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Chaperoning histones at the DNA repair dance☆,☆☆

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Abstract

Unlike all other biological molecules that are degraded and replaced if damaged, DNA must be repaired as chromosomes cannot be replaced. Indeed, DNA endures a wide variety of structural damage that need to be repaired accurately to maintain genomic stability and proper functioning of cells and to prevent mutation leading to disease. Given that the genome is packaged into chromatin within eukaryotic cells, it has become increasingly evident that the chromatin context of DNA both facilitates and regulates DNA repair processes. In this review, we discuss mechanisms involved in removal of histones (chromatin disassembly) from around DNA lesions, by histone chaperones and chromatin remodelers, that promotes accessibility of the DNA repair machinery. We also elaborate on how the deposition of core histones and specific histone variants onto DNA (chromatin assembly) during DNA repair promotes repair processes, the role of histone post translational modifications in these processes and how chromatin structure is reestablished after DNA repair is complete.

1. Introduction

The packaging of eukaryotic nuclear genomes together with histone proteins into the structure known as chromatin was long considered an inconvenient hurdle for nuclear processes to navigate. Chromatin comprises an array of nucleosomes which have approximately 1.75 turns of DNA around the outside of an octamer of two molecules of each core histone, H2A, H2B, H3 and H4, and this compaction of the DNA into chromatin limits accessibility to the DNA. Although the structure of the nucleosome has been known for over 20 years [1], we have only recently begun to understand how the packaging of the genome into nucleosomes facilitates and tightly regulates DNA repair. A variety of changes in the chromatin accompany and regulate multiple DNA repair processes. Here we review what we consider to be the ultimate way to provide access to the DNA template to promote DNA repair, which is disassembly of nucleosomes involving removal of histones from the DNA

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by histone chaperones. Histone chaperones are key players in histone metabolism involved in escorting histones and mobilizing them in and out of chromatin [2,3]. The list of known histone chaperones has been growing significantly, but only a few have been associated with the DNA damage response [1,2]. During chromatin disassembly and assembly by histone chaperones, they are assisted by ATP-dependent nucleosome remodelers which use energy of ATP hydrolysis to evict / exchange histones [3]. Other chromatin alterations also play an important role in facilitating DNA repair that will only be covered here where they impinge on chromatin disassembly / reassembly and have been reviewed extensively elsewhere. These include histone post-translational modifications (PTMs) to recruit repair proteins and to modulate chromatin compaction [4], nucleosome remodeling to slide histone octamers out of the way of the DNA lesion [5], and incorporation of histone variants [6]. Following such chromatin changes that facilitate repair processes, it is important that the chromatin is restored to its original pre-damage configuration after repair is completed so that the epigenetic information can be reinstated, and normal cellular processes can resume. This is achieved in part by chromatin assembly and will also be discussed here.

2. The “prime-access-repair-restore” model

One of the major constraints that DNA repair pathways encounter is the organization of the genome into chromatin which causes DNA lesions to be buried within a relatively inaccessible nucleoprotein structure. Repair factors require access to sites of damage to successfully perform their roles, and one way in which cells address this issue is by temporarily evicting histones from the proximity of the damage, by chromatin disassembly, to allow DNA repair proteins to localize to the lesion and perform their repair functions. After repair, and equally important, the nucleosomes are reassembled to restore the original chromatin state. Initially, the “access-repair-restore” model was put forth to explain this cellular strategy of temporarily removing the chromatin obstruction near damage sites to facilitate repair processes and then ultimately restoring the original chromatin conformation [7-9]. This preliminary model then went on to be modified into the “prime-access-repair-restore” model as roles and interactions of the chromatin with repair factors became better understood [1,10] (Fig. 1). Importantly, this modified model incorporated the idea that histones and nucleosomes do not act merely as obstacles to DNA repair but play important roles by “priming” the repair pathways in multiple ways, such as recruiting specific proteins and imposing regulatory constraints, and consequently influencing the choice and efficiency of downstream repair processes. The “access” step is then mediated by histone chaperones and ATP-dependent nucleosome remodelers that create a local “clearance” by disassembling nucleosomes or sliding the histone octamer away from the DNA lesion, which then allows repair factors to localize to these sites and perform their functions. Finally, the “restore” step occurs in which chromatin organization is returned to its original state and is mediated by histone chaperones that deposit histones post-repair. Below we discuss different chromatin disassembly and reassembly strategies that cells use and their mechanisms involved in various DNA repair pathways.

3. Nucleosome disassembly and reassembly during DNA repair

3.1. Homologous recombination

One of the major pathways that cells use to repair double strand breaks (DSBs) in the DNA is homologous recombination (HR), where breaks are repaired using a homologous DNA template. DSBs are one of the most deleterious kinds of damage that DNA can undergo, which can then lead to mutations or genome rearrangements if the breaks are repaired improperly and cell death if they are left unrepaired. Early steps of HR involve resecting one of the strands of DNA on either side of the DSB in the 5′ to 3′ direction. Resection is initiated by the Mre11-Rad50-Xrs2 (MRX) complex and Sae2 in yeast creating short 3′ overhangs, and long-range resection is then carried out by the Exo1 and Dna2 nucleases, the latter's activity being promoted by the Sgs1-Top3-Rmi1 (STR) helicase-topoisomerase complex [11,12]. The 3′ single-strand DNA (ssDNA) generated during resection is protected from degradation by binding of Replication Protein A (RPA), which is then displaced by Rad51, with the aid of yeast Rad52, from the 3′ ends of the ssDNA. This leads to a strand invasion process in which the Rad51 nucleoprotein filament invades a stretch of homologous double strand DNA (dsDNA) by displacing the complementary strand to form a displacement loop (D-loop). DNA synthesis mediated by polymerases and the replication processivity clamp PCNA then takes place at the 3′ end of the invading strand using the homologous donor strand as a template, followed by resolution of the interlinked DNA joint molecules. There exist multiple sub-pathways of HR such as the canonical double strand break repair (DSBR) pathway, the synthesis-dependent strand annealing (SDSA) pathway and the single strand annealing (SSA) pathway. For detailed reviews on mechanisms of HR and its sub-pathways, see [13,14].

3.2. Nucleosome disassembly during HR

Chromatin dynamics at the site of the DSB appears to play critical roles in facilitating the repair via HR. Immediately after the formation of a DSB, a variety of chromatin modifications followed by reorganization and disassembly of nucleosomes occurs in the vicinity of the break to facilitate and provide access to repair factors. Early studies in *S. cerevisiae* showed that histone levels decrease in the vicinity of a DSB as inferred from chromatin immunoprecipitation (ChIP) experiments followed by quantitative PCR (qPCR) of DNA regions surrounding the DNA break [15-17]. These studies also showed increased susceptibility of DNA near a DSB to digestion by micrococcal nuclease, and taken together, indicated compromised nucleosome integrity and likely histone eviction near a DNA break. Similar eviction of histones surrounding a DSB has been observed in mammalian systems and was found to be dependent on the Mre11-Rad50-Nbs1 (MRN) complex (MRX in yeast) and the DNA damage response ataxia-telangiectasia (ATM) kinase [18,19]. Consistent with earlier work, a more recent study in budding yeast performing MNase digestion followed by qPCR showed that nucleosome occupancy around a break is reduced by more than 75% due to 5′ to 3′ resection at the break [20]. Moreover, a high resolution MNase-seq genome mapping in yeast demonstrated that nucleosomes in the immediate vicinity (~200 bp) of an inducible site-specific DSB were removed rapidly, followed by a more gradual reorganization and eviction of nucleosomes up to ~8 kb on either side of the break in an MRX-dependent manner [21]. In agreement with the above studies, recent work in

budding yeast showed using strand-specific ChIP-seq that ssDNA binding proteins such as RPA, but not histones, are detected near an induced site-specific DSB in a strand-specific manner, pointing to a model where histones are evicted near a DSB and are not found as a persistent species on resected ssDNA [22]. Analogous to nucleosome dynamics in DSB repair in somatic cells, nucleosomes surrounding DSBs generated during meiosis in yeast have also been shown to be disassembled after programmed breaks are formed across the genome [23]. Finally, although relatively underexplored, linker histones appear to be evicted from the vicinity of DSBs as well. A study in human cell lines showed that the linker histone isoform H1.2 suppresses ATM activity, protecting chromatin from aberrant ATM loading and activation, and upon DNA damage, undergoes rapid PARP1-dependent chromatin dissociation through poly-ADP-ribosylation (PARylation) of its C terminus and further proteasomal degradation to permit full activation of ATM [24]. This is consistent with earlier work in budding yeast which showed that the linker histone H1 inhibits HR and its depletion increased resistance to DNA damaging drugs [25]. A similar study in mouse embryonic cells also showed that depletion of the linker histone H1 caused hyper-resistance to DNA damage by increased activation of damage related signaling pathways and checkpoints [26]. Taken together, these studies demonstrate using various techniques that histones are evicted during HR from the vicinity of the DNA break.

The precise mechanisms and players involved in nucleosome disassembly in the vicinity of a break and their coordination and crosstalk with repair processes are not fully understood. The use of site specific nucleases such as the HO endonuclease in budding yeast and the I-PpoI and AsiSI nucleases in mammalian cells has enabled histone occupancy to be measured around DSBs by ChIP analysis, greatly enhancing the ability to detect and study chromatin disassembly and assembly around DSBs [18,27,28]. Histone removal appears to be closely intertwined with DNA end resection. Multiple studies in yeast and mammalian cells have shown that components of the yeast MRX (or MRN in mammals) complex that initiate short range resection, are also required for the eviction of histones surrounding a break [15,18,19,29] (Fig. 2). Various studies have also shown roles for ATP-dependent nucleosome remodelers that mediate DNA end resection also promote chromatin disassembly. For example, nucleosome remodelers such as Fun30 and INO80 in yeast that are required to facilitate DNA end resection, also facilitate removal of histone H3 from around DSBs undergoing HR [19,30-32] (Fig. 2). Due to its central position in the nucleosome if H3 is removed by default the entire nucleosome is disassembled. Additionally, knocking down either the p400 ATPase, which belongs to the INO80 family of ATP-dependent nucleosome remodelers, or Rad51, with which it interacts to form a complex, leads to a decrease in histone loss around DSBs in human cells [33]. Micrococcal nuclease mapping of nucleosomes around the yeast HO lesion revealed that the yeast ATP-dependent nucleosome remodeler RSC also mobilizes nucleosomes to promote HR [16]. In the absence of any of these factors, HR is defective. As such, the evidence for nucleosome mobilization and disassembly during HR, and its requirement for HR, is convincing.

One aspect that was not completely clear, however, is if nucleosome removal near a break precedes 5′ to 3′ resection or is a consequence of the latter. In this regard, the studies by Shim et al. indicate a 30 min delay in DNA end resection compared to nucleosome mobilization, [16], while other studies find chromatin disassembly, as detected by ChIP

analysis, and end resection to be kinetically inseparable [17]. *In vitro* studies have shown that resection by *S. cerevisiae* Sgs1-Dna2 and Exo1 is blocked by nucleosomes, yet Exo1 resects quickly and with high processivity in vivo near meiotic breaks, indicating that nucleosomes are destabilized, or histones are removed prior to end resection [23,34]. Furthermore, while ATP-dependent nucleosome remodelers such as INO80 and Fun30 have been shown to be important for the removal of histones such as H3 and histone variants such as H2AZ from around a DSB in yeast, Fun30 has also been shown to promote resection by both Sgs1-Dna2 and Exo1 pathways and INO80 promotes DNA end resection, raising the possibility that nucleosome remodeling and eviction by Fun30 and INO80 facilitate subsequent end resection [30,35-37]. Consistently a recent study in budding yeast showed using strand-specific ChIP-seq that reduced histone eviction in the absence of RSC and SWI/SNF complexes led to a decrease in resection [22]. The answer to this question was finally provided by a recent high resolution spatiotemporal micrococcal nuclease mapping analysis of nucleosome occupancy and positioning upon induction of an unrepairable HO lesion [38]. This study found that immediately after induction of the DSB, one nucleosome flanking the break disappears while the adjacent nucleosome on either side of the break repositioned themselves further from the DSB in a manner independent of DNA end resection. This is followed by MRX mediated end resection and concomitant disassembly of nucleosomes up to 8 kb away from the DSB. As such, the initial local changes to the chromatin structure at a DSB occur in a manner independent of end resection, but the bulk disassembly of histones around a DSB is dependent on end resection [38] (Fig. 2).

The histone chaperones that mediate chromatin disassembly during HR are less clear. At least for DSBs induced within the rDNA loci, knocking down both isoforms A and B of human chaperone anti-silencing function 1 (ASF1) was shown to attenuate eviction of histones H3-H4 from sites of HR, while knocking down the nucleolar protein nucleolin attenuated eviction of H2A-H2B from sites of HR in the nucleolus [19] (Fig. 2). Other factors that regulate histone eviction during HR include PTMs of histones, such as ubiquitination of H2B by the ubiquitin ligase Bre1, that was shown to be important for its eviction from the vicinity of DSBs in yeast [39]. After eviction of histones from around DSBs, their fate appears to be degradation as treatment of yeast with a radiomimetic drug Zeocin that induces global DSBs, causes a 20–40% loss of total core histone proteins (H2A, H2B, H3, H4) from yeast cells [40]. Levels of the histone variant H2A.Z, however, remained relatively stable. This global histone loss was shown to be from chromatin and was proteasome mediated in addition to being dependent on the DNA damage checkpoint and the INO80 nucleosome remodeler, and functionally enhances chromatin mobility and the homology search [40].

3.3. Chromatin reassembly during HR

While disassembly of nucleosomes is important for allowing access of break sites to repair factors, reassembly of nucleosomes is important for restoring the chromatin conformation of the damage sites to their original state and resumption of the cell cycle. Nucleosome assembly during HR has been shown to be coupled with DNA synthesis and is mediated by histone chaperones such as Chromatin Assembly Factor 1 (CAF-1) in yeast, in a PCNA-interaction dependent manner [41-44] (Fig. 2). Aiming to understand the precise role of such

nucleosome reassembly, multiple studies have shown that chromatin assembly mediated by histone chaperones Asf1 and CAF-1 is not required for repairing the DSB per se in budding yeast but is needed for turning off the DNA damage cell cycle checkpoint, termed checkpoint recovery (Fig. 2) [17,45,46]. Acetylation of H3 K56 by Asf1 and the histone acetyl transferase Rtt109, is required to reassemble nucleosomes on repaired DNA and turn off the DNA damage checkpoint in yeast after HR [17]. Furthermore, the role of Asf1 in chromatin assembly in yeast can be bypassed by a mimetic of acetylation of H3 K56, which is presumably because this acetylation increases the ability of Asf1 to transfer histones H3-H4 to CAF-1 which in turn transfers the H3-H4 to newly-synthesized DNA [17,47]. CAF-1 and Asf1 mediated chromatin reassembly after HR in yeast promotes removal of Rad51, and the checkpoint sensors Ddc1 and Ddc2, to enable checkpoint recovery in budding yeast [46].

While all the evidence indicates that ongoing chromatin assembly is not required for HR in budding yeast, chromatin assembly appears to be intrinsically required for HR per se in fission yeast and metazoans. DNA synthesis dependent assembly of nucleosomes in fission yeast have been shown to stabilize joint molecules formed during HR occurring at replication forks and prevent disassembly of D-loops by the RecQ helicase Rqh1 [44,48]. In mammalian cells, chromatin assembly by both ASF1 and CAF-1 are required for Rad51 loading onto ssDNA, and in their absence DNA end resection and RPA coating extends extensively [49]. Another recent study providing evidence of repair synthesis coupled chromatin assembly, showed in mammalian cells that the ATP-dependent nucleosome remodeler ATRX along with the histone chaperone DAXX and PCNA function to deposit the histone variant H3.3 during G2, and in the process facilitated long range DNA synthesis and sister chromatid exchange [50] (Fig. 2). An important question that emerges is how final steps of repair such as joint molecule resolution or dissolution, gap filling, and ligation occur in the presence of nucleosomes that are deposited earlier in a manner coupled to the DNA synthesis step. DNA synthesis coupled nucleosome deposition during HR in yeast was shown to only partially restore the nucleosome occupancy level in a cell cycle independent manner after HR, and further restoration of nucleosome occupancy to levels seen before DSB initiation was only seen much later after resumption of the cell cycle [20]. It is tempting to speculate that such a mechanism of partial restoration of nucleosomes during HR stabilizes joint molecules while still allowing sufficient access for HR factors to complete final repair steps, following which the cell cycle resumes and nucleosome deposition restores its occupancy to pre-break levels (Fig. 2).

3.4. Non-homologous end joining

A second major pathway (and the predominant pathway of choice in mammalian cells) that is utilized to repair DSBs is non-homologous end joining (NHEJ), where the two ends of a DSB are ligated together in a flexible manner, allowing a variety of DNA end configurations to be repaired. During NHEJ, the Ku70–80 complex (KU) binds to free DSB DNA ends soon after a break is formed, providing a platform for the recruitment of a variety of factors involved in NHEJ and simultaneously suppressing Exo1 and Dna2-mediated end resection that promotes HR [12,51,52]. KU and the MRX/MRN complex act antagonistically to each other to regulate the level of resection and thereby influence the repair pathway choice between NHEJ and HR. Additionally, KU recruits downstream NHEJ factors such as the

ligase complex Dnl4-Lif1 (LIG4-XRCC4 in mammals) that enables the ligation of the DSB ends and Nej1 (XLF in mammals) which apart from stabilizing KU at DSB ends, inhibits Dna2 and stimulates the ligase activity of Dnl4-Lif1 [53,54]. Interestingly, the MRX/MRN complex is known to be important for both NHEJ and HR: its structural features are important for tethering of the DSB ends, and the catalytic activity is required for resection [55].

3.5. Nucleosome disassembly during NHEJ

Like HR, repair of a DSB by NHEJ necessitates disassembly of nucleosomes at least locally to provide access to repair factors. In this regard, Goldstein et al. observed that only H2A-H2B was lost from regions surrounding a break in the rDNA locus in G1-arrested mammalian cells which was likely going through repair by NHEJ as HR is downregulated in G1 phase cells and the NHEJ factor XRCC4 was recruited to the break [19]. Meanwhile DSBs in cycling cells showed loss of all four core histones near the break and was accompanied by recruitment of the ssDNA binding protein RPA, indicating that the repair in the cycling cells was by homologous recombination. In contrast, Li and Tyler showed in mammalian cells that DSBs at euchromatic loci that were repaired by NHEJ experienced a complete loss of all four core histones within a 750 bp range on either side from the DNA ends in a manner independent of end resection, but dependent on INO80 and the ATM kinase [56] (Fig. 3). In the absence of INO80 and ATM, NHEJ was compromised, supporting a model where localized finite nucleosome disassembly allows the access of NHEJ factors, while at the same time avoiding the atleast transient loss of epigenetic information that accompanies extensive nucleosome loss. The reasons for the discrepancy in these studies findings, as to whether H2A-H2B or all four core histones gets removed during NHEJ, are unclear, although the former study examined chromatin disassembly during NHEJ at heterochromatin regions while the latter examined chromatin disassembly during NHEJ at euchromatin regions. Recently in mammalian cells, a DNA repair factor APLF, that provides a scaffold for NHEJ factors, has been shown to bind both H2A-H2B and (H3-H4)2 and have histone chaperone activity [57-59]. This raises the possibility that APLF may function in transiently disassembling and storing histones while NHEJ factors repair the DSB, and subsequently may reassemble the nucleosomes back onto the ligated DNA after the completion of repair [59].

3.6. Nucleosome reassembly after NHEJ

Our current understanding of nucleosome reassembly after NHEJ is incomplete but appears to involve the so called “replication-dependent” chromatin assembly pathway despite no known occurrence of significant DNA synthesis during NHEJ. Early genetic epistasis analysis indicated that the “replication-dependent” CAF-1 histone chaperone complex is involved in both HR and NHEJ mediated repair of DSBs in budding yeast [42]. Additionally, CAF-1 was shown to be induced upon generation of DSBs in quiescent human cells and was shown to colocalize with the NHEJ factor XRCC4 [60]. Moreover, PCNA, a known interactor of CAF-1, has also been shown to interact with the KU heterodimer in human cells [61,62]. However, more recent high resolution MNase-seq approaches probing NHEJ repair in yeast have indicated that the local chromatin architecture is restored rapidly via nucleosome reassembly in a manner independent of DNA replication in G1 arrested yeast

cells, suggesting that repair-coupled but replication-independent chromatin reassembly is involved in restoring nucleosome patterns surrounding DSBs following NHEJ repair [38]. Strikingly, the nucleosomes return to their original pre-lesion locations on the DNA after repair by NHEJ [38]. Why full chromatin assembly after HR of the HO lesion requires passage through the cell cycle [20] while chromatin assembly after NHEJ of the HO lesion does not require DNA replication [38], despite both processes involving Asf1 and CAF-1 mediated chromatin assembly, is unclear. It is possible that both replication-dependent (i.e., CAF-1 dependent assembly of H3.1-H4 onto DNA) and replication-independent (i.e., HIRA/DAXX dependent assembly of H3.3-H4 onto DNA) mechanisms of nucleosome assembly play roles in restoring nucleosome integrity at the repair site after the completion of NHEJ. Consistent with this idea, Li and Tyler demonstrated using human cells that nucleosome reassembly around DSBs that were repaired by NHEJ was facilitated by the replication-independent HIRA histone chaperone as well as the replication-dependent CAF-1 histone chaperone in an inter-dependent manner, in conjunction with ASF1 [56] (Fig. 3). The exact mechanisms by which such replication-dependent histone reassembly pathways may facilitate NHEJ where there is hardly any DNA synthesis is yet to be explored, as are the mechanisms of coordination between the various reassembly modes. Finally, apart from core histones, certain histone variants also seem to play a dynamic role near DSBs. For instance, the histone H3.3 variant was shown to be deposited near DSBs by the chromatin remodeler CHD2 and plays a role in recruiting NHEJ core factors such as KU and XRCC4 in mammalian cells [63]. Similarly, the incorporation of H2A.Z facilitates the loading of Ku70, and its subsequent removal by the histone chaperone ANP32e is important for completion of NHEJ [64,65]. Clearly chromatin disassembly and assembly both facilitate the access / recruitment of the repair machinery during NHEJ.

3.7. Mismatch repair

Polymerase misincorporation errors during DNA replication are repaired by the mismatch repair (MMR) pathway, and defects in this pathway lead to accumulation of mutations in the cell. In budding yeast, various kinds of mismatches are initially recognized by the MutS homolog heterodimers Msh2-Msh6 (MutSα) or Msh2-Msh3 (Mutsβ), which then enter a sliding-clamp conformation that allows their diffusion on DNA [66,67]. The MutS homologs then recruit MutL homolog heterodimers, primarily Mlh1-Pms1, whose endonuclease activity is then activated by PCNA resulting in nicking of the newly synthesized strand of DNA in an ATP-dependent manner. Subsequently, these nicks may act as loading sites of Exo1 whose exonuclease activity results in excision of the newly synthesized DNA strand across the mismatch, or an alternate Polδ / Polε-dependent pathway involving strand-displacement synthesis may remove the nascent strand containing the mismatch. Finally, DNA polymerases re-synthesize the excised DNA, thus correcting the mismatch.

3.8. A delicate tug of war between chromatin assembly and mismatch repair

Advances have been made in our understanding of how the chromatin context closely interacts and communicates with the MMR machinery to regulate DNA repair. DNA replication is tightly coupled with nucleosome disassembly ahead of the replication fork and reassembly behind the fork that enables genome stability maintenance and epigenetic inheritance. Several histone chaperones such as CAF-1, Asf1, Rtt106 and FACT have

been implicated in nucleosome assembly after DNA replication [47,68-72]. Chromatin disassembly ahead of the replication fork is a poorly understood process. Regardless, after replication-dependent chromatin disassembly, when a mismatch is detected following a misincorporation event during replication, the cell must ensure that it is repaired before nucleosomes are assembled on the newly replicated DNA. Recent advances have been made in understanding interactions between histone assembly and mismatch repair, and how these two processes regulate each other.

It appears that the MMR machinery actively impairs chromatin assembly over the mismatch. On one hand, nucleosomes have been shown in vitro to have an inhibitory effect on mismatch recognition, ATPase, or ADP-binding, and sliding of human MutSα when interacting with DNA heteroduplexes [73,74]. Nucleosome deposition has also been shown to protect discontinuous mismatch-containing strands from excessive degradation by the MMR apparatus [75,76]. On the other hand, several studies have demonstrated using reconstituted biochemical systems that human MutSα inhibits CAF-1 and ASF1A-H3-H4 dependent formation of H3-H4 tetramers on DNA in the presence of mismatches [75-77] (Fig. 4). Consistent with the mutually inhibitory roles of MMR and nucleosome deposition, CAF-1 was shown to physically interact with mismatch repair factors MutSα and PCNA, which also interact with each other [41,47,77-79]. Finally, it was also shown using *Xenopus* egg extracts as a model system that nucleosomes are excluded from a > 1-kb region surrounding a mismatch in a MutSα-dependent but MutL homolog-independent manner, countering CAF-1 and HIRA mediated nucleosome assembly [80]. Together these studies point to a model in which replication coupled nucleosome assembly and MMR are in a delicate tug of war to ensure that genomic stability and epigenetic inheritance are maintained.

On the other side of the coin, chromatin assembly factors in turn regulate mismatch repair (Fig. 4). Consistent with its interaction with members of the MMR pathway, CAF-1 was shown to suppress a parallel activity of the MMR machinery, namely the cytotoxic response to Sn1-type methylating agents [81]. Other histone chaperones have also been implemented in regulating MMR. For example, Terui et al. showed data suggesting that the histone chaperone FACT along with the chromatin remodeling ATPase Smarcad1 assists nucleosome exclusion from the surrounding DNA in the presence of a mismatch [80]. Additionally, CAF-1 and Rtt106 were shown using genetic assays to suppress heteroduplex rejection, a pathway in which MutS homolog proteins promote the fidelity of HR by identifying mismatches during strand invasion and unwinding the heteroduplex by recruiting the STR complex [82,83]. Further in vivo studies are required to get a better understanding of the interplay between nucleosome deposition and MMR.

3.8.1. Excision repair—Base excision repair (BER) is the primary mechanism that removes base lesions that result from oxidation, alkylation, deamination, and spontaneous hydrolysis [84]. So far, about 100 nucleobase lesions have been identified in vitro, and many of them have been identified in cellular DNA [85]. Given the fact that ~10^4 nucleobase lesions occur per cell per day, cells need to efficiently repair them to maintain genomic integrity and prevent mutagenesis [85,86]. Several enzymes are required for BER, including a DNA glycosylase, apurinic/apyrimidinic (AP) endonuclease, gap-filling DNA polymerase,

and DNA ligase [87]. These enzymes are coordinated in a sequential manner to ensure efficient repair and prevent accumulation of deleterious BER intermediates such as AP sites or strand breaks [88].

Additionally, environmental factors such as UV radiation and chemotherapeutic drugs (e.g., cisplatin) can induce bulky lesions, which cause significant distortion to the structure of the DNA double helix. Bulky lesions are generally more harmful to the cell than base damage, because they can effectively block DNA replication and transcription [89]. The major repair pathway for bulky lesions is nucleotide excision repair (NER), which is a multi-step process comprising ~30 repair proteins [89]. Mutations of many NER genes are associated with severe human diseases such as Xeroderma pigmentosum (XP) and Cockayne syndrome (CS) [90]. XP patients are at extremely high risk of developing skin cancers, while CS patients are characterized by neurological degeneration and premature aging. Collectively, excision repair (ER), including BER and NER, acts as an essential 'first-line' defense mechanism in the cell to maintain genome stability by removing a wide spectrum of common DNA lesions. On the other hand, ER is a double-edged sword for chemotherapy. DNA adducts induced by chemotherapeutic agents may be removed by ER factors in cancer cells. The removal of these lethal DNA adducts in tumors can compromise chemotherapy and cause drug resistance [91].

ER proteins have to recognize and remove damage in all chromatin, at different levels of chromatin compaction [92]. Therefore, a central challenge of DNA repair studies in eukaryotes is to understand how repair factors cope with chromatin to efficiently repair DNA damage and avoid mutations. Biochemical data indicates that even the first level of chromatin compaction – the nucleosome – can significantly inhibit BER and NER [93,94]. These studies suggest that DNA damage in nucleosome-occupied DNA is more likely to persist and potentially cause mutations. In addition to affecting repair, the nucleosome structure has also been shown to modulate the formation of certain types of DNA lesions (e.g., UV photoproducts) [92].

4. Nucleotide excision repair

Genome-wide surveys of NER activity revealed that UV damage repair is strongly modulated by the chromatin state [95,96]. Specifically, fast NER preferentially occurs in open chromatin regions characterized with DNase I hypersensitivity and active histone PTMs. In contrast, slow repair is observed in closed and transcriptionally inactive chromatin [95,97]. The impact of chromatin states on NER is correlated with the mutation density in the melanoma genome. Closed chromatin regions, which usually are repaired less efficiently by NER, are associated with high somatic mutations in melanomas while lower mutation density is found in accessible chromatin regions, indicating that accessibility to the NER machinery is generally reduced by the closed chromatin state, independent of the damage type [95,98], [96,99].

4.1. Nucleosome disassembly during NER

It has not yet been demonstrated that core histones are disassembled during NER although ANP32e evicts histone variant H2A.Z from the chromatin and histone H1 is also evicted

from UV-damage chromatin during NER repair (Fig. 5) [100,101]. It is possible that cores histones are disassembled during NER, because factors that reassemble chromatin after NER have been identified and space will be required to allow their reassembly (see below). Furthermore, the histone variant H2A.X is deposited at NER sites by FACT histone chaperone [100], which is likely to depend on the concomitant removal of H2A at sites of UV damage. Several ATP-dependent nucleosome remodelers promote NER, but whether this is via promoting nucleosome disassembly per se has not been shown. In mammalian cells, both SWI/SNF and INO80 remodeling factors stimulate NER as their down-regulation confers hypersensitivity to UVC, associated with inefficient removal of UV damage and impaired recruitment of early/intermediate NER factors [102-106]. The coupling between remodelers and NER factors is further supported by co-immunoprecipitation experiments revealing interactions between the SWI/SNF complex subunits BRG1 and SNF5/INI1 with XPC [104, 106] and between INO80 and DDB1 [102]. Human ISWI isoform SMARCA5/SNF2H and the binding partners ACF1 and WSTF are rapidly recruited to UV-C induced DNA damage to specifically facilitate CSB proteins binding and to promote lesion-stalled transcription recovery [107].

Histone PTMs appear to promote access of the NER machinery, potentially via promoting chromatin disassembly. Acetylation was the first histone PTM shown to promote UV-damaged chromatin accessibility and to stimulate NER, as reported in yeast and mammalian cells [108]. Histones H2A, H3 and H4 are ubiquitylated in the course of NER in mammals [109-114]. By examining H3 and H2A extractability from damaged chromatin in vitro and in vivo, histone ubiquitylation was shown to destabilize nucleosomal organization, suggesting that histone ubiquitylation during NER could facilitate access to damaged chromatin in vivo by promoting histone displacement from damaged nucleosomes [110,115]. The mechanisms for how this modification are established in response to UVC damage and coupled with NER are still under investigation. Several E3 ubiquitin ligases acting at different steps of the NER pathway have been identified as histone modifiers. The E3 ubiquitin ligase complex RBX1 (Ring-BoX 1)-Cul4 (Cullin 4)-DDB1-DDB2 (DNA Damage Binding protein), a key player in UVC damage detection, was shown to ubiquitylate H2A in vitro and in vivo [109,111]. This complex is also involved in H3 and H4 ubiquitylation stimulated by UVC irradiation [110]. In addition, H2A was found to be ubiquitylated by the ubiquitin ligase RNF2 in a manner dependent on the NER factor XPA [112]. The ubiquitin ligase RNF8 also modifies H2A upon formation of ssDNA, an NER intermediate resulting from lesion processing [114]. While the multiplicity of E3 ubiquitin ligases involved in modifying H2A complicates the analysis of its function in the NER pathway, it clearly underlines a critical role of this modified histone in this process.

Somewhat surprisingly, there also appears to be chromatin assembly of H3.3-H4 even during repair of UVC damage by NER. This was revealed by HIRA depositing H3.3 onto chromatin during NER, recruited via a ubiquitin-dependent segregase VCP [116,117]. The function of this H3.3 incorporation during NER is unclear because it is not required for NER nor for transcription recovery after DNA repair [116,117]. However, HIRA functions in a histone-chaperone independent manner to promote transcriptional restart after UV repair [117]. Perhaps the H3.3 incorporation during NER reflects the dynamic nature of the chromatin around the DNA lesions. Newly synthesized H2A is incorporated at sites of NER

by the FACT histone chaperone and this is required for transcriptional restart after NER [118].

4.2. Nucleosome reassembly after NER

Once NER is complete, chromatin assembly after NER is mediated by CAF-1 dependent assembly of newly synthesized H3-H4, as shown both biochemically and in cells using fluorescently tagged histones. [119-121,122]. Consistent with a role in chromatin assembly after DNA repair, CAF-1 is not required per se for efficient repair of UV lesions or for the recruitment of NER factors to damage in human cells [123]. As is the case during DNA replication, the direct interaction of CAF-1 with the polymerase sliding clamp PCNA helps tether CAF-1 to sites of UV repair [41,119]. ASF1 functions synergistically with CAF-1 to assemble nucleosomes during NER in vitro and helps turning off the DNA damage checkpoint after UV irradiation both in yeast and mammalian cells [45,124,125]. ASF1 acts as a donor of new histones for CAF-1 in chromatin restoration coupled to NER. Another attractive possibility is that ASF1 could also be involved in old histone recycling at damage sites as described at the replication fork [126]. H2A ubiquitylation has also been proposed to occur after repair synthesis and to be dependent on the H3.1 histone chaperone CAF-1 [113]. Histone ubiquitylation, reported to destabilize nucleosomes, might help ATP-dependent nucleosome remodelers to reposition newly formed nucleosomes and could thus be an important player in chromatin restoration upon UVC irradiation. Future studies may also give more insights into the composition of nucleosomes formed upon repair-coupled chromatin restoration by determining whether histone variants other than H3.1 get deposited at NER sites.

5. Base excision repair

General inhibition of BER by nucleosomes has been observed in vitro using purified BER enzymes and reconstituted nucleosomes [127]. By changing the damage location to different rotational positions on the nucleosome (e.g., either facing “in” towards the globular core of the nucleosome or “out” from the globular core), it has been shown that BER of uracil residues is significantly modulated by the nucleosomal rotational settings, presumably because uracil lesions at “out” rotational settings are more easily recognized by the uracil-DNA glycosylase [128,129]. This periodic BER pattern in nucleosomes may in some cases promote a similar mutation periodicity in certain types of human cancer, such as esophageal cancer and gastric cancer [130]. Low BER activity at “in” rotational positions could promote the persistence of unrepaired base damage at inward facing positions, thereby promoting mutagenesis at these positions in cancers. In contrast, the high BER activity at “out” positions may reduce mutation accumulation at outward rotational settings in nucleosomes.

Genome-wide mapping of base damage has provided new insights into BER kinetics in chromatin. Mapping alkylation lesions remaining after repair indicated that BER is strongly modulated by nucleosome organization in gene coding regions. When ~5000 yeast genes were aligned at their transcription start sites (TSS), there was a striking repair periodicity that correlated with the stereotypic nucleosome positioning (e.g., +1, +2, and

so on nucleosomes [131]). BER is elevated in nucleosome-depleted regions (NDR) in gene promoters and also in nucleosomal linker DNA, but repressed within nucleosomes, particularly near the nucleosome dyad axis, indicating that the translational setting of the DNA lesion affects its repair efficiency in vivo [131]. Consistent with BER being less efficient at the DNA at the center of the nucleosome, the mutation density is elevated near the nucleosome center after treatment with alkylating agents, suggesting that the reduced repair of alkylation damage near the central dyad promotes mutagenesis [131].

5.1. Nucleosome dynamics during BER

Our current knowledge of the factors that helps the BER machinery repair DNA lesions within the nucleosome context in vivo is rudimentary. However, we know that the histone chaperone FACT participates in BER through its “co-remodeling” activity and acts in concert with the RSC ATP-dependent nucleosome remodeler to facilitate the removal of uracil from DNA, indicating that FACT could promote the repair of DNA damage in the initial step of BER [132]. The findings of chromatin remodelers cooperating with histone chaperones highlight the sophisticated mechanisms utilized by cells to regulate BER.

There is increasing evidence implicating the participation of other ATP-dependent nucleosome remodelers in BER. In biochemical studies, the activity of BER factors such as OGG1, APE1, and pol β are stimulated by the SWI/SNF complex [133]. A similar observation has been made that the barrier imposed by histones is greatly alleviated by ISW1 and ISW2 complexes for pol β mediated DNA synthesis [134]. Furthermore, an overall increase in BER, especially at inward-facing sites, is achieved by RSC [132,135]. The participation of chromatin remodelers in modulating BER has also been indicated by in vivo studies, although detailed mechanisms need to be further elucidated. One member of the SWI/SNF family of ATP-dependent chromatin remodelers, CSB (Cockayne syndrome group B), has been shown to function in the repair of 8-oxoG lesions [136,137]. Furthermore, CSB co-localizes with OGG1 after γ-radiation, and its knockdown and mutations result in a reduced level of OGG1 expression and 8-oxoG repair [137]. Depletion of subunits of RSC and INO80 complexes increases the sensitivity of yeast cells to alkylating agents [138]. Specifically, for RSC it has been shown that yeast lacking STH1, a critical ATPase subunit of the RSC complex, exhibit genome-wide BER deficiency in removing alkylated bases and their chromatin shows reduced accessibility to micrococcal nuclease digestion in the absence of STH1 [138].

Histone PTMs also regulate BER in a manner that likely functions to influence the accessibility of the DNA within the nucleosome, either directly or indirectly. Histone PTMs enriched toward the 5’ end of active genes (e.g., H3K14ac, H3K4me3) appear to promote BER at the DNA regions near where they exit and enter the nucleosome (the nucleosome edges), but paradoxically repress repair at the dyad, while PTMs that are enriched toward the 3’ end of genes (e.g., H3K36me3 and H3K79me3) display the opposite trend [131,139]. Previous studies have suggested that H3K14ac can promote repair in part by enhancing binding of the ATP-dependent nucleosome remodeler RSC to lesion-containing nucleosomes [140]. RSC-remodeled nucleosomes may have increased DNA accessibility near the nucleosome edges, which could explain the faster BER toward the DNA ends of

H3K14ac nucleosomes [131]. On the other hand, H3K14ac has been shown to strongly inhibit the gap-filling activity of DNA polymerase β in BER near the nucleosomal dyad, which may contribute to the reduced BER at the dyad in H3K14ac-enriched nucleosomes in vivo [131,141]. Although these studies provide a potential mechanism for how histone PTMs affect BER, clearly further studies are needed.

6. Perspectives and future directions

Most of our current understanding of how chromatin impacts DNA repair has come from distinct technical advances that have allowed the field to (1) biochemically reconstitute MMR, NER and BER on chromatin templates, (2) measure repair efficiency within cells upon depletion of chromatin modulating factors, (3) induce site specific DSBs with endonucleases within cells, (4) examine incorporation of histones via SNAP-tag-based pulse-chase imaging, a powerful technique that allows tracking new or old histones in live cells and quantifying their turnover [142] and (5) detect localization of factors to repair foci, or sites of localized UVC irradiation within cells, or by ChIP to induced DSBs. Further improvements in our understanding of the interplay between chromatin dynamics and genome stability will necessitate development of new technologies. An important question that is yet to be well understood is how local and global nucleosome disassembly processes are coordinated after DNA damage [40,143] and what mechanisms relay damage-induced cellular responses from a local to a global level. Additionally, such loss of histones has been implicated in increased chromatin mobility that facilitates the repair process [143,144]. Several studies have subsequently been aimed at understanding mechanisms by which decreased histone levels promote increased chromatin mobility. For example, it was shown in yeast that global nucleosome loss resulted in decompaction of chromatin and ultimately resulted in increased global chromatin mobility that facilitated HR [144]. Another study showed using live cell microscopy and computational simulations that DNA damage led to increased chromatin subdiffusion and intrachromosomal distances, and provided evidence that genome-wide chromatin stiffening (mediated in part by H2A phosphorylation and leading to decreased chromosome folding) that occurred as a consequence of DNA damage was, at least in part, the basis of increased chromatin mobility [145]. A related question that warrants further investigation is how nucleosome loss during HR may be mediated at the template DNA in order to better facilitate strand invasion and stabilize the joint molecules. Such loss of nucleosomes from the template DNA may be simply achieved as a part of the global nucleosome disassembly process as discussed above or at a more local scale by specific signaling cascades ensuing from recognition of template sequences by the broken DNA during strand invasion. Another important area that remains to be fully explored is how mechanisms of nucleosome disassembly and reassembly may be differently regulated in euchromatic and heterochromatic genomic regions. Such context-specific regulation would seem necessary given that heterochromatic regions contain highly repetitive DNA sequences that may result in DNA breaks being repaired inappropriately if nucleosome disassembly isn’t regulated appropriately. Such regulation in heterochromatin may be facilitated by specific heterochromatic histone PTMs upon DNA damage and/or heterochromatic proteins interacting with and regulating histone chaperones following damage. In this regard, a recent study found that UV induced damage in pericentromeric heterochromatin in mammalian

cells leads to heterochromatin compaction changes and linker histone H1 (and possibly to a lesser extent H3.3 and H2B) removal from chromatin facilitated by the UV damage sensor DDB2 [101]. Interestingly, heterochromatin-specific histone PTMs were found to be maintained despite massive unfolding of heterochromatin following damage and was found to play a key role in deposition of new histones in the damaged DNA. The authors found that the deposition of new H3 histones in damaged heterochromatin was executed by histone chaperones such as H3.1-H4 deposition mediated by CAF-1, that has also been implicated in euchromatic DNA repair, and H3.3-H4 deposition mediated by HIRA, that was shown to accumulate on damaged heterochromatin in a manner comparable to damaged euchromatin, and possibly to a lesser extent DAXX, that was shown to be specifically recruited to damaged heterochromatin but not euchromatin.

Another important area that remains is “how is the epigenetic information restored after DNA repair?” We know that newly synthesized histones are incorporated after DSB repair and UV repair. This incorporation of newly synthesized histones challenges the maintenance of epigenetic information because newly synthesized histones are known to bear PTMs that differ from parental nucleosomal histones [146]. Thus, deposition of new histones could lead to substantial changes in the chromatin in repaired regions that if not reversed, would alter the transcriptional output of the repaired regions. Revealing how this happens would require approaches to determine histone PTM patterns specifically over the repaired DNA at multiple time points before and after repair at known genomic locations. We know from DNA replication that the parental histone PTMs are diluted 2-fold during replication, and it takes up to a cycle to modify the new histones to mirror the parental histones, while other modifications are added to both the parental and new histones continuously [147]. Notably, the dynamics of pre-existing histones and other variants also needs to be considered, and histone deposition of H3.3 at earlier steps in the NER process cannot be excluded. Further investigation of histone variant dynamics coupled to repair in vivo should now be possible by exploiting SNAP-tagging. Advances in our knowledge promise to further highlight the intertwined dance of histone chaperones and repair factors to ensure the maintenance of genome integrity.

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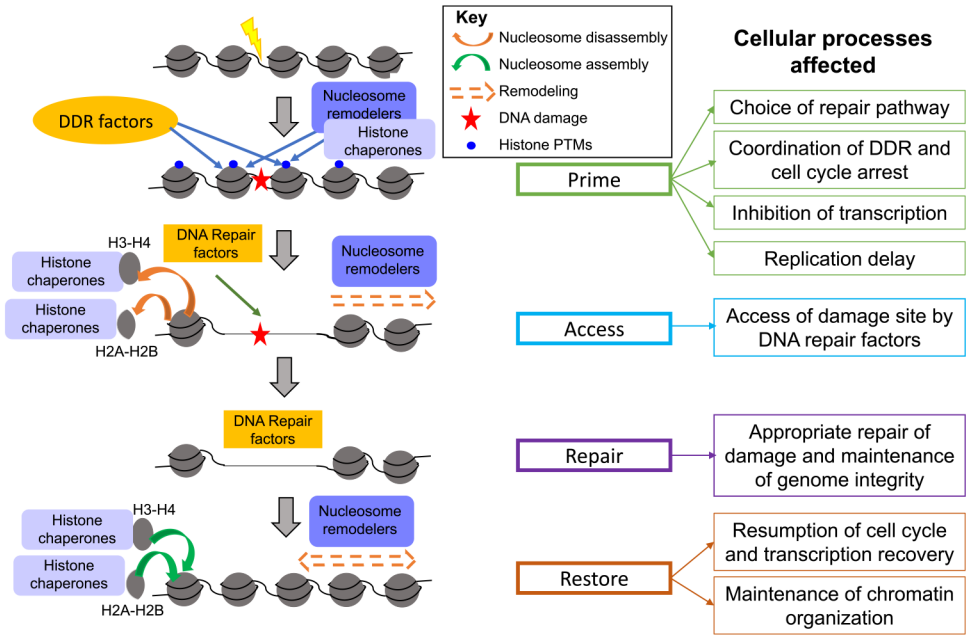

Fig. 1.

The Prime-Access-Repair model. The Prime-Access-Repair-Restore model explains how DNA is repaired in a chromatin context, as explained in the text. Only a subset of the histone PTMs are represented (those involved in recruitment on DDR factors, histone chaperones and chromatin remodelers).

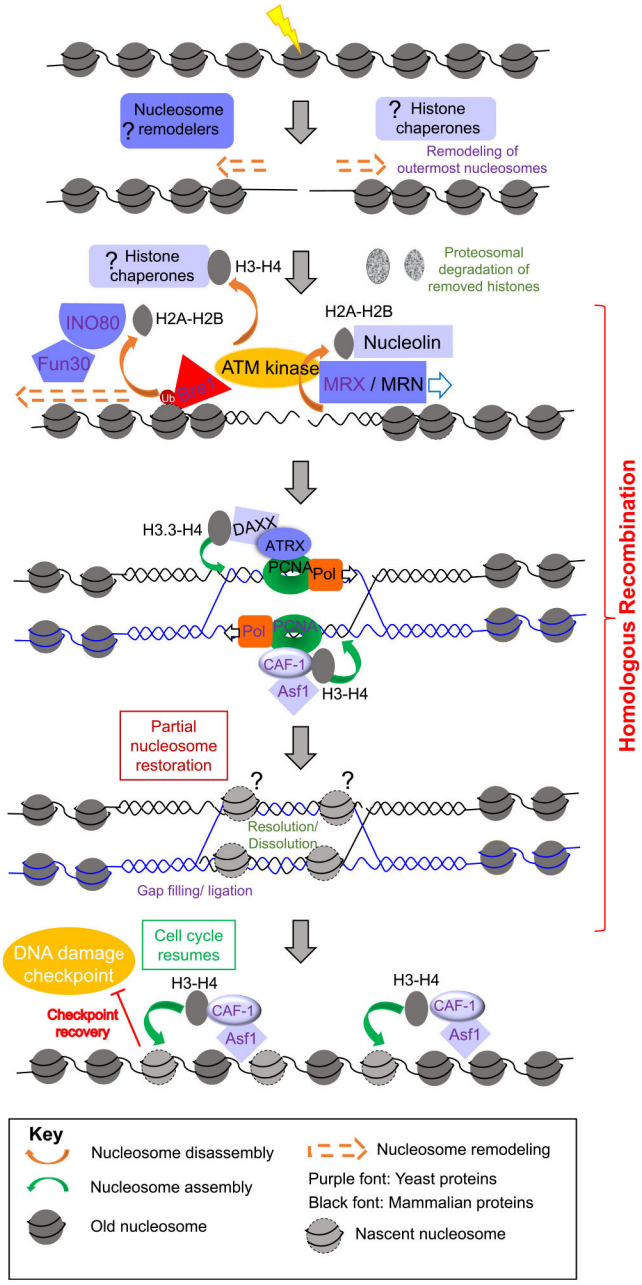

Fig. 2.

Chromatin disassembly and reassembly during homologous recombination. After DSB induction, a single nucleosome at the DSB is disassembled and the two adjacent nucleosomes reposition themselves away from the DSB, prior to DNA end resection. Subsequently, extensive chromatin disassembly around the DSB occurs concomitant with DNA end resection during HR, and the removed histones are degraded. Chromatin also appears to be reassembled during HR to promote various steps during HR, and once HR is complete chromatin is reestablished fully and the cell cycle checkpoint is inactivated via checkpoint recovery. The question marks indicate likely events, but that have not yet

been proven to occur. The font color corresponds to either yeast or mammalian systems, as indicated in the key.

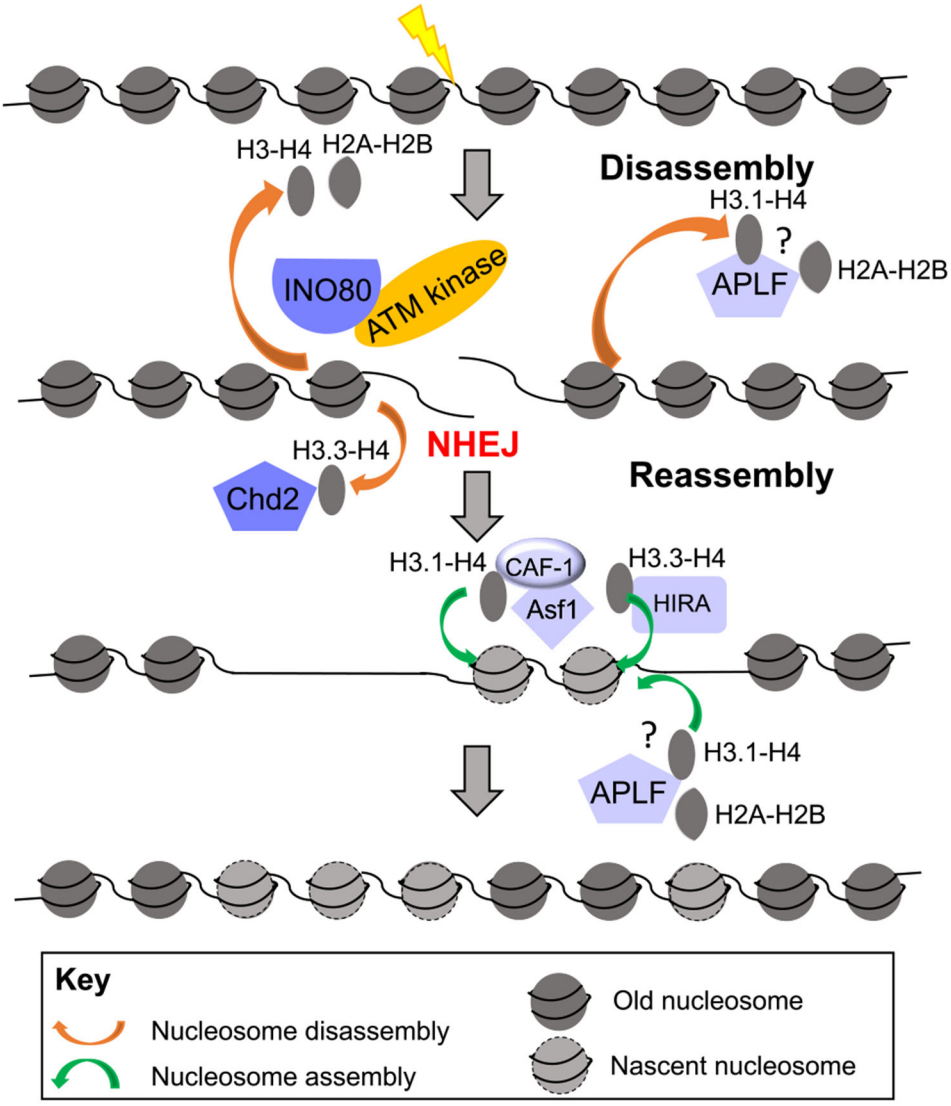

Fig. 3.

Chromatin disassembly and reassembly during non-homologous end joining. Chromatin is disassembled during NHEJ to promote DNA repair, and chromatin is reassembled after NHEJ, as described in the text.

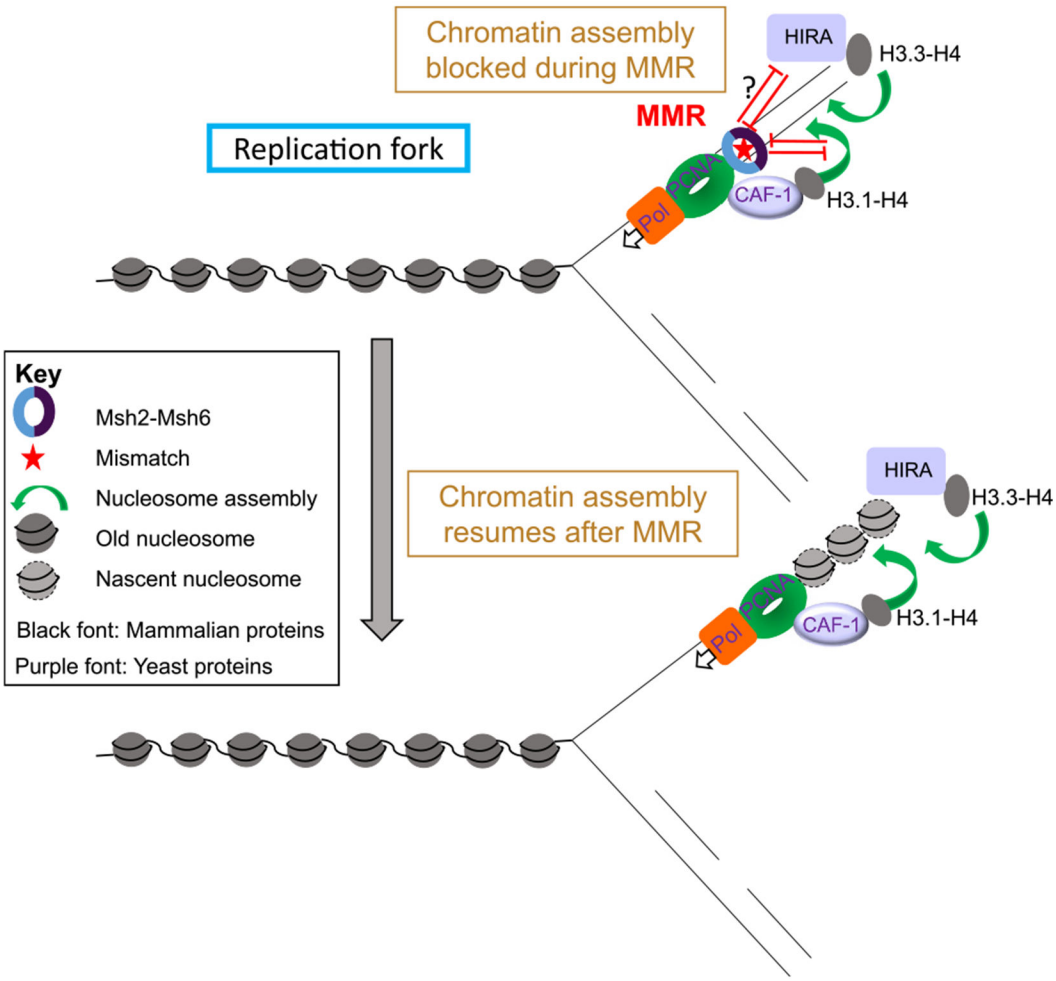

Fig. 4.

The interplay between chromatin disassembly / reassembly during mismatch repair. Replication-dependent chromatin assembly after DNA replication is halted when a mismatch is encountered while other factors promote the accuracy of MMR, as described in the text. Nucleosomes are deposited on DNA after mismatch is corrected.

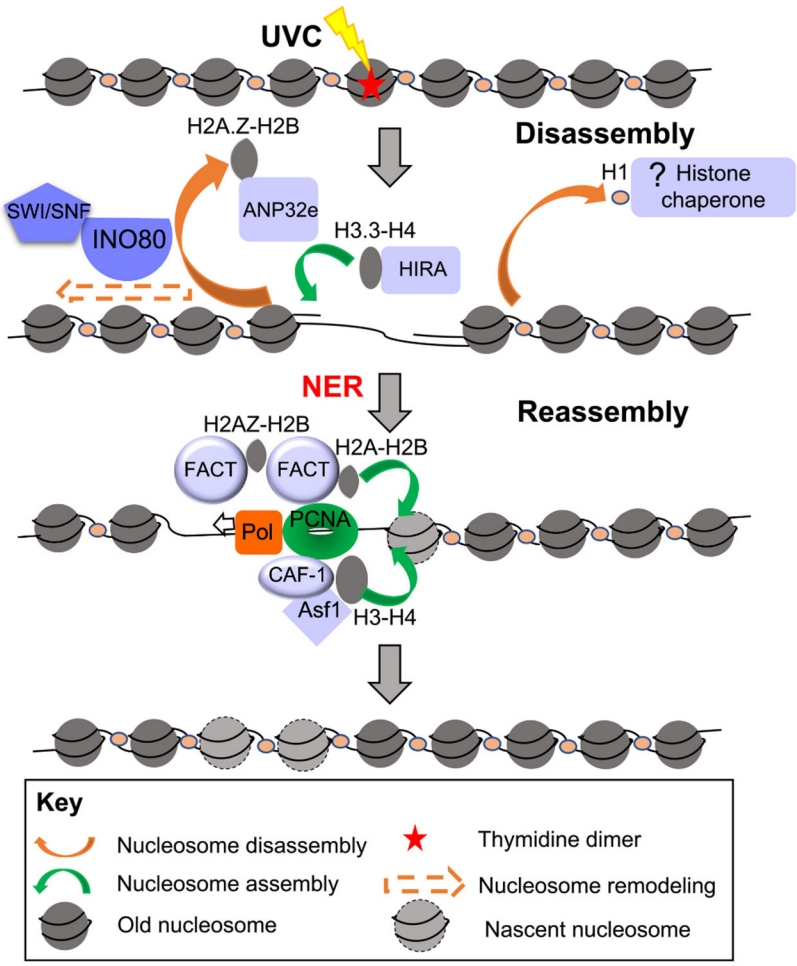

Fig. 5.

Chromatin disassembly and reassembly during nucleotide excision repair. Chromatin remodelers facilitate NER, while histones / histone variants are assembled during or after NER as described in the text. Mammalian proteins are shown here.