REVIEW

Cellular machineries for chromosomal DNA repair

Craig L. Peterson[1,3] and Jacques Côté[2]

[1]Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, Massachusetts 01605, USA; [2]Laval University Cancer Research Center, Hôtel-Dieu de Québec (CHUQ), Québec City, Québec, G1R 2J6 Canada

Each day a cell must face a constant onslaught of DNA lesions. Although we tend to worry most about environmental sources of DNA damage (e.g., chemical agents, UV radiation, ionizing radiation), a human cell must repair over 10,000 DNA lesions per day to counteract endogenous sources of DNA damage (Lindahl 1993). DNA itself has a measurable half-life—spontaneous depurination can generate abasic sites in DNA strands at an estimated rate of 2,000–10,000 lesions per human cell per day (Lindahl 1993). Indeed, it has been proposed that much of the DNA repair machinery has evolved to contend with DNA damage generated by the byproducts of cellular metabolism—reactive oxygen species, endogenous alkylating agents, and DNA single- and double-strand breaks resulting from collapsed DNA replication forks or from oxidative destruction of deoxyribose residues (Lindahl and Wood 1999; Lindahl 2000). Failure to repair such lesions can lead to a deleterious mutation rate, genomic instability, or cell death. In higher eukaryotes, the damage that occurs in genes responsible for DNA repair and/or cell cycle regulation can lead to threatening diseases such as cancer.

The timely and efficient repair of eukaryotic DNA damage is further complicated by the realization that DNA lesions must be detected and repaired in the context of highly condensed, 100–400-nm-thick chromatin fibers (Belmont and Bruce 1994). The nucleosome is the first level of DNA compaction in the nucleus and is formed by the wrapping of 147 bp of DNA around a histone octamer composed of two H2A–H2B dimers and a H3–H4 tetramer. Linear arrays of nucleosomes are then folded into more compact structures, stabilized by linker histones such as histone H1. These compact structures are well known to hinder nuclear processes like transcription, and several in vitro studies have demonstrated that the assembly of DNA lesions into chromatin greatly hinders their detection and subsequent repair (see below). Within cells, of course, the repair machinery has created the means to contend with chromosomal structures, and an enormous number of DNA lesions are faithfully repaired each cell cycle. Here we review recent studies that have begun to elucidate this cellular machinery that facilitates DNA repair within the context of chromatin.

[3]**Corresponding author.**
EMAIL craig.Peterson@umassmed.edu; FAX (508) 856-5011.
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Chromatin-modifying and remodeling enzymes

Genetic and biochemical analysis of transcriptional regulatory mechanisms has led to the identification of two classes of highly conserved "chromatin-remodeling/modification" enzymes that regulate the accessibility of DNA in chromatin (for reviews, see Fry and Peterson 2001; Peterson 2002; Fischle et al. 2003; Kurdistani and Grunstein 2003; Lusser and Kadonaga 2003). As described in more detail below, such enzymes have now been directly implicated as key components of the DNA repair machinery. One class of chromatin-remodeling/modification enzymes catalyzes the covalent attachment or removal of posttranslational histone modifications (e.g., lysine acetylation, serine phosphorylation, lysine and arginine methylation, lysine ubiquitylation, and ADP-ribosylation). Each of the four core histones (H2A, H2B, H3, and H4) contains a 20–35-amino acid N-terminal "tail" domain that extends from the surface of the nucleosome and includes the majority of sites for posttranslational modifications. Histone H2A also contains a C-terminal tail domain that harbors sites for phosphorylation and ubiquitinylation. Although the histone tails are not required for nucleosome assembly or stability, their removal eliminates the folding of nucleosomal arrays into more compact structures in vitro (Hansen et al. 1998).

What is the role of histone modifications in chromatin structure and function? Although an enormous effort has been focused on this question, only modest mechanistic detail has been elucidated. In the case of lysine acetylation, it is clear that more than six acetates per octamer can disrupt the folding of chromatin (Tse et al. 1998). One histone acetyltransferase, NuA4, does acetylate as many as eight lysines per nucleosome (Allard et al. 1999; Suka et al. 2001), and thus this enzyme may facilitate nuclear processes by destabilizing chromatin condensation. However, many other histone acetyltransferases, such as yeast Gcn5 (Kuo et al. 1996; Grant et al. 1999) or mammalian PCAF (Schiltz et al. 1999), modify only a

few specific lysines within a histone tail domain, levels that are unlikely to perturb folding dynamics. Likewise, given that the histone tails are not required for the stability of individual nucleosomes, it seems unlikely that their modification will have a marked effect on this level of chromatin structure. Indeed, phophorylation of histone H3 at Ser 10, a histone mark that has been implicated in transcriptional activation, does not cause a detectable defect in nucleosome assembly or DNA accessibility (Shogren-Knaak et al. 2003).

In contrast to the paucity of evidence for a structural role for specific histone modifications, there are now numerous examples where site-specific histone marks control the binding of nonhistone proteins to the chromatin fiber. For instance, lysine acetylation can recruit proteins that harbor the ~80-amino acid bromodomain (Dhalluin et al. 1999; Hudson et al. 2000; Agalioti et al. 2002; Hassan et al. 2002), and sequence variation among bromodomains appears to control binding of proteins to nucleosomes that harbor distinct sites of lysine acetylation (Agalioti et al. 2002; Hassan et al. 2002). Indeed, the interaction between bromodomains and acetylated histones is believed to play a key role in orchestrating a stepwise assembly of different chromatin-remodeling proteins at some gene promoters (Syntichaki et al. 2000; Fry and Peterson 2001; Agalioti et al. 2002; Hassan et al. 2002). Similar to the bromodomain-acetylated lysine connection, some chromodomains have been shown to direct interactions with methylated histones. For instance, the 50-amino acid chromodomain within the heterochromatin protein, HP1, facilitates binding to histone H3 that is methylated at Lys 9 (Bannister et al. 2001; Lachner et al. 2001; Nakayama et al. 2001). Thus, there is clearly an emerging paradigm that implicates site-specific histone modifications in controlling the recruitment of regulatory proteins to the chromatin fiber.

In addition to histone-modifying enzymes, a distinct class of chromatin-remodeling/modification enzymes comprises a family of related ATP-dependent complexes that use the free energy derived from ATP hydrolysis to enhance the accessibility of nucleosomal DNA (Vignali et al. 2000). This family can be subdivided into three groups based on their biochemical properties and overall sequence similarity of their ATPase subunits: (1) SWI/SNF, (2) ISWI, and (3) Mi-2/CHD (Boyer et al. 2000a). Whereas many members of the ISWI-like and Mi-2/CHD-like subgroups appear dedicated to transcriptional repression pathways (Kehle et al. 1998; Deuring et al. 2000), most SWI/SNF-like enzymes play roles in the activation of transcription (Peterson and Workman 2000). In contrast to these transcriptional roles, some ISWI-based enzymes, such as ACF, may play roles in nucleosome assembly (Ito et al. 1997), and other family members may facilitate other diverse chromatin-based processes, such as homologous recombination and DNA repair (Peterson 1996).

In the case of ATP-dependent remodeling enzymes, "chromatin remodeling" refers to a variety of in vitro, ATP-dependent changes in a chromatin substrate, including disruption of histone–DNA contacts within nucleosomes, movement of histone octamers in *cis* (along the same DNA molecule) and in *trans* (between different DNA molecules), loss of negative supercoils from circular minichromosomes, and increased accessibility of nucleosomal DNA to transcription factors and restriction endonucleases (Peterson and Workman 2000). Only members of the SWI/SNF subgroup can generate the entire spectrum of remodeled products, although all ATP-dependent remodeling enzymes can mobilize histone octamers in *cis*. In fact, the ability to change nucleosome positioning may be a prerequisite for production of nearly all types of remodeled nucleosome products (for discussion, see Peterson 2000). Recent genetic and biochemical studies have also led to the suggestion that SWI/SNF may disrupt higher order chromatin folding in vivo (Krebs et al. 2000; Horn et al. 2002).

How do ATP-dependent remodeling enzymes disrupt chromatin structure? Recent models have exploited the DNA-tracking activity of these enzymes (Saha et al. 2002; Jaskelioff et al. 2003; Whitehouse et al. 2003), suggesting that ATP-dependent remodeling enzymes may push a DNA duplex into the nucleosome or that the enzyme itself tracks along the DNA gyres through the nucleosome. The primary consequence of this type of reaction would be a disruption of histone–DNA contacts and changes in nucleosome positioning in *cis*. Although disruption of histone–histone interactions are clearly not required for these enzymes to enhance nucleosomal DNA accessibility (Côté et al. 1998; Boyer et al. 2000b), a byproduct of this ATP-dependent remodeling reaction is a destabilization of the histone H2A–H2B dimer–H3–H4 tetramer interface (Bruno et al. 2003). Indeed, Wu and colleagues have recently shown that the Swr1 remodeling enzyme can replace a canonical H2A/H2B dimer with a H2A.Z/H2B dimer in an ATP-dependent reaction (Mizuguchi et al. 2003). H2A.Z is a variant of H2A that harbors unique C- and N-terminal tail domains, and incorporation of H2A.Z into nucleosomal arrays alters their folding properties (Fan et al. 2002). Furthermore, and most relevant to this review, yeast that lack H2A.Z are sensitive to a variety of DNA-damaging agents (Mizuguchi et al. 2003; N. Bouchard and J. Côté, unpubl.), suggesting that this histone variant may play a key role in various DNA repair pathways.

Although chromatin-remodeling enzymes have been studied primarily in the context of transcriptional control, the occlusion of the genome within chromatin fibers necessitates that DNA repair enzymes utilize additional players to facilitate access to damaged DNA and to restore chromatin structure after their action. Because the mechanisms by which DNA is repaired vary greatly depending on the type of DNA lesion, it seems likely that the enzymatic machinery that facilitates access to chromatin might also be lesion specific. By an expansion of the original "access, repair, restore" (ARR) model (see Fig. 3A, below; Smerdon 1991), we describe below chromatin-remodeling and assembly factors that play key roles in numerous steps of double-strand break (DSB), nucleotide excision repair (NER), and base excision repair (BER).

Repair of DNA double-strand breaks within chromatin

DNA double-strand breaks (DSBs) arise in eukaryotic DNA due to environmental insults such as ionizing radiation or chemical exposure. DSBs also play an important role as intermediates in yeast mating-type switching, meiotic and mitotic crossing over, and immunoglobulin V(D)J recombination. DSBs can also be a consequence of stalled or collapsed DNA replication forks. Two major pathways for repairing DSBs have evolved and are highly conserved throughout eukaryotes (Fig. 1; for review, see Paques and Haber 1999). Nonhomologous end joining (NHEJ) involves the religation of the two DNA ends, and because this reaction is not guided by a DNA template, it can be error prone. Homologous recombination (HR) is a major pathway of DSB repair in all eukaryotes and has a distinct advantage over other mechanisms in that it is mostly error free. HR requires members of the *RAD52* epistasis group, defined by the yeast *RAD50*, *RAD51*, *RAD52*, *RAD54*, *RAD55*, *RAD57*, *RAD59*, *MRE11*, and *XRS2* genes. These genes are highly conserved among all eukaryotes (Paques and Haber 1999; Haber 2000; Sung et al. 2000), highlighting the importance of these proteins for cell survival. Genetic and biochemical studies in yeast have indicated that repair of DSBs by NHEJ requires the DNA end-bind-

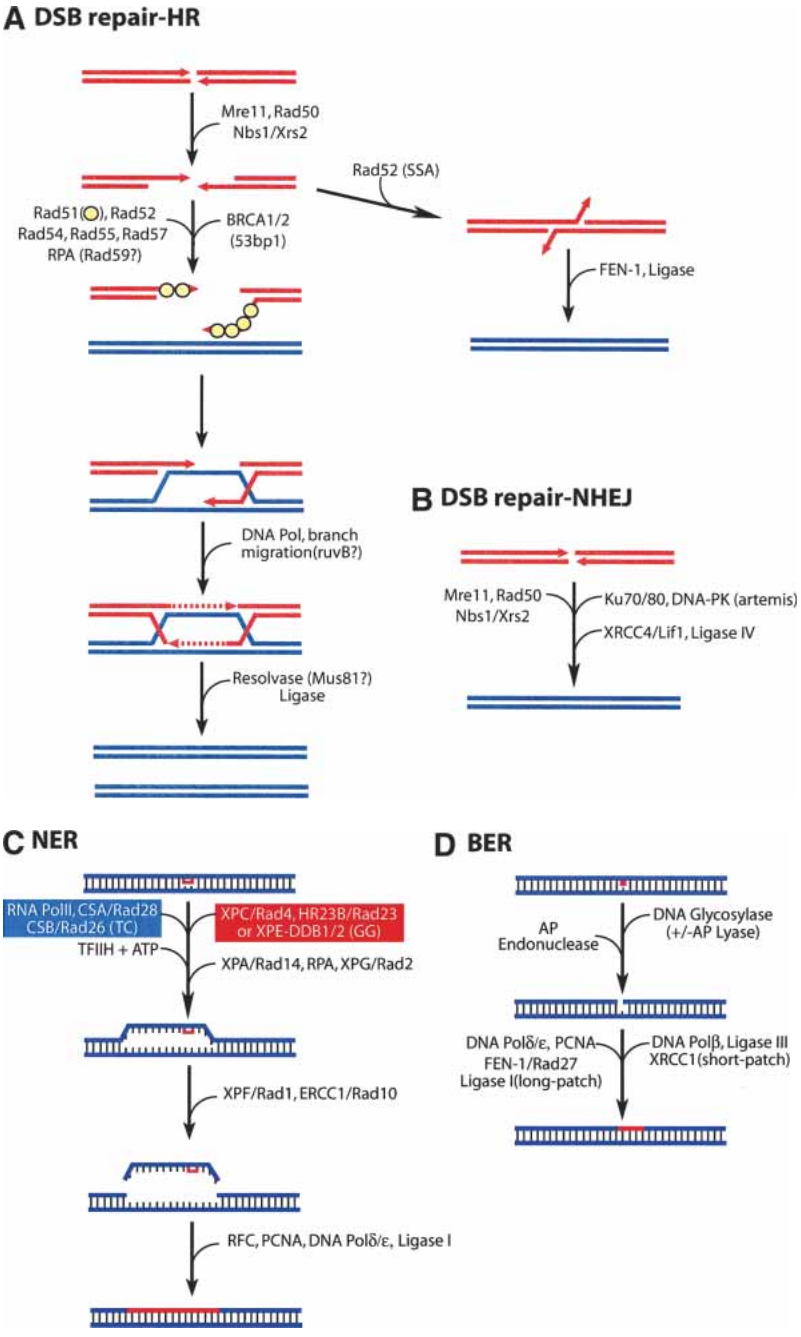

Figure 1. Major pathways of DNA repair in eukaryotes. (*A*) One pathway for repair of DNA double-strand breaks (DSBs) is homologous recombination (HR). After detection of the DSB, the 5′ strands are resected, producing long 3′ single-stranded DNA tails that then serve as a substrate for assembly of a Rad51 nucleoprotein filament. This presynaptic complex also contains Rad52, Rad54, Rad55, and Rad57. This complex searches the genome for DNA sequence homology that is then used for subsequent strand invasion. Branch migration of this joint DNA molecule, DNA synthesis, ligation, and resolution of Holliday junctions restores the DNA templates. An alternative HR repair pathway (single-strand annealing, SSA) uses Rad52 to search for homologous sequences on the resected 3′ ends. The FEN-1 endonuclease removes the "flap" DNA ends and ligation occurs. This pathway leads to DNA sequence deletions. Protein names are from mammalian cells and budding yeast (when different). (*B*) An alternative pathway for DSB repair is nonhomologous end-joining (NHEJ). In this case, the two broken ends are processed and ligated directly. NHEJ generally leads to small DNA sequence deletions. (*C*) Bulky DNA lesions like cyclobutane pyrimidine dimers (CPDs) and 6–4 photoproducts (6–4 PPs) are removed by the nucleotide excision repair pathway (NER). DNA damage recognition differs between global genome (GG-NER, proteins in red box) and transcription coupled (TC-NER, proteins in blue box) subpathways. Subsequent steps are shared and include local duplex unwinding, DNA strand dual incision, DNA synthesis, and ligation. (*D*) Base excision repair (BER) is a process that corrects nonbulky damage to bases. BER has two subpathways, both of which are initiated by a DNA glycosylase. Glycosylase action creates an apyrimidinic/apurinic (AP) or abasic site, which is processed by an AP endonuclease. In the "short-patch" subpathway, a single nucleotide is added, followed by ligation. In the long-patch subpathway, DNA synthesis of multiple nucleotides occurs and the displaced oligonucleotide overhang is removed by the FEN-1 endonuclease.

ing heterodimer Ku70/Ku80, DNA ligase IV, and the Mre11/Rad50/Xrs2 complex (Paques and Haber 1999; Haber 2000; Wilson 2002). A NHEJ role for the analogous Mre11/Rad50/Nbs1 (MRN) complex in higher eukaryotes is less well established, and in contrast to yeast, NHEJ in higher eukaryotes also involves DNA-dependent protein kinase (DNA-PKcs; for review, see Lieber et al. 2003).

Studies in yeast have exploited the inducible expression of the HO endonuclease to follow the sequence of molecular events that occur following formation of a single DNA DSB (Fig. 1A; Paques and Haber 1999; Symington 2002; Sugawara et al. 2003; Wolner et al. 2003). First, the 5′ ends of DNA that flank the break are resected by an unknown exonuclease, leaving long 3′ single-stranded DNA tails. Rad51p, a functional homolog of the *Escherichia coli* RecA recombinase, then binds these exposed tails, forming a right-handed, helical nucleoprotein filament. In vitro and in vivo, Rad52p (Sung 1997a; Wolner et al. 2003), Rad54p (Wolner et al. 2003), and a Rad55p/Rad57p heterodimer (Sung 1997b; Wolner et al. 2003) can promote this early step by overcoming the inhibitory effects of the heterotrimeric single-stranded DNA-binding protein, RPA. The Rad51 nucleoprotein filament then searches for a homologous pairing partner to form a heteroduplex "joint molecule" (Petukhova et al. 1998, 2000). The homologous donor sequence is often located on the sister chromatid following DNA replication, but remarkably the HR machinery has the capacity to locate DNA homology even if the donor is present on a different chromosome (Haber and Leung 1996). This amazing capacity to sample for DNA homology throughout the genome is not unique to yeast—Jasin and colleagues (Richardson et al. 1998) have used regulated expression of the I-SceI restriction enzyme to demonstrate that repair of a single DNA DSB in mammals is proficient even when the homologous donor is located on a different chromosome. Thus, the homology search appears insensitive to higher order chromosomal domains within the nucleus. Once a joint molecule is formed, the incoming DNA strand is extended by DNA polymerases and branch migration, ultimately leading to restoration of the genetic information spanning the break (for review, see Paques and Haber 1999).

Notably, if a homologous DNA donor is not present (e.g., if cells are within the G1 phase), the DSB can be shuttled into the NHEJ pathway (Fig. 1B). How the cell makes this decision is unclear, especially in light of the fact that both NHEJ and HR components appear to co-occupy DNA adjacent to a single HO-induced DSB in vivo in yeast (B. Wolner and C.L. Peterson, unpubl.). The efficiency of NHEJ in various yeast mutants is routinely assayed by transforming yeast with a linearized plasmid that harbors a selectable marker (e.g., Downs et al. 2000). Religation of the plasmid is required for subsequent plasmid maintenance, and thus transformation efficiency provides a measurement of NHEJ. Indeed, disruption of genes encoding the DNA end-binding proteins, Ku70 or Ku80, leads to a severe defect in NHEJ measured by the religation assay (Downs et al. 2000). However, it is important to remember that the substrate for NHEJ in this assay is unlikely to harbor a canonical chromatin structure. The introduced DNA is "naked," and replication-coupled nucleosome assembly is unlikely to occur prior to NHEJ. Thus, the results of this assay should be interpreted with caution, especially when the contributions of chromatin components are evaluated.

Histone phosphorylation is a marker for DSB repair

What happens to chromatin during the repair of a DSB? One of the first events that occurs within minutes after formation of a DSB is phosphorylation of the C-terminal tail of histone H2A (in yeast) or the histone H2AX variant (in higher eukaryotes; Fig. 2; Rogakou et al. 1999; Downs et al. 2000; Redon et al. 2003). The extent of H2AX or H2A phosphorylation (often called γ-H2AX) around a single DSB is very large, covering megabases of chromatin in mammals and kilobases in yeast (Rogakou et al. 1998, 1999; Redon et al. 2003; J. Downs, S. Allard, A. Auger, N. Bouchard, L. Galarneau, S.P. Jackson, and J. Côté, in prep.). This histone modification is carried out by members of the well-known phosphatidylinositol-3 kinase-related kinase (PIKK) family (Smith and Jackson 1999). In mammals there are three members of this family that have been implicated in DNA repair, Ataxia Telangiectasia mutated (ATM), AT-related (ATR), and DNA-dependent protein kinase (DNA-PK). Likewise, yeast contains two homologs of ATM/ATR that are known to play a central role in DNA repair, Mec1p and Tel1p. Burma et al. (2001) established that ATM is the major kinase responsible for histone H2AX phosphorylation in response to DNA DSBs in murine fibroblasts, whereas ATR is also responsible for H2AX phosphorylation following replication blocks (Ward and Chen 2001). In yeast, H2A phosphorylation in response to DSB formation requires both ATM/ATR homologs (Downs et al. 2000; Redon et al. 2003).

How ATM/ATR kinases "sense" the presence of DNA damage is still unclear. Biochemical studies have shown that the Mec1 kinase has an affinity for DNA ends, suggesting a simple model where DSB formation directly targets ATM/ATR kinases. In contrast, a recent study (Bakkenist and Kastan 2003) suggests that DNA DSBs may trigger changes in higher order chromatin structure, leading to a global activation of the ATM kinase. Specifically, these authors found that the formation of only a few DNA DSBs per mammalian cell was sufficient to induce the autophosphorylation (and activation) of much of the cellular pool of ATM. It seems unlikely that a couple of DSBs could rapidly recruit and activate thousands of molecules of ATM, leading Bakkenist and Kastan to suggest that DSBs may activate ATM via a more indirect route. They proposed that DSBs may disrupt topological constraints present within higher order chromatin domains, and such changes in chromatin structure signal to ATM activation. Consistent with this hypothesis, treatment of cells with a histone deaceylase inhibitor (trichostatin A) or other types of agents that induce changes in chromosome structure (hypotonic

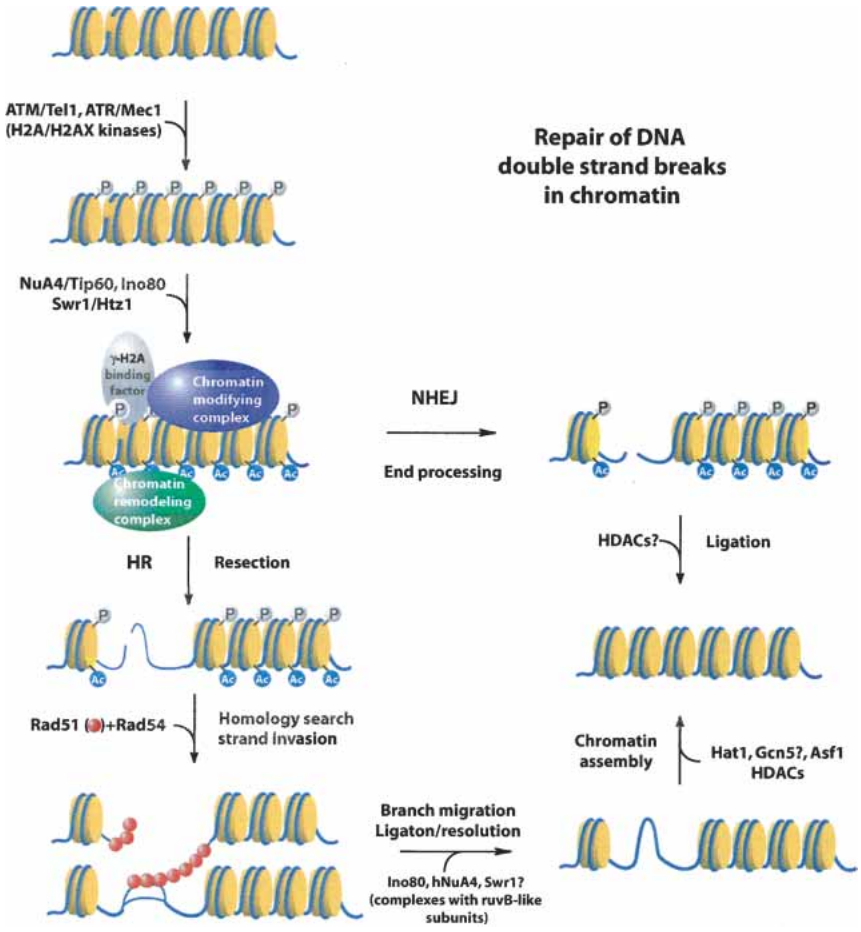

Figure 2. Repair of DNA DSBs in chromatin. Initial ATM/ATR-dependent phosphorylation of histone H2A/H2AX C-terminal tails surrounding a DSB allows binding/retention of several chromatin-remodeling/modifying and DNA repair factors. Subsequent histone acetylation/nucleosome remodeling allows processing of DNA ends for either the NHEJ pathway or for HR. Rad54 assists Rad51 for the homology search and strand invasion on chromatin templates. These steps may also be facilitated by the histone-remodeling/modifying enzymes recruited via histone phosphorylation. Subsequent branch migration on chromatin may also be facilitated by remodeling/modifying complexes that contain ruvB-like helicases. Chromatin assembly is finally required to restore the original structure. This step may be not required in the case of NHEJ, but histone deacetylation is expected. γ-H2AX, phosphorylated H2A or H2AX.

conditions or chloroquine) lead to the activation of ATM even in the absence of DSB formation. Thus, these data do raise the intriguing possibility that the monitoring of higher order chromatin structures is an integral component of the DNA damage surveillance machinery.

The recognition motif for PIKK kinases, Ser–Gln–Glu (SQE), is present at the C terminus of histone H2A in yeast and histone H2AX in higher eukaryotes. To verify if H2A and its phosphorylation play a role in DNA repair in yeast, Downs et al. (2000) tested several mutants for their sensitivity to DNA-damaging agents. Yeast mutants in which the SQE motif is deleted or mutated display sensitivity to phleomycin and methyl methane-sulphonate (MMS), drugs that introduce DSBs in vivo. These H2A mutants show genetic interactions with components of both the HR and NHEJ pathways, suggesting that H2A phosphorylation may facilitate multiple pathways of DSB repair. Redon et al. (2003) analyzed a similar set of yeast H2A mutants and found that H2A phosphorylation was required for efficient repair of topoisomerase-1-mediated DSBs induced during S phase. Consistent with studies in yeast, $H2AX^{-/-}$ mice show a variety of DNA repair phenotypes, including radiation sensitivity, defective immunoglobulin class switching, and genomic instability of isolated mouse embryo fibroblasts (Bassing et al. 2002; Celeste et al. 2002). Indeed, inactivation of only one copy of H2AX enhances the tumor susceptibility of p53 deficient mice (Celeste et al. 2003a).

What role does H2A phosphorylation play in DNA DSB repair? The rapid induction of H2A phosphorylation in response to a DSB led to the initial suggestion that this histone modification might be required for recruitment of repair factors to the DSB (Rogakou et al. 1999). However, a recent study has nicely shown that H2AX phosphorylation is not required for the initial recruitment of many repair factors to the DSB, including Brca1, 53bp1, and subunits of the MRN complex (Celeste et al. 2003b). Likewise, H2A phosphorylation is not required for activation of the intra-S phase DNA damage checkpoint in yeast (Redon et al. 2003). In mammalian cells, the initial recruitment of DNA repair factors to the DSB is followed by formation of large, irradiation-induced foci (IRIFs) that are visualized by indirect immunofluorescence. These foci contain thousands of molecules of repair factors, and recent studies in both yeast and mammalian cells indicate that such foci may represent the sequestration of multiple DNA DSBs (Lisby et al. 2003; Aten et al. 2004). Strikingly, loss of H2AX, or removal of the phosphorylation site, eliminates formation of IRIFs that contain known markers of active repair, such as Nbs1, Brca1, and 53bp1 (Bassing et al. 2002; Celeste et al.

2002). This specific requirement for H2AX phosphorylation in promoting IRIF formation led Celeste et al. (2002) to suggest that histone phosphorylation may facilitate the spreading and retention of repair factors surrounding the DNA lesion.

The sequestration and spreading of repair factors adjacent to the DSB is likely to be mediated by direct interactions between phosphorylated H2AX and numerous repair factors. Recently, several groups have demonstrated that the 90-amino acid BRCT (BRCA1 COOH-terminal) domain is a novel phosphoserine/phosphothreonine-binding module specific for ATM/ATR targets (Manke et al. 2003; Rodriguez et al. 2003; Yu et al. 2003). BRCT domains are widespread among DNA repair factors, and the BRCT domains of Nbs1 (Kobayashi et al. 2002) and MDC1 (Xu and Stern 2003) have been shown to interact directly with phosphorylated H2AX. Furthermore, an intact BRCT domain is required for formation of Nbs1 IRIFs in vivo, and overexpression of the MDC1 BRCT domain disrupts formation of Mre11, Nbs1, 53BP1, phospho-H2AX, and CHK2 phospho-T68 IRIFs (Xu and Stern 2003). Thus, although H2AX phosphorylation does not control the initial recruitment of repair factors, interactions with the H2AX phosphoserine via BRCT domains may help to stabilize the binding of many repair factors, or to sequester sites of DSB repair into large IRIFs.

Histone acetylation and DSB repair

Recently, Bird et al. (2002) reported that lysine substitutions within the N-terminal domain of yeast histone H4 cause sensitivity to DNA DSB-inducing agents, MMS and camptothecin (CPT). These H4 alleles were not sensitive to UV irradiation, suggesting that modification of histone H4 lysines may play a specific role in DSB repair. Moreover, Esa1, the catalytic subunit of the yeast NuA4 histone acetyltransferase (HAT) complex (Allard et al. 1999), whose substrate includes these same H4 lysines, is also required for DNA DSB repair. Specifically, esa1 mutants that abrogate HAT activity exhibit the same sensitivity to MMS and CPT as histone H4 mutants, and again, no sensitivity to UV radiation is observed (Bird et al. 2002). Esa1 is believed to be the yeast homolog of the human Tip60 protein, and cells that express a HAT-deficient tip60 derivative accumulate DNA DSBs upon γ-irradiation and fail to undergo apoptosis (Ikura et al. 2000). Another connection has been made between NuA4 and sensitivity to DNA damage via the subunit Yng2 (Choy and Kron 2002), a homolog of the ING family of tumor suppressors that is found exclusively in NuA4 (Nourani et al. 2001, 2003). Inactivation of Yng2 eliminates the HAT activity of the NuA4 complex (Nourani et al. 2001), and mutants of *YNG2* show sensitivity to agents that induce replication fork collapse, which indicates a role for NuA4 in intra-S-phase DSB repair (Choy and Kron 2002). Furthermore, deletion of *YNG2* makes NHEJ essential for yeast viability, providing genetic evidence that NuA4 may play roles in several pathways of DNA repair. Inactivation of the histone H3 HAT, Gcn5, shows phenotypes similar to a yng2 mutant (Choy and Kron 2002), suggesting that acetylation of several histones is important for DSB repair.

Although changes in histone acetylation have not yet been reported within chromatin surrounding a DSB (nor at the homologous donor locus), the NuA4 HAT complex does appear to be recruited to a DSB in vivo, as monitored by chromatin immunoprecipitation of either the Esa1 or Arp4 subunits (Fig. 2; Bird et al. 2002; J. Downs, S. Allard, A. Auger, N. Bouchard, L. Galarneau, S.P. Jackson, and J. Côté, in prep.). Furthermore, because NuA4 seems to preferentially acetylate histones within linear nucleosomal arrays as compared with circular ones, Bird et al. (2002) suggested that the complex might be targeted to DNA ends. Recently, we found that the NuA4 complex interacts specifically with the phoshorylated form of histone H2A, suggesting that histone phosphorylation may facilitate recruitment or retention of the NuA4 HAT complex at the DSB (J. Downs, S. Allard, A. Auger, N. Bouchard, L. Galarneau, S.P. Jackson, and J. Côté, in prep.). Although it is not clear how histone acetylation facilitates DSB repair, it is intriguing to note that the human homolog of the NuA4 complex (hNuA4 or Tip60 complex) contains a subunit that harbors two bromodomains as well as a SWI/SNF-like ATPase subunit (p400/*domino*, a human homolog of yeast Swr1; Fuchs et al. 2001; Cai et al. 2003; Doyon et al. 2004). Furthermore, hNuA4 harbors eukaryotic homologs of the bacterial ruvB protein (RUVBL1,RUVBL2; Ikura et al. 2000), a hexomeric DNA helicase required for branch migration during homologous recombination and recombination-dependent DNA repair in prokaryotes (West 1997). Given the known connections between histone acetylation and bromodomains in transcriptional control, it seems likely that one consequence of histone acetylation during DSB repair is the enhanced retention of an ATP-dependent chromatin-remodeling complex at the DSB.

Recent studies suggest that this connection between histone acetylation and ATP-dependent remodeling can also be extended to yeast. Two recent studies have shown that the yeast Swr1 ATPase is the catalytic subunit of a chromatin-remodeling complex that contains ruvB-like subunits (Krogan et al. 2003; Mizuguchi et al. 2003). In addition, Krogan et al. (2003) find that the Swr1 complex also contains the double bromodomain-containing protein, Bdf1. Swr1 and *bdf1* mutants are sensitive to DNA damaging agents (Chua and Roeder 1995; Chang et al. 2002; Matangkasombut and Buratowski 2003; Mizuguchi et al. 2003), and *SWR1, BDF1,* and *HTZ1* all show strong genetic interactions with subunits of the NuA4 complex (Krogan et al. 2003; Matangkasombut and Buratowski 2003; A. Auger, N. Bouchard, and J. Côté, unpubl.). Thus, it seems likely the Swr1 and NuA4 complexes will both be recruited to DNA adjacent to DSBs, and NuA4-dependent acetylation may facilitate retention of Swr1 via the bromodomain-containing subunit, Bdf1 (Fig. 2). The Swr1-associated ruvB-like helicases may then be involved in the homology search process or junction movement. Given that the Swr1 com-

plex also controls the chromatin incorporation of the H2A.Z histone variant (Krogan et al. 2003; Mizuguchi et al. 2003), recruitment of Swr1 may also alter the composition of the chromatin fiber, leading to enhanced repair capacity. Two other ATP-dependent remodeling enzymes also appear to be recruited to DNA DSBs (INO80; J. Downs, S. Allard, A. Auger, N. Bouchard, L. Galarneau, S.P. Jackson, and J. Côté, in prep.; and Rad54; see below). The INO80 complex also contains ruvB-like subunits, and ino80 mutants are sensitive to DSB-inducing agents (Shen et al. 2000). Thus the chromatin-modification/remodeling machinery at this type of lesion seems extraordinary (Fig. 2). To date it is still not clear which step(s) is facilitated by these remodeling and modification enzymes. Although some enzymes may facilitate the processing of the DNA ends, others may participate in the homology search and strand invasion reactions. Complexes that harbor ruvB-like subunits may also facilitate branch migration of the heteroduplex DNA joint (Fig. 2). Thus, the complex chromatin machinery at a DSB may be necessary to facilitate multiple steps in the HR or NHEJ pathways.

Rad54: a multifunctional ATP-dependent remodeling enzyme

Rad54p is a member of the RAD52 epistasis group that is essential for repair of DSBs by the HR pathway. In vivo and in vitro studies have indicated that Rad54 functions at several steps in this pathway, including assembly of the Rad51p nucleoprotein filament, DNA strand invasion at the homologous donor, and heteroduplex DNA extension (Fig. 2; Solinger and Heyer 2001; Solinger et al. 2001; Wolner et al. 2003). Biochemical studies of Heyer and colleagues have also suggested that Rad54p may facilitate the dissociation of Rad51p from the postsynaptic complex (Solinger et al. 2002). Rad54p is a member of the SWI2/SNF2 family of DNA-stimulated ATPases and DNA helicases (Eisen et al. 1995), and because several members of this ATPase family use the energy of ATP hydrolysis to disrupt chromatin structure, it was suggested that Rad54p might facilitate repair of DSBs by contending with chromatin (Peterson 1996). Recently, our lab and others have found that Rad54p possesses many of the biochemical properties of bona fide ATP-dependent chromatin-remodeling enzymes (Alexiadis and Kadonaga 2002; Alexeev et al. 2003; Jaskelioff et al. 2003). For instance, Rad54p can enhance the accessibility of DNA within nucleosomal arrays, generate superhelical torsion, and translocate along DNA in an ATP-dependent reaction. Furthermore, Rad51 and Rad54 are necessary and sufficient for DNA strand invasion reactions in which the homologous donor is assembled into chromatin (Alexiadis and Kadonaga 2002; Alexeev et al. 2003; Jaskelioff et al. 2003). Because Rad54 physically interacts with the Rad51–DNA nucleoprotein filament (Mazin et al. 2000), we proposed that Rad54 might translocate along DNA, using the energy of ATP hydrolysis. This movement, in addition to facilitating the homology search process, could generate superhelical torsion, leading to enhanced nucleosomal DNA accessibility (Jaskelioff et al. 2003). Interestingly, we and others find that Rad54 is not required for the homology search in vivo (Sugawara et al. 2003; B. Wolner and C.L. Peterson, unpubl.), suggesting perhaps that other chromatin-remodeling or modification enzymes participate in this process in vivo. In contrast, Rad54 is essential for DNA strand invasion, and this Rad54-dependent step may involve disruption or movement of nucleosomes that might block joint molecule formation and/or branch migration.

Nucleosome assembly: recovering from DNA damage

The repair of DNA DSBs by either the NHEJ or HR pathway creates a final product that lacks a full complement of nucleosomes (Fig. 2). For instance, the rapid resection of the 5′ DNA strand after initial DSB formation is likely to displace many nucleosomes. After repair of the lesion, restoration of a canonical chromosome structure will require discontinuous DNA synthesis as well as nucleosome assembly. Furthermore, strand invasion of the homologous donor sequence, followed by DNA replication and branch migration, will also require subsequent nucleosome assembly. Thus, as is the case for repair of DNA lesions via NER and the long-patch repair pathway of BER (see below), a requirement for DNA synthesis will invoke a need for reassembly of nucleosomes.

Assembly of a new nucleosome involves the stepwise deposition of an H3–H4 tetramer followed by addition of two heterodimers of H2A–H2B. In vivo, nucleosome assembly is usually coupled to DNA synthesis and is mediated by the activity of histone chaperones (for review, see Green and Almouzni 2002). Biochemical studies have shown that the CAF-1 and Asf1 chaperones bind to newly synthesized forms of histones H3 and H4, and that they function synergistically in replication-coupled deposition of the H3–H4 tetramer in vitro. Addition of the H2A–H2B dimers involves an additional chaperone, most likely the NAP-1 protein. In yeast, Asf1 is coordinately expressed with DNA replication and repair factors just prior to the onset of S phase, and inactivation of Asf1 leads to a lengthening of S phase and accumulation of cells with a G2/M phase DNA content (Tyler et al. 1999). Each of these phenotypes is exacerbated by inactivation of CAF-1, indicating partially overlapping roles for these two chaperones in nucleosome assembly during S phase in vivo (Tyler et al. 1999). Genetic studies in yeast, as well as biochemical studies with the human chaperone complexes, have also implicated both CAF-1 and Asf1 in nucleosome assembly following repair of UV-damaged DNA (Tyler et al. 1999; Mello et al. 2002). Indeed, CAF-1 is recruited to sites of UV lesion repair in vivo (Green and Almouzni 2003).

Inactivation of yeast Asf1, but not CAF-1, leads to sensitivity to DSB-inducing agents (Tyler et al. 1999), and asf1 mutants are defective in HR repair of a single HO-induced DSB (Qin and Parthun 2002). Interestingly, yeast Asf1 interacts physically and functionally with the DNA damage checkpoint kinase Rad53, which may be involved in targeting Asf1 to the site of DSB repair (Emili

et al. 2001; Hu et al. 2001). This functional connection between Asf1-dependent nucleosome assembly and the Rad53 kinase may play a key role in signaling completion of the DNA repair event and subsequent restoration of cell cycle progression.

Qin and Parthun (2002) recently suggested a link between DNA DSB repair and the acetylation of newly synthesized histones by Hat1. In contrast to the type A HATs, which are localized exclusively to the nucleus and acetylate nucleosomal histones, Hat1 is a type B HAT that acetylates newly synthesized histones prior to their assembly into chromatin. Hat1 generates a specific pattern of histone H3 and H4 acetylation that is diagnostic of newly assembled chromatin, and acetylation of histones by Hat1 is believed to facilitate histone chaperone function during replication-coupled nucleosome assembly. Although inactivation of Hat1 does not disrupt bulk nucleosome assembly during S phase, a hat1 mutant is sensitive to DNA DSB-inducing agents and it is defective in recombinational repair of a single, HO-induced DSB (Qin and Parthun 2002). Likewise, substitution of a subset of lysine residues within the histone H3 tail also leads to MMS sensitivity and defects in DSB repair by HR repair. Specific lysine residues seem more important than others for efficient DNA repair, with either Lys 14 and Lys 23 of H3 being sufficient for resistance to MMS. Consistent with a role for Hat1 and histone H3 lysines in nucleosome assembly during DSB repair, Qin and Parthun (2002) also showed that *hat1* and *asf1* mutants are epistatic, suggesting that they function together in the same pathway. These observations led to the proposal that Hat1 and histone H3 lysine residues are important for DSB repair at a chromatin assembly step that occurs either during or after recombination (Qin and Parthun 2002). Notably, defects in chromatin assembly appear to block formation of the final recombination product, suggesting that nucleosome assembly may provide a checkpoint function that ensures that recombination is not completed prior to restoration of chromatin structure.

Nucleotide excision repair

The nucleotide excision repair pathway is used for the removal of a variety of bulky, DNA-distorting lesions, including UV-induced *cis*-syn cyclobutane-pyrimidine dimers (CPDs) and pyrimidine (6–4) pyrimidone photoproducts (6–4 PPs; for reviews, see Thoma 1999; Mitchell et al. 2003). This repair pathway is usually divided into two classes—global genome repair (GG-NER) and transcription-coupled repair (TC-NER). GG-NER is responsible for repair of DNA lesions within nontranscribed DNA throughout the genome, whereas TC-NER repairs DNA lesions specifically within the transcribed strand of expressed genes. In both cases, removal of a lesion involves four steps: (1) DNA lesion detection; (2) recruitment of the TFIIH complex, which directs unwinding of DNA surrounding the damaged base; (3) recruitment of the endonucleases ERCC1-XPF and XPG, which generate the 5′ and 3′ incisions surrounding the lesion; and (4) DNA synthesis directed by DNA polymerase δ/ϵ, PCNA, and other accessory factors (Fig. 1C). Both GG-NER and TC-NER use overlapping sets of enzymatic machineries, with the primary difference being how the DNA lesion is detected. The TC-NER pathway employs a unique set of "coupling" factors, CSA and CSB, which are believed to target the basic NER machinery to RNA polymerase II that is stalled at a DNA lesion (Mitchell et al. 2003). In the case of GG-NER, several protein complexes have been implicated in damage recognition (including the UV-DDB/XPE complex) although the mammalian XPC–hHR23B complex appears to be the primary damage detection factor in vivo (Volker et al. 2001).

Several studies have demonstrated that in vitro repair of numerous NER substrates, including UV-induced DNA lesions (CPDs and 6–4 PPs), N-acetoxy-2-acetylaminofluorence (AAF) adducts, and cisplatin-induced lesions, is severely inhibited in vitro by nucleosome assembly (Thoma 1999; Hara et al. 2000; Ura et al. 2001; Wang et al. 2003). In vivo, however, such lesions are efficiently repaired even when they occur on the surface of nucleosomes. Early work of Smerdon and colleagues demonstrated that chromatin structure is altered during NER repair of UV-induced DNA lesions (Smerdon and Lieberman 1978), and treatment of human cells with a histone deacetylase inhibitor (butyrate) leads to increased levels of histone acetylation and an enhanced efficiency of NER (Smerdon et al. 1982). More recent studies have also shown that in vivo repair of UV-damaged chromatin is associated with increased levels of histone acetylation (Brand et al. 2001). Several studies provide further links between histone acetylation and NER. In human, a Gcn5-containing HAT complex, TFTC (highly related to the yeast SAGA HAT complex), has been shown to contain a 130-kD protein termed SAP130 (spliceosome-associated protein 130; Will et al. 1999) which is 50.7% similar to DDB1, a component of the UV-DDB factor that is recruited to UV-induced lesions in vivo (Brand et al. 2001; Green and Almouzni 2003). In vitro, the TFTC HAT is preferentially recruited to UV-damaged DNA, and TFTC prefers to acetylate UV-damaged nucleosomes (Brand et al. 2001). Brand and colleagues (2001) also demonstrated that TFTC subunits are recruited in parallel with the nucleotide excision repair protein XP-A. All these data taken together suggests that one function of the human TFTC complex is to participate in DNA repair (Fig. 3B; Brand et al. 2001).

In another report, Martinez et al. (2001) established a link between DNA repair and a distinct Gcn5-containing HAT complex called STAGA. They also detected the presence of SAP130 in the human STAGA complex, but they showed that this complex also contains both subunits of UV-DDB, the DDB1 and DDB2 proteins. DDB2 protein binds directly to UV-damaged DNA, and thus one can speculate that the presence of DDB2 within STAGA is responsible for targeting histone acetyltransferase activity to specific DNA lesions (Fig. 3B). Because the UV-DDB complex also seems to associate with the CBP/p300 family of histone acetyltransferases (Datta et al. 2001), there appears to be multiple mechanisms to

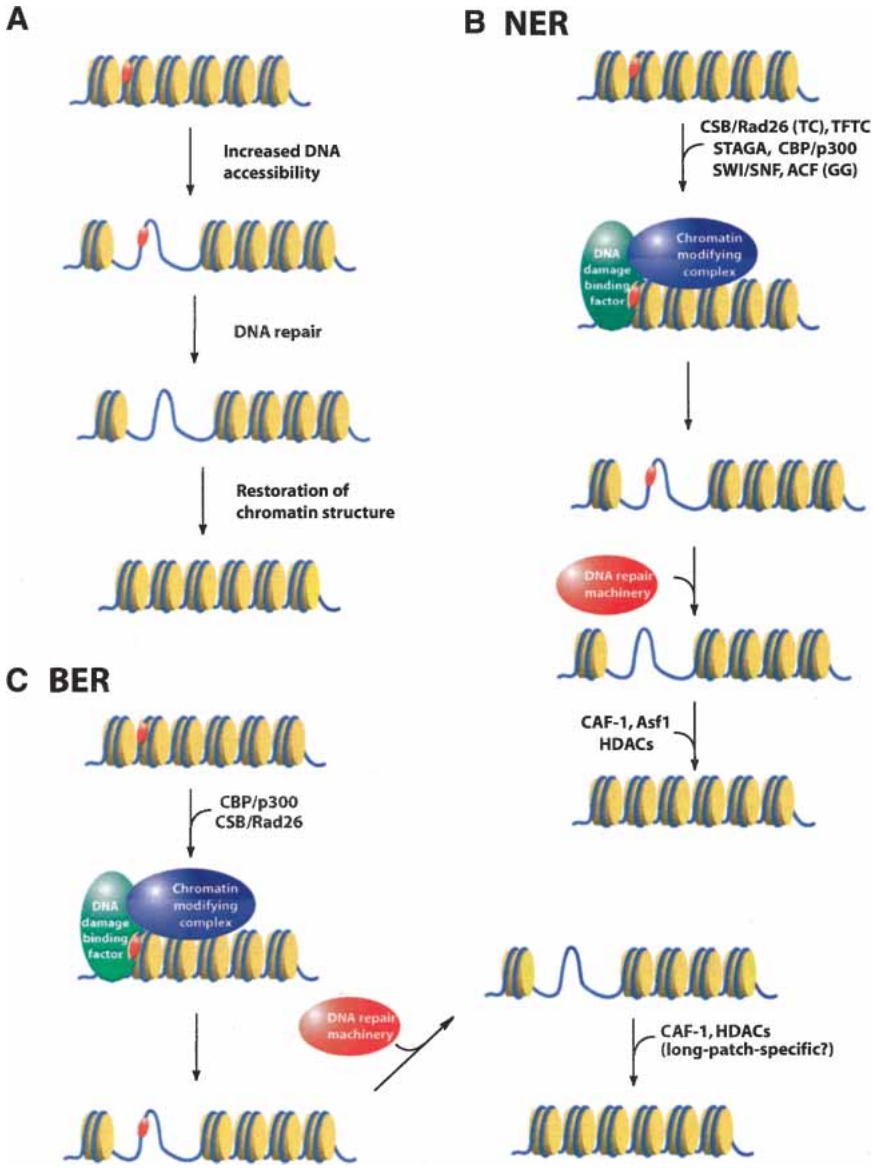

Figure 3. Nucleotide and base excision repair in the context of chromatin. (*A*) Representation of the "access, repair, restore" (ARR) model proposed by Smerdon (1991) and Green and Almouzni (2002). (*B*) In the case of the transcription-coupled NER subpathway (TC-NER), increased accessibility to the damage site may be provided by the ATP-dependent remodeling enzyme, CSB/Rad26. In the global genome (GG-NER) subpathway, damage recognition factors (e.g., DDB-UV) can recruit histone acetyltransferase (HAT) activities that may facilitate the functioning of ATP-dependent remodeling enzymes that further increase access to the damage site. Following DNA synthesis, chromatin assembly is required to restore chromatin. (*C*) In the BER pathway, histone-modifying/remodeling factors may also facilitate recognition and access of repair factors to the damage site. In the case of thymine DNA glycosylase, damage recognition may lead to the recruitment of the CBP/p300 HAT, which then facilitates subsequent steps in repair. The CSB/Rad26 remodeling enzyme may also facilitate the BER pathway on chromatin. For the "long-patch" subpathway of BER, nucleosome assembly steps may be required to restore chromatin structure.

target this histone modification to UV-induced DNA lesions. Chromatin acetylation might facilitate binding and/or function of the NER machinery at the site of DNA damage. Alternatively, histone acetylation may also regulate the binding of bromodomain-containing ATP-dependent remodeling enzymes, such as SWI/SNF (see below).

Besides HAT activities, several ATP-dependent chromatin-remodeling complexes have also been implicated in NER (Fig. 3B). In an early study, Ura et al. (2001) demonstrated that the *Drosophila* ACF complex could facilitate NER on damaged chromatin in vitro, but ACF only stimulated repair when the DNA lesion was located in the linker DNA between two nucleosomes. Two recent studies from Hara and Sancar (2002, 2003) have implicated the prototypical ATP-dependent remodeling complex, yeast SWI/SNF, in stimulating NER on nucleosomal substrates in vitro. Using a 200-bp mononucleosome substrate, Hara and Sancar (2002) demonstrated that AAF-G adducts present on that fragment are more readily removed by human excision nuclease in the presence of SWI/SNF complex, whereas no such facilitation was observed on naked DNA. Repair stimulation within the nucleosome core could be explained by an increased accessibility to the DNA lesion due to ATP-dependent remodeling by SWI/SNF. Moreover, XPA, XPC, and RPA were found to enhance the remodeling activity of SWI/SNF (Hara and Sancar 2002). Although a simple model suggests that SWI/SNF is recruited to DNA lesions by these repair factors, SWI/SNF might also be present on the site prior to the binding of repair factors, and in this case chromatin remodeling might be utilized to accelerate assembly of the repair machinery.

In another study, Hara and Sancar (2003) demonstrated that the type of lesion present on DNA modulates the ability of SWI/SNF to enhance DNA repair by excision

enzymes. In fact, AAF-G adducts and 6–4 PPs are more easily removed in the presence of SWI/SNF, whereas repair of CPDs seems to be unaffected. In contrast, Gaillard et al. (2003) showed that SWI/SNF and ISW2 complexes can facilitate the repair of CPDs through the photoreactivation pathway. In this pathway, different photolyases bind with high affinity to either CPDs (CPD photolyase) or 6–4 PPs (6–4 photolyase), and once the lesion is detected, the enzyme catalyzes cleavage of the cyclobutane ring in a light-dependent reaction. Nucleosomes that are positioned over a UV-induced lesion inhibit photoreactivation by photolyase, and this inhibition is nearly abolished by addition of SWI/SNF to the reaction (Gaillard et al. 2003). A greater accessibility to the damage site seems again to be the key to SWI/SNF-enhanced repair. Although these in vitro observations suggest a role for SWI/SNF (and ACF) in DNA repair, a strong genetic demonstration of that link has yet to be made.

Whereas SWI/SNF and ACF have been implicated in the GG-NER pathway, the CSB protein is believed to be the ATP-dependent chromatin-remodeling enzyme associated with the TC-NER pathway (Fig. 3B). CSB is a DNA-dependent ATPase of the SWI2/SNF2 family that can enhance the DNA accessibility of chromatin substrates in vitro (Citterio et al. 2000). CSB also directly interacts with RNA polymerase II (Tantin et al. 1997), and thus CSB is believed to function early in the TC-NER pathway, perhaps by increasing accessibility of NER enzymes to the DNA lesion. CSB may also play an important role in other repair pathways, and notably, several studies have now implicated CSB in base excision repair (see below).

Whereas genetic studies have implicated histone H2A variants in DSB repair, recent work has shown that a nonhistone component of the chromatin fiber, HMGN1, facilitates repair of UV-induced DNA lesions (Birger et al. 2003). HMGN1 (known previously as HMG14) is an abundant component of mammalian chromatin, and it has long been known as a biochemical hallmark of actively transcribed genes. Interestingly, a *Hmgn1*$^{-/-}$ mouse is viable, but isolated embryo fibroblasts are hypersensitive to UV treatment and the repair of CPDs is markedly decreased. Furthermore, loss of HMGN1 leads to chromatin fibers that are more generally resistant to nucleases, suggesting that HMGN1 may facilitate repair of UV-induced lesions by destabilizing the chromatin fiber. This study, in concert with data showing that the H2A.Z histone variant can alter chromatin folding dynamics (Fan et al. 2002), indicates that both higher order chromatin folding, as well as the structure of individual nucleosomes, can impact repair processes.

Base excision repair

The base excision repair pathway is responsible for repair of oxidized and alkylated DNA bases, as well as abasic sites generated by spontaneous depurination (Lindahl 2000). In general, DNA lesions that are substrates for BER include those that do not distort the DNA backbone sufficiently to stall DNA replication forks, and consequently inactivation of the BER pathway can be highly mutagenic. Perhaps the most prevalent and highly mutagenic of the DNA lesions that must be corrected by BER is the oxidized base, 8-oxoGuanine (also known as 8-oxoG or 8-oxo-7,8-dihydroguanine), which can base pair efficiently with either cytosine or adenine. If left undetected, 8-oxoG results in G:C → T:A transversions, which are the second most common mutation found in human cancers (discussed in Bruner et al. 2000). Unlike the broad spectrum of DNA lesion recognition by the NER machinery, there exist a large number of different DNA glycosylases that recognize a limited number of different BER substrates. For instance, detection and removal of 8-oxoG within chromatin is the role of the OGG1 DNA glycosylase/β-lyase (Klungland et al. 1999; Bruner et al. 2000), whereas several methylated bases are repaired by alkyladenine DNA glycosylase (Engelward et al. 1997). Crystallographic X-ray analysis of DNA glycosylases in complex with their cognate DNA lesion has shown that the damaged DNA base is "flipped out" of the base stack into the enzyme active site, and furthermore that interactions with the DNA minor groove lead to a dramatic bending of the DNA away from the glycosylase (Bruner et al. 2000).

The AP site that is generated by a DNA glycosylase can be repaired by two distinct pathways (for review, see Hoeijmakers 2001). The short-patch pathway involves a single base replacement catalyzed by three proteins: DNA polymerase β, an AP endonuclease (APE1), and DNA ligase III and XRCC1 (Fig. 1D). This simple mechanism has long been thought to be the predominant pathway of BER, but recent studies indicate that a long-patch repair pathway may be more prevalent than once believed (Sattler et al. 2003). In the long-patch pathway, the replicative DNA polymerase δ/ϵ (and assorted accessory factors, such as PCNA) performs more extensive DNA synthesis, displacing a flap of parental DNA. This displaced DNA flap is subsequently removed by the Fen1p endonuclease and DNA is ligated by DNA ligase I and XRCC1 (Fig. 1D). Although studies suggest that only 2–12 nt are synthesized by this pathway (Sattler et al. 2003; see also Hoeijmakers 2001), there is potential for more extensive DNA synthesis involved in long-patch BER, and thus repair by this pathway may also involve new nucleosome assembly.

Several in vitro studies have shown that assembly of DNA lesions into nucleosomes inhibits repair by the BER pathway (Ishiwata and Oikawa 1982; Nilsen et al. 2002; Beard et al. 2003). Nucleosome assembly is known to decrease the binding affinity of DNA polymerase β for an AP site (Beard et al. 2003), although some glycosylases seem competent to function within chromatin (Beard et al. 2003). On the other hand, it seems likely that the DNA bending induced by DNA glycosylases may be incompatible with DNA wrapped onto the histone octamer (Bruner et al. 2000; Chen et al. 2002), and indeed the efficiency of uracil excision by uracil–DNA glycosylase is markedly reduced by nucleosome assembly (Nilsen et al. 2002). In contrast, the enzymatic activities

of Fen1 (Huggins et al. 2002) and DNA ligase I (Chafin et al. 2000) are proficient on chromatin substrates in vitro. Thus, only a subset of the steps leading to BER are blocked by nucleosome assembly. One or more of these steps may be facilitated by ATP-dependent remodeling, as Bohr and colleagues have found that the DNA repair roles of the CSB protein can be expanded to base excision repair of 8-oxoG and 8-hydroxyadenine lesions (Tuo et al. 2001, 2002b, 2003; Sunesen et al. 2002). Although it is not yet known how CSB facilitates repair of 8-oxoG, recent work suggests that CSB may enhance the activity of the OGG1 glycosylase-lyase (Tuo et al. 2002a).

One recent study has also implicated histone acetylation in the repair of DNA lesions by BER (Fig. 3C). Tini et al. (2002) demonstrated that the CBP/p300 HAT interacts with thymine DNA glycosylase (TDG), suggesting that this HAT may play a key role in the repair of T/U and G/U mismatches. Interestingly, CBP/p300 can acetylate TDG in vitro and this event can stimulate subsequent recruitment of the APE endonuclease (Tini et al. 2002). Thus, although the BER pathway has received less attention, it does appear that both HATs and ATP-dependent chromatin-remodeling enzymes will play roles in this process.

The majority of in vitro studies have focused on the repair of DNA lesions within single nucleosome substrates. In vivo, the repair machinery must deal with long nucleosomal arrays that are folded into more compacted structures. In particular, the repair of lesions within dense heterochromatin represents a particularly difficult challenge. A hallmark of constitutive heterochromatin in mammals is the hypermethylation of cytosines within CpG dinucleotides (for review, see Wade 2001). It is estimated that nearly 70% of all CpG dinucleotides are methylated at position 5 of cytosine, and that most of the unmethylated CpGs are located in small islands adjacent to actively expressed genes. 5-mC is of particular importance for DNA repair pathways, as this modified base is subject to spontaneous hydrolytic deamination that yields thymine (cytosine deamination forms uracil). Failure to repair the resulting T/G (or U/G) mismatches leads to a high mutation rate that is characteristic of genomic regions that contain high levels of 5-mC.

Repair of T/G or U/G mismatches is controlled by several DNA glycosylases, including methylpurine-DNA glycosylase (MPG), MBD4 (also known as MED1; Parsons 2003), and thymine DNA glycosylase (TDG). MBD4 contains a methyl-DNA-binding domain (MBD) that targets this enzyme to genomic regions that contain a high density of 5-mC within CpG dinucleotides. Interestingly, Watanabe et al. (2003) have shown that methylpurine-DNA glycosidase associates with MBD1, another methylated DNA binding protein. MBD1 is a repressor of gene expression, and it is believed to establish repressed domains of 5mC-containing chromatin by histone deacetylation-dependent and -independent mechanisms (Wade 2001). MBD1 also directly interacts with the histone methyltransferase, Suv39h1, as well as the heterochromatin protein HP1 (Fujita et al. 2003). Thus, MBD1 may facilitate association of MPG glycosylase with methylated DNA as well as orchestrate several protein–protein interactions that establish and maintain heterochromatic states. Interestingly, MMS-induced DNA damage leads to the rapid release of MBD1 from chromatin, whereas MPG remains bound (Watanabe et al. 2003). Release of MBD1 may facilitate chromatin unfolding and subsequent histone acetylation and repair of lesions by methylpurine-DNA glycosidase (and MBP4). Thus, in the case of genomic regions that are enriched for 5mC, the DNA lesion itself may catalyze chromatin unfolding by directly impacting the binding of chromatin regulators.

Perspectives

In retrospect, it may not seem surprising that the DNA repair machinery functions in concert with histone-modifying and ATP-dependent chromatin-remodeling enzymes. Like transcriptional control, detection and repair of damaged DNA requires access to the DNA strands; thus, assembly of the genome into compact chromatin fibers is expected to inhibit lesion detection and repair. What was not expected, however, is the degree of overlap between chromatin-remodeling enzymes that play roles in both transcription and DNA repair. The actions of Gcn5-containing HAT complexes, as well as SWI/SNF, Swr1, and Ino80 remodeling complexes, can be targeted to particular genes or to DNA lesions. Furthermore, the functional coupling among HATs and ATP-dependent remodeling enzymes, which was established for transcriptional regulation, may also be emerging as a hallmark of DNA repair. Dramatic distinctions, however, are likely to exist between how the chromatin-remodeling/modification machinery is utilized in transcriptional control and DNA repair. Histone methylation may be one such example. To date there are no known demethylases that can remove a methyl group from a histone lysine or arginine residue, and, consequently, this histone modification may be quite stable and could serve as a heritable mark for active or inactive transcriptional states. In the case of DNA repair, a cell may not want to "remember" where DNA damage was repaired, and thus if histone methylation is utilized during DNA repair, it may be restricted to early events such as damage detection. Subsequent assembly of new nucleosomes at the conclusion of the repair process might then remove a histone methyl mark.

Although several chromatin-modification and remodeling enzymes have been functionally connected to DNA repair, these examples are likely to reflect only the "tip of the iceberg." To date there have only been a few systematic investigations into the role of histone tails or their posttranslational modifications in DNA repair processes (e.g., see Qin and Parthun 2002). A recent study of the histone H2A C-terminal domain does suggest that multiple serine residues may serve as key phospho acceptors required for DNA repair (Wyatt et al. 2003). Given the complicated DNA "gymnastics" that are inherent to the enzymology of DNA repair, we should prepare ourselves for the inevitable deluge of reports describing DNA repair-associated histone modifications,

novel combinations of histone marks, and new chromatin-remodeling enzymes whose functions are specialized to facilitate DNA repair.

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Cellular machineries for chromosomal DNA repair

Craig L. Peterson and Jacques Côté

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