DNA Repair 107 (2021) 103210

Contents lists available at ScienceDirect

DNA Repair

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

Heterogeneity of DNA damage incidence and repair in different chromatin contexts☆,☆☆

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ARTICLE INFO

Keywords:
Chromatin
DNA damage
Double-strand break
DNA repair
Genome instability

ABSTRACT

It has been long known that some regions of the genome are more susceptible to damage and mutagenicity than others. Recent advances have determined a critical role of chromatin both in the incidence of damage and in its repair. Thus, chromatin arises as a guardian of the stability of the genome, which is altered in cancer cells. In this review, we focus into the mechanisms by which chromatin influences the occurrence and repair of the most cytotoxic DNA lesions, double-strand breaks, in particular at actively transcribed chromatin or related to DNA replication.

1. Introduction

The genetic information must be safely stored in the DNA molecule and faithfully replicated and segregated in each cell division. In order to comply with its physiological roles during replication, transcription, repair and segregation, DNA is covered by basic proteins that play a key role in its structure and function. In eukaryotes, the DNA molecule is safely packed in nucleosomes, protein-DNA complexes in which 147 base pairs (bp) of DNA are wrapped around a histone octamer that generally contains two copies of each of the four core histones (H3, H4, H2A and H2B) and also with the linker histone H1 in compacted chromatin. Different chromatin structures are established by a multilayer of epigenetic marks, including DNA methylation, histone posttranslational modifications (PTMs), histone variants, and chromatin-related factors such as histone chaperones and ATP-dependent chromatin remodeling complexes [1–3]. Thus, eukaryotic chromatin plays a key role not only in chromosome structure but most importantly in the regulation of DNA physiology.

Despite a major goal of life being the transmission of genetic information with the highest fidelity, DNA is continuously exposed to exogenous and endogenous sources of damage that challenge its integrity. Interestingly, it has long been known that some DNA regions are more susceptible to mutation or fragility than others. This is in large part due to the different impact that transcription and replication may have in some regions due to secondary DNA structures or specific sequence features, replication timing, etc. Nevertheless, these differences may also be partially explained by the impact of chromatin that might be indirect, affecting transcription and replication, or direct, as changes in chromatin structure influence the accessibility of the DNA molecule to both DNA damaging agents and repair factors (Fig. 1).

The chromatin context influences both the vulnerability to DNA damage and the DNA repair timing and efficiency. Indeed, DNA damage response (DDR) factors work in tight coordination with chromatin remodelers to sense and repair DNA lesions [4]. Here, we revise the recent literature on how the chromatin context influences the incidence of DNA damage and its repair. Excellent reviews have been published on related topics considering also the context of chromatin and nuclear architecture [5–11], aspects that this we will not cover here or only partially. We focus in the repair of the most cytotoxic DNA lesions, DNA double-strand breaks (DSBs), the specific role of chromatin and its impact on the different DNA processes that can subsequently conduct to compromise genome integrity, by interfering either with the DDR or with DNA replication mainly.

2. Influence of chromatin in the incidence of DNA breaks

The occurrence of DNA breaks is not homogenous throughout the genome. Recurrent DNA breakage has been reported in certain regions,

☆ This article is part of the special issue DNA damage response. ☆☆ This Special Issue is edited by Sukesh R. Bhaumik.

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https://doi.org/10.1016/j.dnarep.2021.103210
Received 16 June 2021; Received in revised form 2 August 2021; Accepted 11 August 2021
Available online 13 August 2021

known as fragile sites, particularly upon replicative stress, and indeed, fragility is mainly attributed to their difficulty to be replicated [12]. In addition, the fact that fragile sites map within transcribed regions highlights the strong contribution that active transcription has in DNA damage incidence. Indeed, transcribed DNA is more vulnerable to DNA damage, acquiring increased frequencies of mutation and recombination [13–15]. This phenomenon, known as transcription-associated genome instability, is conserved from bacteria to humans and is well documented to be caused by the increased accessibility of the DNA during transcription and by the ability to stall replication fork progression causing transcription-replication (T-R) conflicts [13,16]. More recent studies suggest that DSBs also occur independently of replication, their incidence being dependent on the formation of chromatin loops at transcribed loci that results in a torsional stress that drives aberrant topoisomerase resolution [17–19]. These conclusions have mainly emerged from the development of new tools for the genome-wide profiling of DSBs. Since this has been recently revised [10,11], in this section, we will review how the epigenetic stage of chromatin influences the incidence of DNA damage by controlling the accessibility of DNA damaging agents and the occurrence of T-R conflicts as well as how chromatin can hamper the progression of replication forks constituting itself a source of DNA damage.

2.1. Influence of chromatin on transcription-replication conflicts

Provided that one major source of genome instability are T-R conflicts [20], it is important to note that depletion of several chromatin-associated factors has been shown to increase T-R conflicts, particularly by enhancing the formation of R loops formed by co-transcriptional DNA-RNA hybrids and the displaced DNA strand. This was shown for the FACT complex in budding yeast and human cells [21], and later on for the fission yeast Fft3 SNF2-like chromatin remodeler [22], mouse histone H1 [23], and for the human INO80 [24] and SWI/SNF chromatin remodeler complexes [25]. Chromatin alterations can thus result in R loops and consequently lead to transcription-associated genetic instability. In turn, R-loops were shown to cause T-R conflicts by their ability to drive chromatin alterations, such as H3S10-P and H3K9me2, which are related with chromatin compaction [26–28]. Therefore, chromatin alterations appear as the source of the transcription-associated genetic instability caused by R loops.

In addition, chromatin marks indirectly influence T-R conflicts by regulating the rate of both the transcription and replication rates. In this regard, the human histone acetyl-lysine binding protein BRD4 prevents T-R conflicts by its role in transcription elongation [29,30] and it has been proposed that H3K4me levels mitigate T-R conflicts by slowing down replication forks [31]. Thus, chromatin influences the tight coordination that must exist between transcription and replication processes in order to avoid T-R conflicts potentially leading to DSBs. The mechanisms by which each chromatin remodeling factor controls the conflicts may be varied and still need further research.

2.2. Incidence of DNA damage in heterochromatin

Heterochromatin is highly condensed, gene-poor and transcriptionally silent. Its integrity is required for chromosome segregation, telomere protection and for the suppression of illegitimate recombination between repetitive sequences and transposon activity [32,33]. Despite its inherently less accessible state, transcription must occasionally occur in heterochromatin regions. Thus, it is necessary to open this compacted state of the chromatin in a very precise window of time and the heterochromatin marks must be reconstituted once transcription is completed. A prolonged exposure of the repeated sequences located in heterochromatin can be harmful as these sequences are a source of aberrant recombination and DSBs [33].

In particular, there is ample evidence that heterochromatin maintenance is crucial in telomeric and rDNA regions to prevent genetic instability. Telomere integrity is disturbed upon the loss of heterochromatin marks that cause elevated transcription at telomeres or upon the deregulation of telomeric repeat-containing RNA (TERRA) and/or TERRA-associated DNA-RNA hybrid formation [34–37]. Similarly, Sir2-mediated histone deacetylation leads to the transcriptional repression within the rDNA copies to maintain rDNA stability in yeast [38]. Supporting the role of heterochromatin in genome protection, the loss of H3K9me2,3 heterochromatin marks causes decompaction and leads to genetic instability and tumorigenesis in mouse models [39,40]. Along the same line, the loss of BRCA1, which is involved in the maintenance of heterochromatin integrity, shows decompaction and transcriptional deregulation of repetitive sequences increasing mitotic defects and DNA damage [41]. Similarly, the loss of H3K9 methylation in *C. elegans* or the linker histone H1 in *Drosophila* leads to increased chromatin accessibility and R-loops in repeated DNA regions leading to DNA damage [42,43].

Despite the fact that heterochromatin maintenance is crucial to prevent genome instability, its condensed state can hamper the progression of replication forks thus potentially leading to DSBs. Indeed, specific factors are required to replicate heterochromatin. In mammalian telomeres, the TRF1 and TRF2 factors from the shelterin telomere-protective complex, recruit BLM and RTEL1 DNA helicases in order to facilitate telomere replication [44–46]. Recent observations suggest that this mechanism is not limited to telomeres and TRF2 controls heterochromatin replication genome-wide [47]. Additionally, the ACF1-SNF2H ISWI-related complex facilitates DNA replication through heterochromatin [48]. Similarly, deficiency in the SMARCA4 chromatin-remodeling complex that promotes heterochromatin accessibility leads to increased stalled forks [49] further arguing that the repressive state of pre-existing chromatin could be a potential impediment for replication forks that can end up in DSBs. Moreover, chromatin compaction impairs fork progression even within transcribed euchromatin, as discussed above for R-loops-induced chromatin compaction [26–28]. Thus, a delicate balance between heterochromatin maintenance and cellular processes such as transcription and replication prevents DSB occurrence.

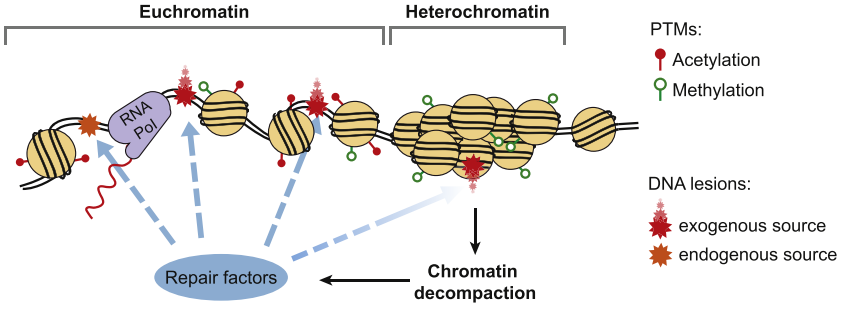

Fig. 1. The chromatin context influences DNA damage incidence and repair. A multilayer of epigenetic marks, including histone posttranslational modifications (PTMs) such as methylation and acetylation, establishes euchromatin and heterochromatin domains, which influence the occurrence of DNA damage from both exogenous and endogenous sources and the accessibility of repair factors. While euchromatin is accessible to repair factors, heterochromatin is refractory and requires decompaction prior to repair.

3. Damage-induced chromatin changes with an active role in repair

The chromatin landscape contributes not only to the incidence of DNA damage but also to guarantee its repair. Focusing in the most cytotoxic DNA lesions, DSB repair can occur though two major pathways known as non-homologous end joining (NHEJ) and homologous recombination (HR) [50]. The choice between these pathways is governed by the control of end resection, which is controlled by several negative and positive regulators, such as the mammalian 53BP1 factor, which blocks resection, and BRCA1, that counteracts 53BP1 [50]. In S-phase, when the intact sister chromatid is available as a homologous template to restore the genetic information, the preferred HR reaction is sister chromatid recombination (SCR), which is favored by the presence of cohesin rings that hold both sister chromatids together (Fig. 2) [51–54]. Sister chromatid cohesion is established during replication but also upon DNA damage thus ensuring the preferential use of the sister chromatid for DSB repair by HR [55–58].

In this section we will review how chromatin actively participates in the regulation of DSB repair at multiple levels that range from DNA damage sensing and recruitment of repair factors for the regulation of the DSB repair pathway choice to the selection of the sister chromatid as a homologous repair template. In addition, we will describe how DSB induction causes massive chromatin reorganizations at both local and global scales.

3.1. Chromatin marks promote damage signaling and loading of repair factors

One of the first outcomes of a DSB is the phosphorylation of yeast H2A at serine 129 or mammalian H2AX at serine 139 (γ-H2AX) in the flanking nucleosomes [59,60]. This serves to spread the signal and promote the recruitment of downstream DDR factors. To ensure that there is sufficient amount of γ-H2AX at chromatin regions that are susceptible to DNA damage, H2AX is deposited de novo at damaged sites by the FACT histone chaperone, as shown for UV-induced damage in mammalian cells [61]. γ-H2AX is then recognized by the MDC1 mediator, which triggers a positive feed-forward loop that spreads the signal around the DSB [62]. Yeast lacks an ortholog of MDC1, but the Rad9 mediator is recruited to facilitate the activation of downstream factors [63–65]. Moreover, the γ-H2AX domains can further extend tens or hundreds of kilobases along the chromatin in a process independent of yeast Rad9 and mammalian MDC1 but dependent on DDR kinases (yeast Tel1 and Mec1, mammalian ATM) [66,67]. In mammalian cells, γ-H2AX and the binding of MDC1 to DSBs generate an ubiquitylation cascade in the site of the lesion that starts with the recruitment of the RNF8 and RNF168 ubiquitin ligases which, in association with other ubiquitin ligases, mediate H2A ubiquitylation and the exposure of the H4K20me2 mark (reviewed in [68,69]). These histone ubiquitylation and methylation marks are key for the recruitment of general and specific repair factors to the break influencing the DSB repair pathway choice. In addition, the human Tip60 component from the NuA4 histone deacetylase complex promotes DNA end resection [70] whereas histone deacetylation by human HDAC1 and HDAC2 or yeast Sin3 and Rpd3 promotes NHEJ [71,72]. Thus, chromatin influences the repair pathway choice at multiple levels. Chromatin marks and remodelers are also involved in favoring the repair by SCR by the promotion of damage-induced cohesion. This has been shown so far for the damage-induced γ-H2AX [58,73,74], constitutive methylation of H3K79 [74] and the RSC chromatin remodeling complex [75].

3.2. Local chromatin reorganization after a DSB

Upon DSB induction, there is a transition to a more open and accessible chromatin as originally observed by the major accessibility of UV- or IR- irradiated cells to nuclease digestion [76,77]. Along this line, nucleosome loss was observed at the yeast *MAT* locus after its cleavage by the HO endonuclease [78] and chromatin opens upon DSBs in human cells [79]. This chromatin opening process seems crucial for the access of different repair factors to the lesion as suggested long ago in the classical "access-repair-restore" model [80]. This model suggests that the steps needed to repair DNA damage involve the detection of the lesion, the remodeling of the chromatin and finally the restoration of the chromatin organization after repair. Chromatin opening is due to chromatin decompaction/unfolding and transient nucleosome disassembly and is mechanistically mediated by chromatin remodeling, histone loss, histone modification and other chromatin-related processes. Importantly, members of the INO80 family mediate chromatin remodeling around DSBs and the DDR induces the loss of core histones at DNA breaks as shown in human cells [81–84] and in yeast [78,85,86]. Furthermore, the human Poly [ADP-ribose] polymerase 1 (PARP-1) factor favors the recruitment of the nucleosome remodeler CHD2 to DNA breaks to promote chromatin expansion [87] and the histone chaperone nucleolin was shown to promote histone loss at DNA lesions [88]. In addition to the loss of core histones around DSBs, histone H1 was shown to be evicted at breaks in human cells [89]. Histone modifications that control chromatin decompaction around DSBs include histone H2B ubiquitylation, mediated by yeast Bre1 and mammalian RNF20-RNF40 [90–93], histone acetylation by the NuA4 complex and other histone acetyl-transferases [94–97] and histone PARylation [98]. In mammalian cells, histone acetylation and histone PARylation also recruit the BRG1 and BRD4 chromatin remodelers and the FACT complex, respectively, to promote chromatin remodeling in order to repair the DSB [98–100]. The new open and flexible chromatin created at the break site favors the ubiquitylation by RNF8 and the subsequent loading of different repair factors [94,95]. Consequently, the depletion of the factors involved in this chromatin opening sensitizes cells to DNA damage and causes chromosome aberrations (reviewed in [69]). Once the repair is completed, the chromatin landscape must be reestablished. This is well exemplified with the dual role of the CHD7 remodeler, which after

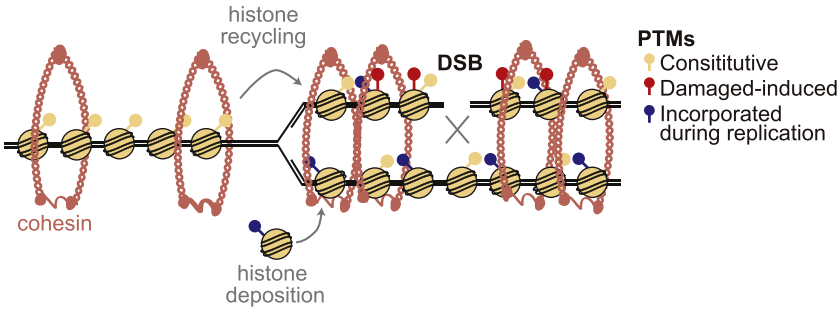

Fig. 2. Histone posttranslational modifications (PTMs) promote sister-chromatid recombination. Damage-induced phosphorylation of H2AX around double-strand breaks (DSBs) is crucial for signaling and accurate repair with the sister chromatid. In addition, newly replicated chromatin contains both recycled parental histones and newly synthesized histones that are deposited *de novo*. Such post-replicative chromatin status influences repair by promoting recombination with the intact sister chromatid, as it has been shown for acetylated H3K56 in yeast or unmethylated H4K20 in human cells. Moreover, sister-chromatid recombination is facilitated by sister chromatid cohesion by the cohesin complex. In turn, cohesion is also influenced by histone PTMs as shown for Rpd3L and Hda1-driven histone acetylation, which affects general cohesin loading and the constitutive methylation of

H3K79 by Dot1, which affects cohesin loading specifically at DSBs.

stimulating chromatin opening recruits HDAC1 to closed chromatin [101]. Moreover, chromatin reassembly after DNA repair requires the chromatin assembly factor CAF-1 and the histone chaperone HIRA [84].

In parallel with the chromatin relaxation to favor DSB repair factor accessibility, there is a transient transcriptional shut down. This has been shown in yeast, where it requires DNA end resection but not Tel1 and Mec1 DDR kinases [102] and in mammalian cells, where it relies on DDR factors (ATM, PARP1 and DNA-PKcs) and the recruitment ubiquitin ligases (RNF8 and RNF168), chromatin remodelers (PBAF and PRC1), H2A and H2AX histone ubiquitylation and KDM5A-mediated histone demethylation (reviewed in [103]). Importantly, this transcriptional shut down mediated by chromatin changes contributes to promote accurate repair.

3.3. Large-scale chromatin reorganization after a DSB

From a more global perspective, chromatin undergoes large-scale reorganization after DNA damage. Damaged chromatin fibers have been shown to relocate to different cellular domains such as to the nuclear periphery in yeast and in *Drosophila* cells or to heterochromatin periphery in mammals, to increase nuclear exploration during HR-dependent homology search or even to cluster when there are multiple DSBs [104]. Interestingly, such reorganizations seem to be favored by the action of chromatin remodelers, by the DDR [105], nucleo- and or cytoskeletal filament formation [106] and possibly by liquid-liquid phase separation domains [107]. The interconnection, differentiation and coordination between local and large-scale movement remains to be deciphered but there is clear evidence that some of these processes contribute to maintaining genome stability. In this context, relocation of repair sites away from heterochromatin prevents aberrant recombination events facilitating accurate repair [108,109].

4. The influence of the pre-existing chromatin context in DSB repair

DSB signaling and repair is influenced by the pre-existing chromatin structure, such as that of a transcribed region, condensed heterochromatin or post-replicated chromatin. Considering the chromatin context of transcriptionally actives genes versus non-transcribed regions, it has been shown in yeast that transcription impairs the spread of γ-H2AX [110]. However, since DNA damage would form preferentially at accessible chromatin such as actives genes, it is reasonable to think that actively transcribed regions evolved a preference to repair DSBs, as recently reviewed [10]. The development of a human cell line that conditionally controls the localization of the AsiSI endonuclease has enabled to study the recruitment of HR *versus* NHEJ factors to specific DSBs located in different euchromatin contexts, leading to the conclusion that whereas NHEJ factors are recruited independently of the transcription status, RAD51 is preferentially recruited to actively transcribed regions to promote HR [111]. Similar observations have been obtained using the KillerRed light-excitable ROS-generating protein to induce DSBs in human cells [112]. Interestingly, the preferential recruitment of RAD51 to transcribed regions is controlled by the levels of SETD2-dependent H3K36me3 [111,113], which drives DSB repair by recruiting the resection factor CtIP [113,114]. Hence, it seems that the histone marks of actively transcribed euchromatin channel DSB repair towards HR. This is in agreement with the previous observation of faster repair of DSB induced by the HO endonuclease when happening at active genes in yeast [115]. A recent report has also evaluated the repair of DSBs in different chromatin contexts in human cells using the Cas9 nuclease to induce the breaks and a system to identify repair scars [116]. Although this methodology could not identify HR repair due to the lack of repair scars, it allowed, among other conclusions, to state that H3K27me3-marked heterochromatin is more prone to repair by microhomology-mediated end-joining (MMEJ), an alternative NHEJ pathway that requires short DNA end resection.

When DSBs occur in heterochromatin, dense-packed nucleosomes and multiple heterochromatin-binding proteins hinder the access of signaling and repair factors (Fig. 1). Early observations in yeast and mammalian cells demonstrated that heterochromatin is refractory to γ-H2AX modification [117]. In mammalian cells, heterochromatin containing the compaction factor KAP-1, which further recruits different chromatin co-repressors including CHD3, HP1, HDACs and histones methyltransferases, has been shown to impair DSB repair [118–120]. Cells have evolved different strategies to overcome this limitation. In particular, the DDR kinase ATM drives KAP-1 phosphorylation that releases CHD3 from heterochromatin to promote heterochromatin relaxation [118,119]. Additionally, evidence indicates that HP1 is ejected from chromatin after DNA damage to promote heterochromatin repair [109,121,122]. Moreover, KMD4 histone demethylase is required for heterochromatin DSB repair [123]. Indeed, the observation that heterochromatin causes a temporary block of repair has been proposed to preclude the access of certain repair factors likely to prevent aberrant recombination within repetitive regions that could lead to chromosomal rearrangements, insertions and/or deletions [124].

Finally, the chromatin context that is newly established during DNA replication influences also DSB repair, particularly to promote SCR. In yeast, the levels of acetylated H3K56, which is incorporated to newly synthesized chromatin, affect the efficiency of SCR [125,126]. Similarly, unmethylated H4K20 (H4K20me0), which marks post-replicative chromatin in human cells, is recognized by BARD1 to recruit BRCA1 favoring SCR and the exclusion of 53BP1 thus favoring end resection [127,128]. Additionally, the human factor ATRX deposits H3.3 in newly synthetized strands helping repair synthesis and favoring SCR [129]. Thus, the post-replicative state of chromatin promotes SCR *versus* NHEJ (Fig. 2). Replication-born DSBs thus benefit from the existence of the intact sister chromatid to be repaired by HR. Along this line, Rpd3L and Hda1 histone deacetylase complexes promote the repair of replication-born DSBs by SCR by affecting cohesin loading in a damage-independent manner, arguing that Rpd3L and Hda1 mediated histone deacetylation affect SCR by shaping the pre-existing chromatin [130].

5. Conclusions and perspectives

The chromatin environment influences both the incidence and the repair of DNA damage. Accordingly, cells have evolved intricate pathways involving chromatin itself to ensure that DSBs are efficiently repaired in each chromatin context. New technologies and advances are unraveling all the different chromatin factors and histone modifications that contribute to this task. Current efforts focus in understanding how chromatin helps prevent DSBs, in the epigenetic consequences of DNA breakage in different chromatin contexts and in how is chromatin regulated to promote the accessibility of repair factors and the most efficient repair pathway in each situation. This is a particularly relevant area of research given the recent emergent use of epigenetic compounds in cancer therapies. Hence, it is important to address the many still unresolved questions in the field regarding the mechanistic position of epigenetics in genetic instability as the source of cancer-related diseases and the consequences of epigenetic compounds from the therapeutic point of view.

Author statement

Pedro Ortega: Investigation, Writing - Original Draft, Visualization **Belén Gómez-González:** Writing - Review & Editing, Supervision. **Andrés Aguilera:** Writing - Review & Editing, Funding acquisition.

Funding

Research in AA's lab is funded by the European Research Council, the Spanish Ministry of Economy and Competitiveness, Junta de Andalucía

and the European Union (FEDER).

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Acknowledgements

We apologize for all those works that could not be cited due to space limitations.

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