 3rd, Cockayne syndrome B protein stimulates apurinic endonuclease 1 activity and protects against agents that introduce base excision repair intermediates, Nucleic Acids Res. 35 (12) (2007) 4103–4113.
[154] C. Trapp, K. Reite, A. Klungland, B. Epe, Deficiency of the Cockayne syndrome B (CSB) gene aggravates the genomic instability caused by endogenous oxidative DNA base damage in mice, Oncogene 26 (27) (2007) 4044–4048.
[155] M. Muftuoglu, N.C. de Souza-Pinto, A. Dogan, M. Aamann, T. Stevnsner, I. Rybanska, G. Kirkali, M. Dizdaroglu, V.A. Bohr, Cockayne syndrome group B protein stimulates repair of formamidopyrimidines by NEIL1 DNA glycosylase, J. Biol. Chem. 284 (14) (2009) 9270–9279.
[156] M.D. Aamann, C. Hvitby, V. Popuri, M. Muftuoglu, L. Lemminger, C.K. Skeby, G. Keijzers, B. Ahn, M. Bjoras, V.A. Bohr, T. Stevnsner, Cockayne Syndrome group B protein stimulates NEIL2 DNA glycosylase activity, Mech. Ageing Dev. 135 (2014) 1–14.
[157] E. Citterio, V. Van Den Boom, G. Schnitzler, R. Kanaar, E. Bonte, R.E. Kingston, J.H. Hoeijmakers, W. Vermeulen, ATP-dependent chromatin remodeling by the Cockayne syndrome B DNA repair-transcription-coupling factor, Mol. Cell Biol. 20 (20) (2000) 7643–7653.
[158] I. Cho, P.F. Tsai, R.J. Lake, A. Basheer, H.Y. Fan, ATP-dependent chromatin remodeling by Cockayne syndrome protein B and NAP1-like histone chaperones is required for efficient transcription-coupled DNA repair, PLoS Genet. 9 (4) (2013) e1003407.
[159] H. Dou, S. Mitra, T.K. Hazra, Repair of oxidized bases in DNA bubble structures by human DNA glycosylases NEIL1 and NEIL2, J. Biol. Chem. 278 (50) (2003) 49679–49684.
[160] A. Chakraborty, M. Wakamiya, T. Venkova-Canova, R.K. Pandita, L. Aguilera-Aguirre, A.H. Sarker, D.K. Singh, K. Hosoki, T.G. Wood, G. Sharma, V. Cardenas, P.S. Sarkar, S. Sur, T.K. Pandita, I. Boldogh, T.K. Hazra, Neil2-null mice accumulate oxidized DNA bases in the transcriptionally active sequences of the genome and are susceptible to innate inflammation, J. Biol. Chem. 290 (41) (2015) 24636–24648.
[161] D. Banerjee, S.M. Mandal, A. Das, M.L. Hegde, S. Das, K.K. Bhakat, I. Boldogh, P.S. Sarkar, S. Mitra, T.K. Hazra, Preferential repair of oxidized base damage in the transcribed genes of mammalian cells, J. Biol. Chem. 286 (8) (2011) 6006–6016.
[162] A. Khobta, T. Lingg, I. Schulz, D. Warken, N. Kitsera, B. Epe, Mouse CSB protein is important for gene expression in the presence of a single-strand break in the non-transcribed DNA strand, DNA Repair 9 (9) (2010) 985–993.
[163] N.A. Pestov, N.S. Gerasimova, O.I. Kulaeva, V.M. Studitsky, Structure of transcribed chromatin is a sensor of DNA damage, Sci. Adv. 1 (6) (2015) e1500021.
[164] B.P. Belotserkovskii, A.J. Neil, S.S. Saleh, J.H. Shin, S.M. Mirkin, P.C. Hanawalt, Transcription blockage by homopurine DNA sequences: role of sequence composition and single-strand breaks, Nucleic Acids Res. 41 (3) (2013) 1817–1828.
[165] H. Menoni, J.H. Hoeijmakers, W. Vermeulen, Nucleotide excision repair-initiating proteins bind to oxidative DNA lesions in vivo, J. Cell Biol. 199 (7) (2012) 1037–1046.
[166] N. Paquet, M.N. Adams, V. Leong, N.W. Ashton, C. Touma, R. Gamsjaeger, L. Cubeddu, S. Beard, J.T. Burgess, E. Bolderson, K.J. O'Byrne, D.J. Richard, hSSB1 (NABP2/OBFC2B) is required for the repair of 8-oxo-guanine by the hOGG1-mediated base excision repair pathway, Nucleic Acids Res. 43 (18) (2015) 8817–8829.
[167] J.P. Melis, M. Luijten, L.H. Mullenders, H. van Steeg, The role of XPC: implications

in cancer and oxidative DNA damage, Mutat. Res. 728 (3) (2011) 107–117.
[168] I.V. Kovtun, K.O. Johnson, C.T. McMurray, Cockayne syndrome B protein antagonizes OGG1 in modulating CAG repeat length in vivo, Aging 3 (5) (2011) 509–514.
[169] Y. Lin, J.H. Wilson, Transcription-induced CAG repeat contraction in human cells is mediated in part by transcription-coupled nucleotide excision repair, Mol. Cell Biol. 27 (17) (2007) 6209–6217.
[170] M. Iwafuchi-Doi, G. Donahue, A. Kakumanu, J.A. Watts, S. Mahony, B.F. Pugh, D. Lee, K.H. Kaestner, K.S. Zaret, The pioneer transcription factor FoxA maintains an accessible nucleosome configuration at enhancers for tissue-specific gene activation, Mol. Cell 62 (1) (2016) 79–91.
[171] J.S. Menet, S. Pescatore, M. Rosbash, CLOCK:BMAL1 is a pioneer-like transcription factor, Genes Dev. 28 (1) (2014) 8–13.
[172] M.A. Sammons, J. Zhu, A.M. Drake, S.L. Berger, TP53 engagement with the genome occurs in distinct local chromatin environments via pioneer factor activity, Genome Res. 25 (2) (2015) 179–188.
[173] T. Sekiya, U.M. Muthurajan, K. Luger, A.V. Tulin, K.S. Zaret, Nucleosome-binding affinity as a primary determinant of the nuclear mobility of the pioneer transcription factor FoxA, Genes Dev. 23 (7) (2009) 804–809.
[174] K.S. Zaret, J.M. Caravaca, A. Tulin, T. Sekiya, Nuclear mobility and mitotic chromosome binding: similarities between pioneer transcription factor FoxA and linker histone H1, Cold Spring Harb. Symp. Quant. Biol. 75 (2010) 219–226.
[175] D. Libri, Sleeping Beauty and the Beast (of pervasive transcription), Rna 21 (4) (2015) 678–679.
[176] P. Kapranov, J. Cheng, S. Dike, D.A. Nix, R. Duttagupta, A.T. Willingham, P.F. Stadler, J. Hertel, J. Hackermuller, I.L. Hofacker, I. Bell, E. Cheung, J. Drenkow, E. Dumais, S. Patel, G. Helt, M. Ganesh, S. Ghosh, A. Piccolboni, V. Sementchenko, H. Tammana, T.R. Gingeras, RNA maps reveal new RNA classes and a possible function for pervasive transcription, Science 316 (5830) (2007) 1484–1488.
[177] M.J. Hangauer, I.W. Vaughn, M.T. McManus, Pervasive transcription of the human genome produces thousands of previously unidentified long intergenic noncoding RNAs, PLoS Genet. 9 (6) (2013) e1003569.
[178] R.B. Vegh, K.M. Solntsev, M.K. Kuimova, S. Cho, Y. Liang, B.L. Loo, L.M. Tolbert, A.S. Bommarius, Reactive oxygen species in photochemistry of the red fluorescent protein "Killer Red", Chem. Commun. 47 (17) (2011) 4887–4889.
[179] X. Shu, V. Lev-Ram, T.J. Deerinck, Y. Qi, E.B. Ramko, M.W. Davidson, Y. Jin, M.H. Ellisman, R.Y. Tsien, A genetically encoded tag for correlated light and electron microscopy of intact cells, tissues, and organisms, PLoS Biol. 9 (4) (2011) e1001041.
[180] L. Lan, S. Nakajima, L. Wei, L. Sun, C.L. Hsieh, R.W. Sobol, M. Bruchez, B. Van Houten, A. Yasui, A.S. Levine, Novel method for site-specific induction of oxidative DNA damage reveals differences in recruitment of repair proteins to heterochromatin and euchromatin, Nucleic Acids Res. 42 (4) (2014) 2330–2345.
[181] J. Cadet, K.J.A. Davies, Oxidative DNA damage & repair: an introduction, Free Radic. Biol. Med. 107 (2017) 2–12.