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ATP-Dependent Chromatin Remodeling Factors and DNA Damage Repair

Mary Ann Osley, **Toyoko Tsukuda**, and **Jac A. Nickoloff**
Molecular Genetics and Microbiology University of New Mexico School of Medicine Albuquerque, NM 87131

Abstract

The organization of eukaryotic DNA into chromatin poses a barrier to all processes that require access of enzymes and regulatory factors to their sites of action. While the majority of studies in this area have concentrated on the role of chromatin in the regulation of transcription, there has been a recent emphasis on the relationship of chromatin to DNA damage repair. In this review, we focus on the role of chromatin in nucleotide excision repair (NER) and double-strand break (DSB) repair. NER and DSB repair use very different enzymatic machineries, and these two modes of DNA damage repair are also differentially affected by chromatin. Only a small number of nucleosomes are likely to be involved in NER, while a more extensive region of chromatin is involved in DSB repair. However, a key feature of both NER and DSB repair pathways is the participation of ATP-dependent chromatin remodeling factors at various points in the repair process. We discuss recent data that have identified roles for SWI/SNF-related chromatin remodeling factors in the two repair pathways.

Keywords

NER, DSB repair; ATP-dependent chromatin remodeling

Introduction

The repeating unit of chromatin is the nucleosome, which consists of 146 bp of DNA wrapped approximately two times around a histone octamer of two H2-H2B dimers and an H3-H4 tetramer [1]. Nucleosomes are in turn assembled into arrays of increasingly folded structures that are inhibitory to the interaction of protein factors with DNA. Two classes of chromatin remodeling factors alter chromatin to allow factor access [2,3]. The first class contains modifying enzymes that catalyze a wide variety of post-translational modifications (acetylation, methylation, phosphorylation, ubiquitylation) of residues on both the histone “tails” and core regions[4,5]. Such modifications are postulated to signal downstream regulatory factors or to “loosen” the structure of chromatin [6]. The second class contains enzymes that use the energy derived from ATP hydrolysis to disrupt histone-DNA contacts, leading to structurally altered nucleosomes or to sliding or eviction of nucleosomes [7-13]. The founding member of ATP-dependent chromatin remodeling factors is yeast SWI/SNF, which contains a Swi2/Snf2 ATPase subunit that is present in related forms in a wide variety of chromatin remodeling complexes [14-17]. Although we do not fully understand how either class of remodeling factor alters chromatin *in vivo*, the action of these factors, either singly or

Tel: 505-272-4839 Fax: 505-272-6029 Email: mosley@salud.unm.edu

in combination, is postulated to expose DNA on the surface of the nucleosome to factors involved in transcription, replication, and repair [3,18-21]. Indeed, many of the same remodeling factors have been shown to play regulatory roles in all three processes. This implies that a specific set of signals or factors will be responsible for directing chromatin remodeling activities to their correct chromosomal locations. Extensive studies have shown this to be the case during transcription activation, where chromatin remodeling complexes are recruited to gene promoters through their association with site-specific activators or the RNA polymerase II (Pol II) machinery [22-25].

A useful model for the repair of DNA damage in a chromatin context is the concept of "access-repair-restore" [26,27]. This model posits that at sites of DNA damage, chromatin structure is altered to expose damaged DNA to repair factors, and once repair has taken place, chromatin is restored to its original state. Both classes of chromatin remodeling factors play roles in DNA damage repair, and in this review, we focus on the roles of ATP-dependent chromatin remodeling in the NER and DSB repair pathways (Table 1). The reader is also directed to reviews in this issue that explore the roles of histone modifying and assembly factors in DSB repair.

Types and sources of DNA damage

DNA damage poses a constant threat to genome stability, taking a variety of forms and arising from many endogenous and exogenous sources. There are four broad classes of DNA damage including base damage, helix distorting "bulky" adducts, strand breaks, and mismatches. The first three types comprise broken bonds or other chemical modifications to the DNA structure, whereas base mismatches have a normal chemical structure but lack complementary sequence information on the duplex strands. All of these types of DNA damage can be mutagenic, and many can disrupt normal DNA processes such as replication and transcription.

Base damage includes a wide variety of modifications to nucleotides including broken rings, small-scale chemical adducts and modifications to nucleotides such as alkylation and oxidation, and base loss, which produces apyrimidinic or apurinic lesions (collectively called abasic or AP sites). Some forms of base damage block DNA replication, but others are bypassed by low-processivity, error prone DNA polymerases. Base damage arises from reactive oxygen species (ROS) produced by metabolism or radiation [28-30]. There are a wide variety of helix distorting, bulky adducts including UV-induced cyclobutane pyrimidine dimers (CPDs) and 6,4-pyrimidone pyrimidine dimers (6-4PDs), chemical adducts, and intra- and interstrand DNA crosslinks. DNA strand breaks include single- and double-strand breaks (SSBs and DSBs) produced during normal DNA metabolism, at blocked replication forks, by nucleases, and by radiation [31-33].

DNA repair pathways

DNA repair pathways restore the chemical structure of DNA but do not always preserve genetic information. The known pathways are highly conserved through evolution. Certain lesions can be repaired by direct reversal, such as CPD repair by photolyase, SSB repair by DNA ligase, and O-6 methylguanosine repair by methyl transferases. However, most DNA damage is repaired by one or a combination of multi-step pathways including base-excision repair (BER), nucleotide excision repair (NER), and DSB repair [34]. BER operates on base damage and is initiated by a large number DNA glycosylases with varying degrees of lesion specificity [35]. These enzymes clip off damaged bases, creating an AP site, which is recognized by a 5′-deoxyribose-5-phosphate (dRP) lyase activity, producing a single-base gap that is repaired by a DNA polymerase and ligase. NER is mediated by a single group of proteins that recognize and repair a wide range of bulky lesions and involves as many as 40 proteins in humans [36]. The NER pathway initiates with an excision reaction catalyzed *in vitro* by six factors from

human cells, RPA, XPA, XPC, TFIIH (a complex with six subunits), XPG, and XPF-ERCC1. The respective factors in yeast are RPA, Rad14, Rad4, TFIIH, Rad2, and Rad1-Rad10. RPA augments the functions of XPA and XPC in damage recognition. TFIIH has multiple helicase and other activities that promote dual incisions by XPG and XPF-ERCC1 at sites ~30 nt apart and flanking the damage, and then release of the oligonucleotide containing the damage. Following excision, DNA polymerase δ and LIG1 complete the repair reaction [36]. NER includes two subpathways, global genome repair (GGR) and transcription-coupled repair (TCR). TCR results in increased repair in transcribed strands of transcribed regions and is dependent in part on two proteins defective in Cockayne's syndrome, CSA and CSB (ERCC6).

Double-strand damage (DSBs and interstrand crosslinks) cannot be repaired using the complementary strand as template. Repair is instead effected by non-homologous end-joining (NHEJ) which foregoes a repair template altogether, or by homologous recombination (HR) in which a homologous repair template, such as a sister chromatid or homologous chromosome, is found elsewhere in the genome. HR, and to a lesser extent NHEJ, also function in restarting stalled and collapsed replication forks. Both DSB repair mechanisms comprise multiple sub-pathways that act on different types of DSBs and can produce distinct outcomes [37,38]. NHEJ is often mutagenic, producing short deletions, and is usually mediated by DNA-dependent protein kinase (DNA-PK), comprising Ku70, Ku80, and the catalytic subunit (DNA-PKcs), the ligase IV/XRCC4 complex, and for certain reactions, Artemis [39]. HR is slower, but more accurate than NHEJ, and HR activity increases in S/G2 cell cycle phases when sister chromatids are available as repair templates. Gene conversion is a conservative HR outcome that preserves the gross structure of the genome, but associated crossovers or the non-conservative single-strand annealing (SSA) pathway can result in deletions or other large-scale genome rearrangements [38]. During HR, broken ends at the recipient locus are processed to long, 3' single-stranded tails to which RPA binds and is then replaced with RAD51 to form nucleoprotein filaments capable of searching for, invading, and transferring strands with a homologous duplex (donor locus). RAD51 is assisted by many “mediator” proteins including five RAD51 paralogs in higher eukaryotes (RAD51B, RAD51C, RAD51D, XRCC2, and XRCC3; Rad55 and Rad57 in yeast), RAD52, and RAD54. In higher eukaryotes, the BRCA1 and BRCA2 tumor suppressors also function in HR [40]. After the initial synapsis of the RAD51 nucleoprotein filament with the donor locus, the invading end is extended by DNA polymerase. Cross-strand structures termed Holliday junctions can form and branch migrate to extend heteroduplex DNA. Repair is completed when mismatches in heteroduplex are repaired and HR intermediates are resolved by Holliday junction cleavage and ligation, or by dissociation of the extended strand from the donor and re-annealing to ssDNA on the opposite side of the DSB (termed synthesis-dependent strand annealing).

DNA repair in chromatin

The roles of chromatin changes in DNA repair have been most widely studied for NER and DSB repair, and these are the focus of this review; see Jagannathan et al. [41] for a recent review of chromatin modification during BER. Because DNA repair occurs in a chromatin context, repair factors must overcome the restricted access to DNA in chromatin, particularly in nucleosome cores. The first step in DNA repair is lesion recognition, and although proteins that recognize specific lesions in naked DNA have been identified for each of the repair pathways, new evidence suggests that changes in chromatin also play a role in lesion recognition. In addition to enzymatic modification and repositioning of histones and nucleosomes, lesion recognition may be aided by structural changes in chromatin induced by the lesions themselves. Chromatin also affects later stages of repair, such as recruitment and retention of repair factors. These later-acting repair factors may have affinity for altered chromatin near a lesion, or for lesion-binding proteins in the context of altered chromatin. The extent of chromatin changes associated with different lesions and repair pathways may differ

markedly. Thus, bulky lesions repaired by NER may trigger changes to just a few nucleosomes, consistent with the short repair patches of this pathway. In contrast, DSBs trigger chromatin changes over Kb domains in yeast, and Mb domains in mammalian cells. It has been suggested that the larger-scale changes in mammalian cells reflect a need for greater amplification of DNA damage signals to ensure effective checkpoint control [42]. During DSB repair by HR, chromatin changes are also seen in undamaged donor loci that serve as repair templates.

Although each of the DNA repair pathways were originally defined as distinct processes, increasing evidence points to substantial functional overlap, cooperation, and competition among pathways. HR and NHEJ compete for DSBs [43], and both appear to function in replication fork restart [44,45]. MMR is critical for reducing replication errors and corrects mismatches arising during HR. MMR now appears to interface with both BER and NER [46-48]. DNA crosslink repair requires several pathways including NER, HR, and translesion synthesis [49]. DNA repair pathways are also fully integrated with other cellular stress response systems including the signaling networks that regulate cell cycle checkpoints and apoptosis. Because DNA repair occurs in a chromatin context, we anticipate that another level of integration among repair pathways will depend on chromatin modifications and remodeling activities. In this view, chromatin may regulate pathway efficiency and therefore pathway choice when in competition, pathway integration when multiple pathways are involved, and repair outcome.

Chromatin remodeling and NER

The limited accessibility of bulky lesions in chromatin to the NER machinery has been studied for many years *in vitro*, primarily using reconstituted nucleosomes with short DNA fragments containing defined lesions. Two themes that have emerged from this work are that lesion accessibility is increased when chromatin is “relaxed” by histone acetyltransferases (HATs), or when nucleosomes are altered or moved by ATP-dependent chromatin remodeling complexes. Chromatin structure itself can regulate damage induction, and hence control cellular sensitivity to DNA damaging agents. This was shown in a study of yeast and mouse cell high mobility group proteins, which bind to DNA in chromatin and protect it from UV damage, but do not influence repair [50]. A third theme developed from the well-known roles of chromatin remodeling in transcriptional regulation and its potential connections to enhanced repair in transcribed regions (TCR).

Chromatin remodeling by SWI/SNF family members during NER

It was recognized more than 20 years ago that NER is less efficient in chromatin than in naked DNA, suggesting that enzymes have limited access to DNA buried in nucleosome core regions [51]. Subsequent studies by the Smerdon group showed that NER was more rapid in linker DNA between nucleosomes than in nucleosome cores [reviewed in 52]. Although CPDs cause significant bending and unwinding of duplex DNA, this does not affect the way DNA wraps around nucleosomes *in vitro*, and for lesions in the nucleosome core, those facing outward from the nucleosome surface are not repaired faster than those facing inward [53,54]. These results indicate that DNA packing in nucleosomes is the principal determinant of the rate of NER, presumably because nucleosomes restrict access of NER proteins to segments of DNA, rather than just the lesion itself.

A number of *in vitro* studies focusing on the incision/excision steps of NER have shown that ATP-dependent chromatin remodeling enhances these steps, and that this activity is carried out by factors that contain a Swi2/Snf2-related ATPase. Dual incision by human NER proteins in dinucleosome substrates with defined 6-4PD lesions was enhanced by the ATP-utilizing chromatin assembly and remodeling factor ACF, which appears to move nucleosomes and increase the extent of nucleosome-free DNA in the linker region, rather than by fully displacing

nucleosomes [55]. The prototypical SWI/SNF ATP-dependent chromatin remodeling factor enhances repair catalyzed by purified human NER proteins in a reconstituted mononucleosome with a 200 bp DNA substrate containing a defined acetylaminofluorene-guanosine (AAF-G) lesion in the nucleosome core [56], and UV repair by photolyase was also stimulated by yeast SWI/SNF and the related ISW2 complex [57]. It appears that SWI/SNF increases accessibility to DNA in the nucleosome core, but it is also true that the NER repair factors increase the remodeling activity of SWI/SNF [56]. This suggests a cooperative relationship between repair and remodeling activities and *in vivo* evidence suggests that remodeling factors are recruited to damage before NER factors (see below). Interestingly, SWI/SNF activity is lesion-specific, with yeast SWI/SNF enhancing human excision nuclease repair of AAF-G and 6-4PD lesions, but not CPDs [58]. However, a study of UV damage recognition and incision in reconstituted nucleosomes by *Micrococcal luteus* UV endonuclease and phage T4 endonuclease V showed that human SWI/SNF did enhance CPD repair [59]. These disparate results could be due to differences between human NER proteins and bacterial/phage enzymes, lesion position effects, other differences in the reconstituted nucleosome systems, or differences between yeast and human SWI/SNF activity.

A recent study of UV repair by overexpressed photolyase in yeast showed that repair in transcriptionally active and inactive DNA occurred in seconds. This is faster than would be possible if repair required recruitment of ATP-dependent chromatin remodeling complexes, although repair was still blocked in heterochromatin and centromere regions [60]. Together, these results indicate that repair is enhanced by a combination of factors, including fast conformational changes in chromatin upon DNA damage, and slower changes mediated by chromatin remodeling proteins. The yeast UV response network has been further clarified in studies of the SWI/SNF family member, Rad16, which is a member of the NEF4 complex involved in NER. Rad16 appears to have both ATPase and ubiquitin ligase activities, and its ATPase is important for NEF4 function *in vivo*. In addition, NEF4 controls the level of the Rad4 lesion recognition protein through ubiquitylation of Rad23, a repair protein with links to proteasome function [61]. Although the ATPase activity is essential for Rad16 function, it is not known if this activity plays a role in chromatin remodeling.

A study by the Waters laboratory suggests that SWI/SNF has a significant role in increasing accessibility to repair factors *in vivo*. Interestingly, chromatin accessibility to restriction enzyme digestion increased over time after UV, but this increase in accessibility was attenuated by about 50% in a *swi2*Δ mutant, indicating a significant role for SWI/SNF-dependent chromatin remodeling after UV [62]. This group also investigated the role of Gcn5-mediated histone acetylation in modulating chromatin accessibility. Histones are hyperacetylated soon after UV or cisplatin exposure [63,64], and this enhances both lesion recognition and NER [65]. However, the extent and kinetics of this increase were the same in wild-type and *gcn5*Δ cells, indicating that other HAT activities are involved in the UV response. Together, the results suggest that chromatin modification by SWI/SNF and histone acetylation cooperate to maximize accessibility to UV lesions. This group further showed that both SWI/SNF and Gcn5-dependent chromatin modifications occurred independently of CPD recognition by Rad4 and Rad14, indicating that chromatin remodeling precedes NER. In the absence of Rad4 and Rad14, chromatin restoration to the pre-UV state was delayed [62], arguing that the lesions must be removed to attenuate chromatin remodeling signal. The nature of this signal remains a mystery, but a network that links chromatin changes to repair and other cellular stress responses is currently being defined. In mammalian cells the ING (inhibitor of growth) tumor suppressor proteins regulate cellular responses to UV, including cell proliferation, p53-dependent apoptosis and NER [66,67], and it was recently shown that p33ING2 enhances NER by facilitating histone H4 acetylation and recruitment of the XPA lesion recognition protein to damage sites [68].

ATP-dependent chromatin remodeling and transcription-coupled repair

A Swi2/Snf2 related ATPase, yeast Rad26, is the homolog of the mammalian TCR protein, CSB (ERCC6). Defects in CSB result in Cockayne's syndrome, characterized by UV sensitivity and neurological problems; the latter may reflect CSB roles in general transcriptional regulation [69,70]. Overexpression of Rad26 enhances NER in both transcribed and non-transcribed strands, and partially suppresses the GGR defect of cells lacking Rad7, another member of the NEF4 complex involved in lesion recognition [71]. CSB has been shown to directly modify chromatin structure in an ATP-dependent process in reconstituted nucleosomes, and it also binds to and modifies the DNA helical structure [72]. In that study, purified CSB was shown to increase DNase I sensitivity of DNA in reconstituted mononucleosomes, and to move an array of nucleosomes present on plasmid DNA. These CSB activities appear to depend on both its DNA and histone binding properties. CSB has critical roles in TCR, but is dispensable for GGR. Thus, CSB and Rad26 are SWI/SNF family members with roles in both DNA repair and transcription that appear to depend on chromatin remodeling activity. It has been hypothesized that CSB, through its interactions with RNA polymerase, couples transcription to repair and stimulates repair by remodeling chromatin at damage sites. However, it is important to note that there is as yet no direct evidence that CSB remodels chromatin *in vivo*, and an alternative model is based on evidence that CSB functions as a transcription elongation factor [73,74]. Consistent with this model, transcription is reduced by 50% in CSB-defective cells in the absence of UV damage [75]. In this view, CSB is thought to enhance cell survival after DNA damage independently of TCR, by promoting transcription through sites of damage, as shown for yeast Rad26 [76]. However, a recent report suggests that CSB has a direct role in promoting with data indicating that CSB is recruited to RNA polymerase stalled at UV lesions, and that CSB is critical for recruitment of several NER factors (XPA, XPF, RPA, and TFIIH [77]. Moreover, CSB recruits the p300 HAT, and the high mobility group protein HMGN1 to stalled RNA polymerase, suggesting roles for histone acetylation and HMGN1-mediated chromatin remodeling in TCR [77]. It remains unclear, however, whether recruitment of these repair and remodeling factors by CSB depend on binding to the CSB-RNA polymerase complex, or whether recruitment requires remodeling by CSB itself.

Chromatin remodeling and DSB repair

The most rapid change in chromatin after DSBs are formed involves the phosphorylation of the C terminus of histone H2A (the H2A variant, H2AX, in vertebrates and the major H2A species in yeast). Formation of phosphorylated H2A (hereafter referred to as γ-H2AX) occurs within minutes after a DSB is formed and spreads over a large chromatin domain (Kbs in yeast to Mbs in vertebrates) [78-80]. While the structural consequences of H2A phosphorylation are still not understood, γ-H2AX is required for the accumulation and retention of checkpoint proteins and DSB repair factors in damage foci but not for their initial recruitment [81-85]. In addition to the extended domain of chromatin remodeling characterized by γ-H2AX, more localized changes in chromatin also occur around DSBs. Laser induced DSBs in mouse embryo fibroblast cells lead to a local expansion and increased mobility of chromatin in the vicinity of the break, and a DSB at the yeast *MAT* locus results in the disruption and eventual eviction of positioned nucleosomes in a 5-6 Kb region around the break [86,87]. The local alterations in chromatin structure result from ATP-dependent events, and thus both mechanisms of chromatin remodeling-histone modification and nucleosome disruption-have been linked to the pathways that promote DSB repair.

ATP-dependent chromatin remodeling during DSB repair

At least six different ATP-dependent chromatin remodeling factors have been implicated in repair of DSBs (Table 1). It is believed that their roles in DSB repair are direct based upon

their recruitment to sites of DNA breaks and the repair defects of mutants in these factors. We discuss data primarily drawn from studies in yeast and flies that describe where each of these factors is postulated to act during DSB repair *in vivo*. The assay of choice for many yeast studies has been a genetic system devised by Jim Haber and colleagues, in which a single DSB can be created at the yeast mating type or *MAT* locus by galactose induced expression of the *HO* endonuclease gene [88]. The break at the recipient *MAT* locus can be repaired by either NHEJ or HR, depending on whether donor *HMRa* or *HMLα* sequences are present. The NHEJ pathway is used when donor sequences are absent and the HR pathway when the donors are present. Because the break can be rapidly formed at almost 100% efficiency, the system offers an excellent way to follow the kinetics and level of recruitment of chromatin remodeling and DNA repair factors to a DSB and to measure intermediate steps in the HR repair pathway that leads to a switch in mating type.

INO80

The multi-subunit INO80 complex has been perhaps the most intensely studied of the ATP-dependent chromatin remodeling factors with respect to DSB repair (for review, see [89]). Yeast INO80 has homologs in other eukaryotes and contains approximately 12 subunits and several different enzymatic activities, including a Swi2/Snf2-like ATPase subunit (Ino80) and proteins with homology to the bacterial RuvB helicase [90-94]. Several lines of evidence directly link INO80-dependent chromatin remodeling to DSB repair. First, INO80 is recruited to a DSB created by the HO endonuclease at the yeast *MAT* locus [86,95,96]. Second, the loss of INO80 catalytic activity by deletion of the yeast genes encoding either the Ino80 ATPase, or the ATPase-stimulating Arp5 or Arp8 subunits, results in sensitivity to agents causing DSBs [86,95,96]. INO80 has been implicated in both NHEJ and DSB pathways. Double mutants constructed between *arp5*Δ or *arp8*Δ and *rad52*Δ, which is specifically defective in DSB repair by HR, show enhanced sensitivity to compounds that cause DSBs [86,95,96]. While these data imply that NHEJ depends on INO80, there is no information on where INO80 might act in the NHEJ pathway. Stronger evidence links INO80 to DSB repair by HR in both plants and yeast [86,92]. However, there is some controversy over the step in HR that is dependent on INO80. One group has reported that the initiating step in HR – 3' to 5' resection of broken DNA ends – is deficient in an *arp8*Δ mutant [96]. A second group has found that DNA processing is normal in the absence of INO80 chromatin remodeling but recruitment of factors (Rad52 and Rad51) required for formation of the presynaptic filament is significantly delayed [86]. Yeast cells lacking INO80 have also been reported to show a defect in the phenomenon known as “checkpoint adaptation” [88]. When a repairable DSB is formed, cells arrest in the G2 phase of the cell cycle to allow repair to take place; once repair has occurred, cells release from checkpoint arrest. Following the formation of an unrepairable DSB, cells also arrest in G2, and through the process of adaptation will eventually release from the checkpoint block even in the absence of repair. Unlike wild-type cells, *ino80*Δ mutants remain cell cycle arrested after formation of an unrepairable DSB, indicating the failure of checkpoint adaptation [97]. It is not known if the postulated roles of INO80 in the early steps of HR and checkpoint adaptation are related, or if INO80 has distinct DSB repair and checkpoint functions.

Although INO80 interacts with both DNA and histones and can move nucleosomes *in vitro*, the biochemical mechanism it uses to alter chromatin is not known [90]. During DSB repair *in vivo*, INO80-dependent chromatin remodeling is required for disruption of positioned nucleosomes at the yeast *MAT* locus following an HO-induced DSB [86]. Importantly, this remodeling activity leads to eviction of entire nucleosomes in an ~5-6 Kb region surrounding the DSB. The recruitment of INO80 to the *MAT* DSB is dependent upon prior phosphorylation of the H2A C terminus; however, its chromatin remodeling and nucleosome displacement activity can occur independently of γ-H2AX [95,96]. γ-H2AX-independent chromatin remodeling is also observed at laser-induced DSBs in living mammalian cells [87]. These

results raise important questions about the nature of the relationship between γ-H2AX and ATP-dependent chromatin remodeling during DSB repair. One suggestion is that γ-H2AX is initially dispensable for chromatin remodeling but is important for maintaining the remodeled state to allow repair to be completed [87].

INO80-dependent nucleosome displacement has potentially two consequences. First, as discussed above, it exposes recipient DNA at the *MAT* locus for binding by Rad52 and Rad51 strand invasion proteins during formation of the presynaptic filament. The extent of nucleosome loss in fact correlates well with the extent of DNA that participates in strand invasion (~2.5 Kb on either side of the break). Second, it might play a role in terminating the DNA damage signal. Dephosphorylation of γ-H2AX occurs concomitantly with completion of repair, and in yeast takes place when H2A is not associated with chromatin [98,99]. By evicting nucleosomes around DSB sites, INO80 could thus provide the substrate for the γ-H2AX phosphatase, Pph3. However, INO80 has not been found to be associated with chromatin distal to the *MAT* DSB [95], so it is likely that another factor displaces γ-H2AX containing H2A-H2B dimers >5 Kb from the break site.

An important question is whether a histone chaperone co-operates with INO80 to disassemble nucleosomes at *MAT*. We believe this to be the case because INO80 has not been reported to have histone transfer activity [89,90]. Moreover, nucleosome loss at *MAT* occurs over a fairly extended region (5-6 Kb) [86]. Thus, it is more likely that INO80 initially disrupts nucleosome structure to facilitate subsequent displacement by a histone chaperone. One candidate is the Asf1 histone chaperone, which has a global role in nucleosome displacement coupled to transcriptional activity and is itself implicated in DSB repair [100-102]. The reader is referred to the review by *X et al* in this issue for a more extensive discussion of the role of histone chaperones in DNA damage repair.

SWI/SNF

The yeast SWI/SNF complex contains 11 subunits, and its catalytic subunit, Swi2/Snf2, is the founding member of the class of ATP-dependent chromatin remodeling proteins present in all eukaryotes (see [16] for review). Although SWI/SNF plays important roles in transcription, its activity has also been directly linked to DSB repair [103,104]. Yeast mutants deficient for SWI/SNF-dependent chromatin remodeling are sensitive to agents that cause DSBs, and like INO80, SWI/SNF is recruited to the HO-induced DSB at the yeast *MAT* locus [104]. SWI/SNF does not appear to play an important role in DSB repair by SSA or NHEJ, although this latter pathway has not been exhaustively studied in *swi/snf* mutants. However, strong evidence places SWI/SNF in the HR pathway that repairs the DSB at *MAT*. First, SWI/SNF associates with both the *MATa* recipient locus and the HR donor locus, *HMLα*. Second, in the absence of SWI/SNF chromatin remodeling, synapsis between the invading *MATa* ssDNA and *HMLα* DNA is blocked. Unlike strains deficient for INO80 chromatin remodeling, the Rad52 and Rad51 strand annealing/invasion proteins are recruited with normal kinetics to the recipient *MAT* locus in *swi/snf* mutants. However, these proteins fail to associate with the *HMLα* donor locus. Because INO80 and SWI/SNF are recruited to the *MAT* DSB at approximately the same time, the results suggest a compartmentalization of ATP-dependent chromatin remodeling activities, with INO80 disrupting chromatin at the recipient locus for HR, and SWI/SNF altering chromatin at the donor locus. Thus, INO80 activity is postulated to precede SWI/SNF activity during HR repair, although it is not known if SWI/SNF chromatin remodeling is dependent on INO80.

The biochemical properties of SWI/SNF in chromatin remodeling have been extensively studied with reconstituted nucleosome templates. *In vitro* its remodeling activity alters histone-DNA contacts to (i) slide nucleosomes in *cis*; (ii) “remodel” nucleosomes; (iii) and transfer histone dimers [10,16,105]. Its *in vivo* properties are less well characterized. Yeast SWI/SNF leads to the loss of a defined nucleosome pattern in the regulatory region of the activated

SUC2 gene, and SWI/SNF remodeling activity is a prerequisite for Asf1-mediated displacement of nucleosomes from the activated *PHO5* promoter [106-109]. However, the role of SWI/SNF in strand exchange during HR is not known. The *HMRa* and *HMLα* targets of SWI/SNF are assembled into heterochromatin, a form of folded or condensed chromatin that is refractory to most protein-DNA interactions [110]. Interestingly, yeast SWI/SNF is required for transcription of inducible genes during mitosis, when chromatin is in a more condensed state [111]. Thus, the role of SWI/SNF during HR repair at *MAT* might be to unfold or disrupt higher order chromatin structure at *HM* donor loci to facilitate protein-DNA or DNA-DNA interactions during formation of synaptic filaments [112]. It is worth noting that unlike vertebrate genomes, the yeast genome has only limited regions of heterochromatin. It is therefore possible that SWI/SNF acts uniquely at donor sequences that are assembled into some form of higher order chromatin structure. Alternatively, SWI/SNF could also act on donor sequences present in euchromatin using a different mode of chromatin remodeling.

Detailed studies on DSB repair have not been reported with SWI/SNF from other eukaryotes, with the exception of human SWI/SNF, which appears to play a direct role during rearrangement of immunoglobulin loci. During V(D)J recombination, the RAG1 and RAG2 proteins recognize recombination signal sequences (RSSs) and create a double strand break that is ultimately repaired by NHEJ during a productive gene rearrangement. hSWI/SNF stimulates V(D)J cleavage by RAG proteins on reconstituted monosomes and nucleosomal arrays *in vitro*, and *in vivo* the Brg1 catalytic subunit of hSWI/SNF is broadly associated with immunoglobulin loci that are poised for rearrangement [113-115]. There is also evidence that SWI/SNF proteins play a role in the DNA damage response in the plant *Arabidopsis*. Mutations or RNAi suppression of 11 different SWI/SNF family members led to hypersensitivity to ionizing radiation, and two showed reduced levels of spontaneous HR between inverted repeats [116]. However, no direct measures of DNA repair or chromosome remodeling were performed, and it is not known whether these phenotypes reflect direct SWI/SNF function in repair or recombination or an indirect role in controlling transcription of repair/recombination gene expression.

RSC

The 15 subunit RSC chromatin remodeling complex was first identified in yeast as a factor closely related to SWI/SNF [117]. Like SWI/SNF, RSC has homologs in other eukaryotes and has been implicated in both transcriptional activation and repression [16,118]. RSC is significantly more abundant than SWI/SNF and essential for cell viability, and it also plays a role in DSB repair [104,119,120]. Mutations that disrupt RSC's chromatin remodeling activity confer hypersensitivity to DNA damage caused by DSBs, attributable to defects in repair by both the NHEJ and HR pathways. Although *rsc* mutants were isolated in a screen for yeast genes defective in NHEJ, the role of RSC in this DSB repair pathway is not entirely clear [120]. RSC is rapidly recruited to an unrepairable DSB break at *MAT* around the same time as the MRX (Mre11/Rad50/Xrs2) complex, a factor involved in NHEJ, HR, and checkpoint signaling [104,120-126]. MRX is also required for RSC's association with broken DNA ends [120]. Thus, MRX-dependent recruitment of RSC to a DSB could lead to chromatin remodeling at the break that in turn facilitates the accessibility of DNA to NHEJ factors.

RSC also plays a role in HR repair of a *MAT* DSB when a donor *HMRa* or *HMLα* locus is present [104]. Like SWI/SNF, RSC associates with both recipient and donor chromatin and is dispensable for recruitment of factors involved in strand invasion of the recipient *MAT* locus. In contrast to SWI/SNF, RSC is not required for the association of these same factors with *HM* donor chromatin. RSC only appears to play a role late in the HR pathway, at the point of DNA synthesis or ligation of the repaired strands. This is surprising given that RSC associates with a *MAT* DSB significantly before either INO80 or SWI/SNF, both of which act earlier in

the HR pathway. It is possible that RSC remodels chromatin early in HR to facilitate a late step in repair. An alternative possibility is that RSC regulates the decision to repair a DSB by NHEJ or HR; for example, RSC might channel repair down the NHEJ pathway in the absence of donor sequences, while it would promote repair by HR when donors are present.

Although RSC's biochemical properties are similar in many respects to those of SWI/SNF, its *in vivo* activities are still not completely defined [16]. However, one cellular activity of RSC could account for its roles in both NHEJ and HR. RSC has been reported to load cohesin onto chromosome arms, keeping sister chromatids together until they are separated at mitosis [127-129]. Thus, by loading cohesin onto broken ends during DSB repair, RSC might promote ligation of proximal ends during NHEJ and of distal ends during HR.

TIP60 and *SWR1*

These two multi-subunit, evolutionarily conserved complexes are ATP-dependent chromatin remodeling factors that are specialized for the replication-independent exchange of histone H2A variants into chromatin [130]. Drosophila TIP60 catalyzes the exchange of phosphorylated H2Av for unmodified H2Av, while the yeast SWR1 complex exchanges H2A for the variant H2AZ. Both remodeling factors have been linked to transcriptional regulation, and more recently they have been directly implicated in DSB repair through their histone exchange activities.

A. TIP60

The TIP60 complex was first isolated from human cells and consists of 16 subunits [131, 132]. All of these subunits are also present in the Drosophila TIP60 complex [133]. Multiple activities are present in the TIP60 complex and include an Esa1-like histone acetyltransferase activity (Tip60), as well as ATPase (Domino), helicase, and DNA binding activities [131, 133,134]. TIP60 has multiple cellular roles, and the first evidence that it functions in DNA damage repair came from the observation that ectopic expression of a mutant form of human TIP60 (hTIP60) lacking HAT activity led to the accumulation of cellular DSBs after γ-irradiation [131,135]. TIP60 appears to perform at least two functions in DSB repair. First, the HAT activity of hTIP60 acetylates histone H4 at DSBs, which in turn stimulates HR repair by promoting the recruitment of repair factors to DNA damage foci [131,136]. Second, *Drosophila* TIP60 (dTIP60) exchanges the phosphorylated form of the histone H2Av variant for unmodified H2Av [87]. Like H2AX in vertebrates and H2A in yeast, *Drosophila* H2Av is rapidly and extensively phosphorylated at sites of DSBs [137,138]. Both the HAT and ATP-dependent remodeling activities of dTIP60 are required for phospho-H2Av exchange [87]. The HAT activity acetylates nucleosomal phospho-H2Av on lysine 5 in response to a DSB break and the Domino ATPase subunit catalyzes the exchange of acetylated phospho-H2Av for unmodified H2Av. This has the overall effect of clearing phosphorylated H2Av from chromatin, and thus could play a role in attenuating the DSB signal. Although it has not been investigated, the human TIP60 complex might act in an analogous manner to remove vertebrate γ-H2AX from chromatin.

It is not known how dTIP60 recognizes nucleosomes that contain phospho-H2Av. Human TIP60 accumulates at DSBs that contain nucleosomes with γ-H2AX, and it is therefore likely that dTIP60 is recruited to sites of damaged DNA by its interaction with phospho-H2Av [136]. Possible factors for mediating recruitment are the actin-related proteins (Arps) that are present in the TIP60, INO80, NuA4, and SWR1 complexes [94,130,139-142]. The Arp4 subunit of the NuA4 HAT complex mediates interaction of NuA4 with γ-H2AX, and the analogous BAP55 subunit of dTIP60 might perform the same role by bringing dTIP60 to DSBs that contain phospho-H2Av [133,143]. However, this recruitment mechanism has not yet been directly investigated with either the human or Drosophila TIP60 complex.

B. SWR1

The conserved SWR1 complex was initially identified in yeast as a multi-subunit factor with a Swi2/Snf2 related ATPase subunit (Swr1) [142,144-146]. SWR1 co-purifies with the H2AZ variant, and its ATPase exchanges H2A-H2B dimers in nucleosomal arrays for H2AZ-H2B dimers. H2AZ is widely distributed in yeast chromatin but found predominantly around the transcription start site of inactive genes and at the boundary separating heterochromatin from euchromatin [142,147-150]. The presence of H2AZ in nucleosomes is postulated to provide a chromatin template that is more susceptible to unfolding and nucleosome displacement, and thought to "poise" chromatin for transcription activation and prevent the spread of heterochromatin. Although SWR1 and H2AZ have been intensely studied with respect to their potential roles in transcriptional regulation, SWR1 also appears to act independently in DSB repair. Yeast *swr1* null and catalytic site mutants are sensitive to agents (MMS and HU) that cause DSBs, and SWR1 is recruited to an HO-induced DSB at *MAT* by γ-H2AX, with which it interacts *in vitro* [97,143].

One newly described role for SWR1 in DSB repair relates to the regulation of γ-H2AX levels at DSB sites. A recent study suggests that the SWR1 and INO80 complexes act antagonistically to remodel chromatin at an HO-induced DSB at *MAT* and ultimately control the INO80-dependent checkpoint adaptation response [97]. In the absence of INO80, γ-H2AX levels are reduced both globally and around an unrepairable *MAT* DSB. This is accompanied by an aberrant incorporation of H2AZ into nucleosomes near the break site, an event that is itself dependent on the presence of γ-H2AX. High levels of γ-H2AX are restored in an *ino80*Δ mutant by deletion of *SWR1* or the gene encoding H2AZ (*HTZ1*), and these mutations suppress the *ino80*Δ checkpoint adaptation defect. Thus, the presence of elevated γ-H2AX levels is correlated with the ability of cells to escape checkpoint arrest by adaptation. The implication of the genetic relationship between INO80 and SWR1 is that there is a dynamic interplay between the presence of γ-H2AX and H2AZ at DSBs. By depositing H2A, which can be phosphorylated by Mec1/Tel1 kinases [81], INO80 thus prevents the exchange of γ-H2AX for H2AZ by SWR1. This scenario is the opposite of the role proposed for dTIP60 at DSBs, whereby dTIP60 promotes replacement of phospho-H2Av with unmodified H2Av. Moreover, INO80 has not been shown to have histone exchange activity, so its precise role in inhibiting SWR1-dependent H2AZ deposition awaits further investigation. The model that high levels of γ-H2AX are required for checkpoint adaptation is seemingly at odds with the observation that the failure to dephosphorylate γ-H2AX is associated with a pronounced delay in release from checkpoint arrest in cells containing a repairable DSB [98]. However, the same study also reported that checkpoint adaptation occurred normally in a *pph3* mutant, where γ-H2AX levels remain high. Thus, there is clearly a different requirement for γ-H2AX in release from checkpoint arrest when a DSB can be repaired than when it cannot. Understanding the relationship of histone variants to the regulation of these two checkpoint pathways therefore poses an exciting challenge.

As discussed above, dTIP60 exchanges nucleosomal phospho-H2Av at DSBs only after it has been acetylated by the Tip60 HAT subunit. Interestingly, the NuA4 remodeling factor, which contains a HAT subunit (Esa1) similar to Tip60, is recruited by γ-H2AX to the *MAT* DSB site, where it results in transient histone acetylation [143,151]. However, rather than γ-H2AX, we speculate that the H2AZ variant could be the substrate of this HAT during DSB repair. NuA4 acetylates H2AZ on multiple lysine residues, with lysine 14 (K14) being its major target. H2AZ-K14 acetylation, unlike unmodified H2AZ, is enriched at transcriptionally active promoters, and it has been suggested that acetylation of H2AZ controls a dynamic equilibrium between the assembled (repressed) and disassembled (activated) states of chromatin [152-154]. Thus, when nucleosomes containing H2AZ are lost from promoters upon gene activation, acetylation of H2AZ is postulated to promote redeposition of the H2A variant,

thereby establishing a continuous cycle of nucleosome disassembly-assembly during each round of transcription. NuA4 might perform a mechanistically similar role at DSBs: NuA4-dependent acetylation of H2AZ could promote the SWR1-dependent replacement of the H2A variant for phosphorylated H2A, thus facilitating a dynamic equilibrium between the presence of the two forms of H2A around DSBs and ultimately influencing checkpoint adaptation. One prediction of this model is that the adaptation defect of an *ino80*Δ mutant would be suppressed by the absence of H2AZ K14 acetylation.

Rad54

The Swi2/Snf2-related Rad54 protein is an evolutionarily conserved, dsDNA stimulated ATPase/DNA translocase that acts as a key mediator protein during both early and late stages of HR repair [155,156]. Its early HR role is to help recruit the Rad51 ssDNA binding protein to resected recipient DNA and to stabilize Rad51 presynaptic filaments [157-163]. Its late HR role is apparently to promote branch migration of Holliday junctions and to facilitate stable DNA joints that are substrates for DNA polymerases [160,164-168]. Rad54 remodels nucleosomes *in vitro* in an ATP-dependent manner, and this activity is stimulated by Rad51 [169-171]. Moreover, Rad54 is required for strand invasion by Rad51 on nucleosomal templates *in vitro* [172]. This has led to the hypothesis that Rad54's functions in HR are specific to chromatin. However, recent studies have shown that Rad54's early and late roles in HR differentially depend on its ATPase activity, consistent with genetic data showing that Rad54 has both ATP-dependent and –independent functions [160,168]. The ATPase domain is dispensable for the presynaptic activity of Rad54, but is required to enhance formation of stable DNA joints. This suggests that chromatin is a substrate for Rad54 only during late stages of HR. *In vitro*, Rad54 chromatin remodeling increases the accessibility of DNA in nucleosomal arrays [171]. *In vivo*, Rad54 remodels a single positioned nucleosome that occludes the HO cut site at the *HMLα* donor locus during repair of an HO-induced DSB at *MAT* [160]. By enhancing accessibility of DNA at this position, Rad54 is postulated to promote formation of a stable, intertwined DNA joint that can be extended by DNA polymerase. Thus, during HR between *MATa* and *HMLα*, Rad54 ATPase activity is an example of chromatin remodeling without large-scale movement of nucleosomes, although the extent of its activity at other loci remains to be determined.

Summary and Perspectives

A multiplicity of chromatin remodeling factors with Swi2/Snf2 related ATPases contribute to the repair of DNA lesions by the NER and DSB pathways. These factors alter chromatin structure in a number of ways, including nucleosome displacement and histone exchange, and generally increase the accessibility of damaged DNA to repair factors. Thus, their activity in DNA damage repair is in many respects similar to their activity during transcription. Despite advances in identifying some of the steps in NER and DSB repair pathways that are regulated by ATP-dependent chromatin remodeling, an important issue is to understand why multiple factors are involved. One explanation may be the differential targeting of these factors to DNA damage sites; another may be that different chromatin structures occur at various points in repair processes and these structures can only be acted on by factors with different remodeling activities. Thus, understanding the full nature of the chromatin changes that occur during DNA repair will be key to understanding how ATP-dependent remodeling factors regulate these changes. Another important issue is the relationship between ATP-dependent chromatin remodeling, histone modification, and nucleosome assembly during DNA damage repair. How are these various processes integrated to signal repair factor recruitment to damage sites; to alter chromatin structure in distinct ways; to restore chromatin structure once repair has occurred; and to initiate and terminate damage checkpoint signals? Finally, we are still a long

way from understanding the steps in NER and DSB repair that are regulated by chromatin. Clearly, there are many exciting areas left to investigate in this rapidly moving field.

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Table 1

ATP-dependent chromatin remodeling factors in DNA damage repair

Repair Pathway	Complex	Catalytic subunit	Postulated function in DNA repair	References
NER	ySWI/SNF	ySwi2/Snf2	Stimulates excision repair nuclease activity	[56,58]
	NEF4	yRad16*	Regulates UV damage recognition	[61]
		CSB (yRad26*)	Promotes transcription-coupled repair of UV damaged DNA lesions	[69-72,74,76,77]
DSB	ySWI/SNF	ySwi2/Snf2	Controls synapsis of donor-recipient DNA strands during HR at *MAT*	[104]
	BAF	hBRG1	Stimulates V(D)J cleavage by RAG proteins	[114,115]
	RSC	ySth1	Promotes NHEJ and DNA synthesis/ligation during HR at *MAT*	[104,120]
	yINO80	yIno80	Promotes histone eviction at *MAT* DSB and checkpoint adaptation	[86,97]
		pIno80	Stimulates HR in dose dependent manner	[92]
	SWR	ySwr1	Regulates levels of phosphorylated histone H2A	[97]
		yRad54 dRad54	Promotes stable formation of DNA joints and branch migration during HR at *MAT*; stimulates strand invasion by Rad51	[160,163,164,166,172]
	dTIP60	Domino	Replaces phosphorylated histone H2Av with unmodified H2Av	[131,136]

h, human; y, yeast; p, plant; d, *Drosophila*;

*Direct chromatin remodeling activity not yet demonstrated