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Chromatin dynamics after DNA damage: the legacy of the Access-Repair-Restore model

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Abstract

Eukaryotic genomes are packaged into chromatin, which is the physiological substrate for all DNA transactions, including DNA damage and repair. Chromatin organization imposes major constraints on DNA damage repair and thus undergoes critical rearrangements during the repair process. These rearrangements have been integrated into the “Access-Repair-Restore” (ARR) model, which provides a molecular framework for chromatin dynamics in response to DNA damage. Here, we take a historical perspective on the elaboration of this model and describe the molecular players involved in damaged chromatin reorganization in human cells. In particular, we present our current knowledge of chromatin assembly coupled to DNA damage repair, focusing on the role of histone variants and their dedicated chaperones. Finally, we discuss the impact of chromatin rearrangements after DNA damage on chromatin function and epigenome maintenance.

Keywords

Chromatin assembly; DNA damage repair; Epigenome maintenance; Histone chaperones; Histone variants

1 Introduction

Genome stability is constantly jeopardized by endogenous and exogenous sources of genotoxic stress, which generate a variety of DNA lesions [1–3]. These lesions are processed by dedicated repair pathways that protect cells from the deleterious consequences of mutations and chromosomal aberrations resulting from the accumulation of DNA damage. Among them, the highly conserved Nucleotide Excision Repair (NER) pathway is unique in that it recognizes a broad spectrum of structurally-unrelated lesions, including pyrimidine

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Conflict of interest statement

None

dimers arising from exposure to UVC light and bulky chemical adducts [4,5] (see elsewhere in this issue).

In eukaryotic cells, however, repair machineries operate on a chromatinized substrate; a repeated nucleoproteic structure whose building block is the nucleosome [6]. In the nucleosome core, DNA is wrapped around an octamer of histone proteins comprising an (H3-H4)₂ tetramer flanked by two H2A-H2B dimers, while linker histone H1 associates with internucleosomal DNA. Histone proteins exist in the form of sequence variants [7,8], which have a profound impact on chromatin structure and function, in particular through the modulation of histone post-translational modifications (PTMs) and interacting factors, nucleosome stability and higher-order chromatin folding. Histone variants are deposited onto DNA in a regulated manner by dedicated histone chaperones [9]. Variations in chromatin elementary components (histone variants, PTMs) along with higher-order organization and regulatory factors form the so-called epigenome, which provides a versatile template for specific gene expression and cell functions. Therefore, chromatin not only helps packaging the eukaryotic genome into the cell nucleus, which impacts DNA accessibility, but also provides a major source of information that contributes to genome function.

How cells detect and repair DNA lesions in a chromatin environment and with what consequences on chromatin organization and epigenome maintenance are long-standing questions that have been the focus of intense research. In this context, we describe in this review the stepwise elaboration of the “Access-Repair-Restore” (ARR) model, which provided a molecular framework for integrating nucleosome dynamics in the repair response. Then, we present our current view of chromatin assembly coupled to DNA damage repair in human cells, primarily in the context of NER of UVC-induced DNA lesions, focusing on the role of histone variants and their dedicated chaperones. For the contribution of histone modifications and chromatin remodeling factors to chromatin dynamics in response to DNA damage, the reader is referred to recent reviews [10–13]. Finally, we discuss the impact of chromatin rearrangements after DNA damage on epigenome integrity and plasticity.

2 Emergence of the ARR model: from the original concepts to a molecular framework for chromatin dynamics in response to DNA damage

2.1 Unfolding-refolding model

Evidence for chromatin rearrangements upon DNA damage originally emerged from measuring the accessibility of damaged DNA to nucleases in the chromatin of UVC-irradiated human fibroblasts in which replicative synthesis was suppressed by contact inhibition and hydroxyurea treatment. Interestingly, regions undergoing repair synthesis were more sensitive to Micrococcal Nuclease (MNase) digestion than bulk DNA [14,15]. This was initially interpreted as repair synthesis occurring preferentially and more rapidly in nuclease accessible regions of chromatin, leading to the idea of a non-uniform distribution of NER in chromatin. An alternative interpretation of these findings, however, stemmed from Smerdon’s pioneering observation that the repaired regions recovered nuclease resistance over time. This was based on pulse-labeling of repaired DNA followed by chase times of

several hours [15]. The transient increase in nuclease sensitivity of chromatin regions undergoing NER, confirmed by Bodell & Cleaver using monkey cells [16], was indicative of chromatin unfolding during repair. Similar results were obtained upon chromatin digestion with DNase I [17–19] or restriction enzymes [20]. In addition, UVC-damaged chromatin decondensation was confirmed by cytological observations that were based on analyses of prematurely condensed chromosomes [21]. Remarkably, the increased nuclease sensitivity of damaged regions was independent of the initial distribution of UV photoproducts in chromatin [22], further supporting a chromatin unfolding model rather than NER occurring preferentially in accessible chromatin regions. Altogether, these studies set the first principles of the Unfolding-Refolding model that describes the transitions in chromatin structure during NER, with first chromatin unfolding then followed by refolding of newly repaired DNA into nucleosomes (Fig. 1A). Furthermore, chromatin recovers its native configuration with the same nucleosome repeat length, deposition of linker histone H1 [23] and re-establishment of a canonical DNase I footprint, a 10 bp periodic pattern characteristic of nucleosomal DNA due to its binding to the histone octamer surface [17]. Interestingly, such nucleosome rearrangements are not restricted to NER of UVC-induced damage, as similar observations were made in human cells treated with the alkylating agent methyl methanesulfonate [24] and the radiomimetic drug bleomycin [25].

2.2 Unfolding-Refolding-Repositioning model

Further examination of chromatin dynamics in response to UVC damage in human cells helped refine the above model by revealing that chromatin restoration was actually a biphasic response. A rapid nucleosome refolding phase during the first hours was followed by a slower maturation phase, which might correspond to the repositioning/rephasing of reconstituted nucleosomes within repaired regions, or their packaging into higher-order chromatin structures [26]. Measuring the position of repair patches in nucleosomes after restoration of nuclease resistance indeed revealed that repair patches were initially at the edges of nucleosome core particles and then occupied more random positions, indicative of nucleosome migration [27]. The above-described unfolding-refolding model then incorporated an extra step to take into account nucleosome repositioning (Fig. 1B). Gradually, this model evolved as our understanding of the molecular events underlying chromatin changes increased (see below).

2.3 Access-Repair-Restore model

Based on seminal work presented in the previous sections, in 2002 Green and Almouzni developed the ARR model [28] (Fig. 1C). In this model, transient opening of chromatin by nucleosome mobilization and, or, disruption facilitates the access of repair machineries to DNA lesions. The original chromatin organization is restored after repair is complete. Also, the ARR model incorporates molecular players involved in the Access and Restore steps, including histone chaperones (detailed below), chromatin remodelers and histone modifications. More recently, a refined version of the ARR model [29] integrated the fact that new histone deposition occurs in the Restore step, highlighting that chromatin restoration is not an entirely faithful process that resets it back to its original state. Hence, the incorporation of new histones into repaired chromatin can confer some degree of plasticity to epigenome maintenance after DNA damage, a property that had not been

appreciated before. Noteworthy, the fundamental principles describing NER in chromatin have helped to broaden the scope of the original model to other types of DNA damage, including DNA double-strand breaks (DSBs).

2.4 Access/Prime and Repair/Restore model: elaborating on the basics

The latest version of the model described in [30] elaborates on the basic principles, integrating chromatin dynamics in response to DNA damage, from the nucleosome up to higher-order chromatin structures, like heterochromatin (Fig. 1D). In addition, the most current model also highlights the active role of chromatin and chromatin-associated proteins, which are not only hindering access to repair machineries but are also actively promoting repair. Finally, it reconsiders the boundaries between the three steps of the ARR model, as restoration of chromatin structure after damage is not initiated upon completion of repair but actually starts during the earliest stages of damage detection. Therefore, DNA damage repair and chromatin restoration are now seen as a concerted process. The mechanistic insights into the Access/Prime and Repair/Restore steps in human cells are detailed below, followed by a discussion of the functional consequences of chromatin dynamics in response to DNA damage.

3 Access/Prime step

DNA damage in chromatin is refractory to repair. In particular, NER has long been known to be suppressed by nucleosomes [31]. Indeed, DNA packaging into chromatin restricts the accessibility of DNA lesions to repair factors, even more so in compact heterochromatin [32]. These observations highlight the need for nucleosome rearrangements and, or, disassembly to relieve the structural constraints and to make chromatin a suitable substrate for repair machineries.

3.1 Histone mobilization

Several lines of evidence support the idea that histone proteins are mobilized in the earliest stages of the UV damage response. In fact, UV damage interferes with nucleosome formation *in vitro* by diminishing DNA interactions with histone proteins [33] (see elsewhere in this issue). Also, UV damage causes changes in DNA wrapping around the histone octamer, as measured by Fluorescence Resonance Energy Transfer in reconstituted nucleosomes containing UV photoproducts [34]. In addition to such spontaneous unwrapping and, or, destabilization of damaged nucleosomes, active mechanisms mediating histone modifications and ATP-dependent chromatin remodeling control chromatin rearrangements in response to UVC. In particular, histone ubiquitylation was reported to promote nucleosome destabilization *in vitro* and, although this result is disputed, the levels of soluble ubiquitylated histones increase in response to UVC irradiation *in vivo* [35–37] (see elsewhere in this issue).

Besides histone modifications, the remodeling factors Brahma-Related Gene 1 (BRG1) and, to a lesser extent, INOsitol requiring 80 (INO80) are required for increasing chromatin accessibility upon UVC irradiation of human cells, as revealed by MNase digestion profiles [38,39]. Both remodelers contribute to efficient repair of UV damage but whether they

stimulate chromatin relaxation in the entire nucleus or only locally around damaged sites is still to be determined. It will also be important to integrate into this framework and, thus, to further investigate the role of ISWI (Imitation Switch) remodeling complexes, recently shown to accumulate at UVC-induced damaged sites and to stimulate transcription-coupled NER [40]. Further evidence for remodeling of chromatin in UVC-damaged areas came from a recent report showing an ATP-dependent reduction of core and linker histone density at sites of local UVC irradiation [41]. It is not entirely clear if this involves nucleosome disruption, sliding or chromatin opening but such histone mobilization correlates with efficient repair and is mediated by the UV damage sensor DNA damage binding protein 2 (DDB2). Future studies will determine if DDB2 acts in association with nucleosome remodelers to promote chromatin rearrangement, many of which are known to be recruited to UVC-damaged chromatin and, or, to facilitate repair (reviewed in [11]).

Importantly, histone mobilization is not strictly limited to the UVC-damage response since a transient loss of core histones, indicative of complete or partial nucleosome disruption, has also been observed by chromatin immunoprecipitation in the vicinity of DSBs induced by site-specific endonucleases [42–44] or occurring during programmed recombination in meiosis [45]. Altogether, these studies illustrate the importance of chromatin rearrangements at the nucleosome level in response to various types of DNA damage.

3.2 Extent of chromatin disorganization

Because chromatin integrity is central to cell function and identity, chromatin rearrangements in response to DNA damage may jeopardize epigenome maintenance. Thus, the magnitude of chromatin rearrangements is a critical issue. Specifically, despite the short size of the NER patch (~30 nucleotides in length) [46], chromatin disorganization can extend several kilobases away from the damage site, as shown by probing psoralen accessibility of chromatin in rat hepatocytes upon induction of bulky DNA adducts [47]. Furthermore, relaxation of chromatin affecting the whole nucleus has been reported in response to UVC irradiation of a limited nuclear area. These observations were based on increased sensitivity of chromatin to denaturation by hydrochloric acid [48]. However, loss of histone density was observed only in the damaged area when human cells were exposed to localized UVC irradiation [41]. Thus, how far from the damage site chromatin disorganization can span remains unclear. High-resolution techniques for probing chromatin structure in the vicinity of site-specific lesions should help clarify this issue. In particular, it would be interesting to investigate whether the original chromatin state - euchromatin vs. more compact heterochromatin - can modulate the extent of chromatin rearrangements and more generally if there are structural barriers in the cell nucleus that would restrict damaged chromatin disorganization. It is worth pointing out that the extent of chromatin rearrangements is also likely to be substantially different depending on the type of DNA lesion and repair pathway at work.

3.3 Priming chromatin for repair: not only a matter of access

In the original version of the ARR model [28], chromatin remodeling by destabilizing or disrupting the organization of nucleosomes around DNA damage sites was proposed to facilitate access of damaged DNA to repair factors. However, the recent discovery that

repressive factors, generally associated with chromatin compaction, were recruited to damaged chromatin challenged this view. Factors including Heterochromatin Proteins 1 (HP1), Polycomb Group proteins and subunits of the Nucleosome Remodeling Deacetylase complex, are indeed recruited to DSBs where they facilitate repair (reviewed in [30,49]). Thus, chromatin organization cannot simply be considered as a barrier to repair that must be relieved by unfolding to increase access to DNA lesions. Factors involved in chromatin compaction also play an active role in priming chromatin for repair. At least in part, this is achieved because such factors are involved in transcription inhibition at DSBs [50–53]. It is very likely that a similar scenario occurs in response to other DNA lesions, including UV-induced DNA damage, because repressive proteins like HP1 are also recruited to UVC-damaged chromatin [54].

4 Repair/Restore step

4.1 Chromatin assembly coupled to repair *in vitro*

Once repair is initiated, the process of chromatin restoration starts concomitantly, which involves histone dynamics mediated by histone chaperones. The first evidence for chromatin restoration by repair-coupled chromatin assembly came from *in vitro* experiments that analyzed nucleosome deposition on DNA undergoing NER compared to undamaged DNA. Circular plasmid DNA templates containing UV- or Cisplatin- DNA adducts were incubated in cell-free extracts from *Drosophila* embryos, *Xenopus* eggs or human cells, and the extent of nucleosome assembly was followed by supercoiling and MNase sensitivity assays [55–57]. Also, histone deposition was monitored on UVC-damaged DNA templates immobilized on magnetic beads [58]. The naked damaged DNA substrates were used as proxies for chromatin reorganization observed during NER *in vivo*. These assays established that nucleosome assembly occurred preferentially on damaged DNA, concomitantly with DNA repair synthesis. Moreover, regularly spaced nucleosome arrays propagated bi-directionally from the repair site [55,56]. Notably, Chromatin Assembly Factor-1 (CAF-1) was identified as the histone chaperone responsible for NER-coupled nucleosome assembly [55]. The direct interaction of CAF-1 largest subunit with the polymerase sliding clamp Proliferating Cell Nuclear Antigen (PCNA) constituted the molecular basis for coupling histone deposition and repair synthesis [59]. CAF-1 also interacted and worked in synergy with another histone chaperone, Anti-Silencing Function1 (ASF1), to promote repair-coupled nucleosome assembly *in vitro* [60]. Thus, *in vivo* ASF1 could be a histone donor for CAF-1, providing new histones or recycling parental histones as proposed at the replication fork [61].

4.2 Chromatin assembly coupled to repair *in vivo*

Analyses of repair-coupled chromatin assembly were taken one step further, when the dynamics of histones and histone chaperones were investigated in human cells exposed to DNA damaging agents. Thus, several histone chaperones were shown to be recruited to UVC damaged chromatin, as first demonstrated for CAF-1 [62,63] and, more recently, for Facilitates Chromatin Transcription (FACT) and Histone Regulator A (HIRA) [64,65]. Next, exploring histone dynamics associated with the recruitment of chaperones to UVC damage sites revealed a *de novo* deposition of transiently expressed histone proteins, like H2A and

H3.1 histones [64,66]. The development of the SNAP-tag technology for tracking newly synthesized histones *in vivo* [67,68] was instrumental for visualizing the *de novo* deposition of more histone variants at UV sites. It revealed that in addition to new H3.1, new H3.3 histones were deposited in UVC-damaged chromatin, whereas the centromeric H3 variant Centromeric Protein A (CENPA) was not deposited [65]. Remarkably, H3 variants are incorporated into damaged chromatin by dedicated chaperones (Fig. 2A); new H3.1 histones are deposited by CAF-1 and deposition of new H3.3 at UV sites is stimulated by HIRA [65,66]. In contrast, no contribution of the H3.3-specific chaperone Death domain-associated protein (DAXX) could be identified, although it cannot be excluded that DAXX-mediated H3.3 deposition may be restricted to specific chromatin regions like DNA damage containing heterochromatin domains. Interestingly, HIRA and CAF-1 chaperones appear to act sequentially during repair of UV-induced DNA lesions. While HIRA-mediated deposition of H3.3 at UV sites is coupled to the early steps (UVC damage detection) [65], CAF-1-mediated deposition of H3.1 occurs later and is dependent on DNA repair synthesis [66] (Fig. 2B). Given that CAF-1 also escorts the H3.2 variant [69], it is likely that both H3.1 and H3.2 are deposited by this chaperone in UVC-damaged chromatin. Since recurrent point mutations in H3 variants were recently discovered in several human cancers (reviewed in [70]), questions can be raised about the potential consequences of such mutations on DNA damage-associated histone dynamics, which could play a major role in tumor development.

It is unlikely that the function of CAF-1 and HIRA histone chaperones is restricted to the response of UVC-induced damage, as they are recruited to other types of DNA lesions, including mitotic DSBs in human cells and meiotic DSBs in yeast [45,65,66,71–73]. Regarding new H2A deposition at UV damage sites, it may be promoted by the histone chaperone FACT, which was shown to accelerate the turnover of H2A-H2B in UVC damaged chromatin [64]. In summary, these studies highlight the importance of new histones and their dynamics in the restoration of chromatin organization after UVC-induced DNA damage. We will now discuss their possible consequences on chromatin function and epigenome maintenance.

5 Functional consequences of repair-coupled chromatin assembly

5.1 Contribution to DNA damage repair?

Repair-coupled chromatin assembly could be important for completion of DNA damage repair. However, neither H3.1 deposition by CAF-1 nor H3.3 deposition by HIRA seem to impact UVC damage repair in human cells [65,66]. Similarly, depletion of CAF-1 and HIRA in budding yeast does not impair recombination of meiotic DSBs [45], indicating that chromatin re-assembly in the course of DNA repair is not required for DNA damage repair *per se*. However, fission yeast mutants for the HIRA ortholog are UV-sensitive [74] and H3.3 promotes replication fork progression after UV damage in chicken cells [75]. Thus, it is possible that H3.3 deposition at UV sites may be important for processive replication of damaged DNA, also known as lesion bypass. Future studies will be needed to further dissect the intricate relationship between chromatin restoration and DNA damage repair.

5.2 Fidelity of the restoration process and epigenome maintenance?

Chromatin restoration after DNA damage is a critical step in epigenome maintenance. For nucleosomal arrays to be converted back to their original configuration, both nucleosome structure and positioning need to be re-established. Similarly, to fully reproduce the initial state, histone PTMs and histone variant patterns need to be faithfully reset. While recycling parental histones would be the simplest way to ensure faithful restoration, the observation of an incorporation in damaged chromatin of newly synthesized histones, which differ from the original histones in particular regarding their PTMs [76], added another parameter challenging the maintenance of epigenome integrity. It is tempting to speculate that the new histones deposited at damaged sites could acquire parental histone marks in a manner similar to epigenome inheritance during DNA replication [77]. This could provide means to preserve the original chromatin landscape. Alternatively, one can imagine that new histones deposited at damage sites are maintained in their naive state and act as “damage scars”, which could potentiate the response during a subsequent exposure to genotoxic stress.

5.3 Restoration of chromatin function

Repair-coupled histone dynamics are important not only for restoring chromatin architecture after DNA damage but also for recovering chromatin function. Indeed, both FACT and HIRA chaperones were shown to be required for transcription recovery after UVC damage in human cells [64,65]. The underlying mechanisms are still elusive. In particular, it is not entirely clear whether these chaperones contribute to transcription-coupled repair of UVC damage. Interestingly however, both FACT and HIRA are rapidly recruited to UVC-damaged chromatin [64,65], and it has been proposed that HIRA, through H3.3 deposition, primes chromatin for transcription restart once repair is complete [65]. Thus, chromatin dynamics occurring during the very first stages of the repair response determine the capacity to re-transcribe, by turning damaged chromatin to a poised state for transcription activation. Future work should now address the molecular bases of this poised state, in particular to elucidate whether it involves newly deposited H3.3 or other chromatin marks.

6 Concluding remarks and future directions

Since Smerdon's early studies on chromatin rearrangements in response to UVC-induced damage, much effort has been invested to study DNA damage-associated chromatin dynamics. This has led to the identification of key factors that promote histone dynamics at damage sites. However, the underlying molecular mechanisms are not completely characterized. In particular, the contribution of histone modifications and the role of chromatin remodeling factors in damaged chromatin dynamics deserve further investigation. Furthermore, how DNA damage-associated histone dynamics are affected by the type of DNA damage, the cellular state and the original chromatin configuration are still open issues. Most importantly, the impact of DNA damage induced-histone dynamics on epigenome stability and plasticity needs to be addressed. The recent development of several techniques for high-resolution mapping of UVC damage and UVC damage repair in the human genome [78–80] should help monitor the epigenetic changes that occur after damage in terms of nucleosome positioning, patterns of histone variants and modifications. Finally, our growing knowledge of chromatin dynamics in response to DNA damage should prompt

us to revisit the etiology of human genome instability disorders. At least some of them may arise through defects in repair-coupled chromatin rearrangements rather than solely through DNA damage repair defects.

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Abbreviations

ARR	Access-Repair-Restore
ASF1	Anti-Silencing Function 1
BRG1	Brahma-Related Gene 1
CAF-1	Chromatin Assembly Factor-1
CENPA	Centromeric Protein A
DAXX	Death domain-associated protein
DDB2	DNA Damage Binding protein 2
DSB	Double-Strand Break
FACT	Facilitates Chromatin Transcription
HIRA	Histone Regulator A
HP1	Heterochromatin Protein 1
INO80	INOsitol requiring 80
ISWI	Imitation Switch
MNase	Micrococcal Nuclease
NER	Nucleotide Excision Repair
PCNA	Proliferating Cell Nuclear Antigen
PTM	Post-translational modification
UV	UltraViolet

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Prologue

This mini-review is a tribute to Mick Smerdon's pioneering work on chromatin rearrangements in response to DNA damage in human cells. His seminal work, based on original observations made more than 35 years ago, established the foundations for building a working model now referred to as "Access-Repair-Restore". This model has provided an evolving framework for investigating chromatin dynamics after DNA damage and fueled intense research in the field of chromatin and genome integrity.

Highlights

- The ARR model integrates chromatin dynamics into the DNA damage response
- DNA damage-induced chromatin rearrangements prime chromatin for repair
- Repair-coupled chromatin assembly helps restoring chromatin structure and function
- New histone deposition coupled to repair challenges epigenome maintenance

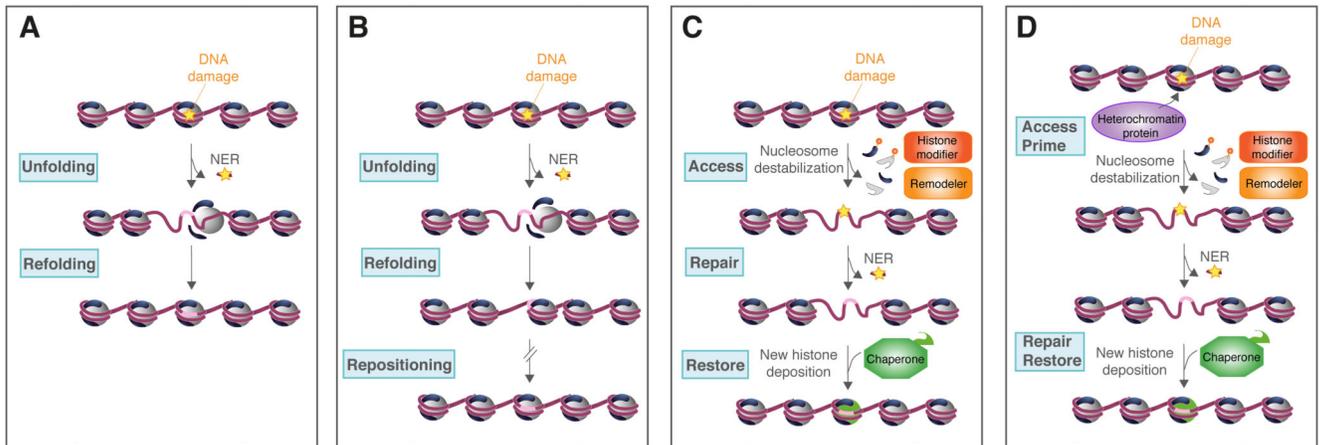


Fig.1. The Access-Repair-Restore model: from the initial concepts to the most recent molecular principles

Nucleosome rearrangements during repair of damaged chromatin in mammalian cells as described in the Unfolding-Repair-Restore model (A), which developed in the Unfolding-Repair-Repositioning model (B), Access-Repair-Restore model (C) and, more recently, in the Access/Prime-Repair-Restore model (D). DNA is represented in purple, the repair synthesis patch in pink, histone modifications in orange, inner core histones in grey, outer core histones in dark blue and newly synthesized histones in green.

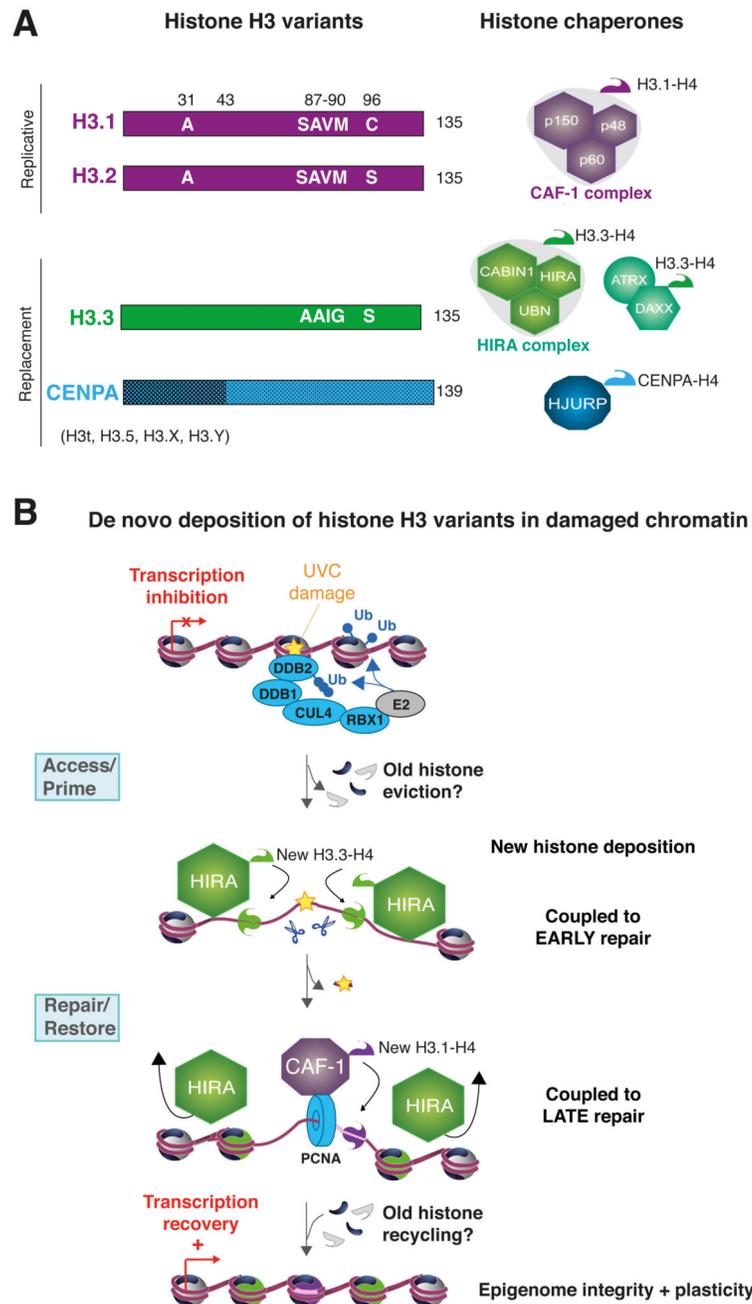


Fig.2. Restoration of UVC-damaged chromatin structure and function through *de novo* deposition of H3 variants

A. Main histone H3 variants and their dedicated chaperones in mammalian cells

Amino acids that differ between the histone variant sequences are indicated except for the more divergent centromeric variant CENPA. Less well characterized H3 variants are listed in parentheses. CAF1, HIRA, HJURP are histone chaperones.

B. Restoration of chromatin organization after UVC damage involves *de novo* deposition of H3 variants

Repair factors that facilitate the recruitment of the histone chaperones HIRA and CAF-1 to UV-damaged chromatin regions are depicted in blue. HIRA-mediated deposition of new H3.3 (green) precedes CAF-1-dependent incorporation of new H3.1 (purple). Early bookmarking of chromatin by the H3.3 chaperone HIRA is required for restoring transcriptional activity (red) after completion of DNA repair. While new histone deposition in UVC damaged chromatin is firmly established, the dynamics of old histones and their contribution to repaired chromatin are still to be determined. Adapted from [81] with permission.