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Five repair pathways in one context: chromatin modification during DNA repair[1]

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Abstract: The eukaryotic cell is faced with more than 10 000 various kinds of DNA lesions per day. Failure to repair such lesions can lead to mutations, genomic instability, or cell death. Therefore, cells have developed 5 major repair pathways in which different kinds of DNA damage can be detected and repaired: homologous recombination, nonhomologous end joining, nucleotide excision repair, base excision repair, and mismatch repair. However, the efficient repair of DNA damage is complicated by the fact that the genomic DNA is packaged through histone and nonhistone proteins into chromatin, a highly condensed structure that hinders DNA accessibility and its subsequent repair. Therefore, the cellular repair machinery has to circumvent this natural barrier to gain access to the damaged site in a timely manner. Repair of DNA lesions in the context of chromatin occurs with the assistance of ATP-dependent chromatin-remodeling enzymes and histone-modifying enzymes, which allow access of the necessary repair factors to the lesion. Here we review recent studies that elucidate the interplay between chromatin modifiers / remodelers and the major DNA repair pathways.

Key words: chromatin, DNA repair, histone modification, NER, DSBR, MMR.

Résumé : La cellule eucaryote doit faire face à plus de 10,000 sortes de lésions à l'ADN par jour. Une incapacité à réparer ces lésions peut conduire à des mutations, à l'instabilité génomique, ou à la mort de la cellule. Ainsi, les cellules ont développé 5 voies de réparation principales, la recombinaison homologue, la ligature d'extrémités non homologues, la réparation par excision de nucléotides, la réparation par excision de base et la réparation des mésappariements, par lesquels différents types de dommages à l'ADN peuvent être détectés et réparés. Cependant, une réparation efficace des dommages à l'ADN est compliquée par le fait que l'ADN génomique est empaqueté avec les histones et les protéines non histones dans la chromatine, une structure hautement condensée qui bloque l'accessibilité à l'ADN et sa réparation subséquente. En conséquence, la machinerie de réparation cellulaire doit contourner cette barrière naturelle afin d'avoir rapidement accès au site endommagé. La réparation des lésions à l'ADN dans le contexte de la chromatine se réalise avec l'aide d'enzymes de remodelage de la chromatine dépendantes de l'ATP et des enzymes de modification des histones, qui permettent aux facteurs de réparation nécessaires d'avoir accès à la lésion. Nous passons ici en revue les études récentes qui élucident les interactions entre les agents qui modifient ou remodèlent la chromatine et les principales voies de réparation d'ADN.

Mots clés : chromatine, réparation de ADN, modification d'histone, REN, RCDB, RM.

[Traduit par la Rédaction]

Introduction

DNA is subject to a continuous assault of exogenous and endogenous genotoxic agents that compromise the functional integrity of the genome. It has been estimated that mammalian cells may be subject to at least 10 000 different lesions every day (Lindahl 1993), which may well represent a low estimate. In turn, cells have developed multiple mechanisms to repair different kinds of DNA lesions, including those introduced by internal mechanisms, as well as external or environmental agents.

Eukaryotic DNA must be tightly packed to fit within the nucleus. Therefore, 147 bp of DNA is wrapped around an octamer of 4 histone proteins (2 copies each of H2A, H2B, H3, and H4). The histone octamer and its associated DNA make up the nucleosome, which is the basic repeating unit of chromatin. Linear arrays of nucleosomes are folded into more compact 30 nm fibers, which are stabilized by linker histones such as histone H1. These fibers are subjected to further levels of higher-order folding to form the final structure of the chromosome. This compact structure of chromatin greatly hinders nuclear processes such as transcription, replication, and repair. However, cells have mechanisms for remodeling and interacting with the chromatin to access

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DNA. Chromatin remodeling can happen through the activities of 2 types of enzymes: histone modifiers and ATP-dependent remodelers.

Histone-modifying enzymes catalyze the covalent attachment or removal of a large suite of post-translational histone modifications, such as lysine acetylation or methylation, or serine phosphorylation. The end result is the control of the condensation state of chromatin via alteration of DNA–histone contacts and (or) recruitment of nonhistone, regulatory proteins to the chromatin (Agalioti et al. 2002; Hassan et al. 2002; Peterson and Laniel 2004; Martin and Zhang 2005). ATP-dependent remodelers use the energy of ATP hydrolysis to alter chromatin structure by disrupting DNA–histone contacts and repositioning or sliding nucleosomes (Tsukiyama 2002; Cairns 2005; Johnson et al. 2005). This results in changes in accessibility of the DNA to other proteins.

Research in the last decade has made it clear that the activities of histone-modifying enzymes and ATP-dependent remodelers are indispensable for DNA repair. In this review, we summarize recent knowledge of how DNA repair enzymes gain access to DNA lesions within chromatin, repair the damaged DNA, and restore the chromatin structure in *Saccharomyces cerevisiae*. Yeast is easy to manipulate at both the physiologic and genetic levels, and has proven to be an ideal model for studying DNA repair in eukaryotes. We have divided different modes of DNA repair in yeast into 2 broad categories: excision repair pathways and double-strand break repair pathways.

Excision repair pathways

All pathways of excision repair involve recognition of DNA damage, dual incisions of the DNA phosphodiester backbone in the damaged strand, excision of the lesion, resynthesis of the deleted nucleotide sequence by DNA polymerase using the complementary DNA strand as a template, ligation of the repaired strand, and restoration of chromatin structure. The entire repair process requires the presence of many repair factors and other large complexes in a chromatin environment. The cell contends with this problem by recruiting and using histone-modifying enzymes, such as histone acetyltransferases (HATs), and chromatin-remodeling enzymes. The three main excision repair pathways are nucleotide excision repair (NER), base excision repair (BER), and mismatch repair (MMR).

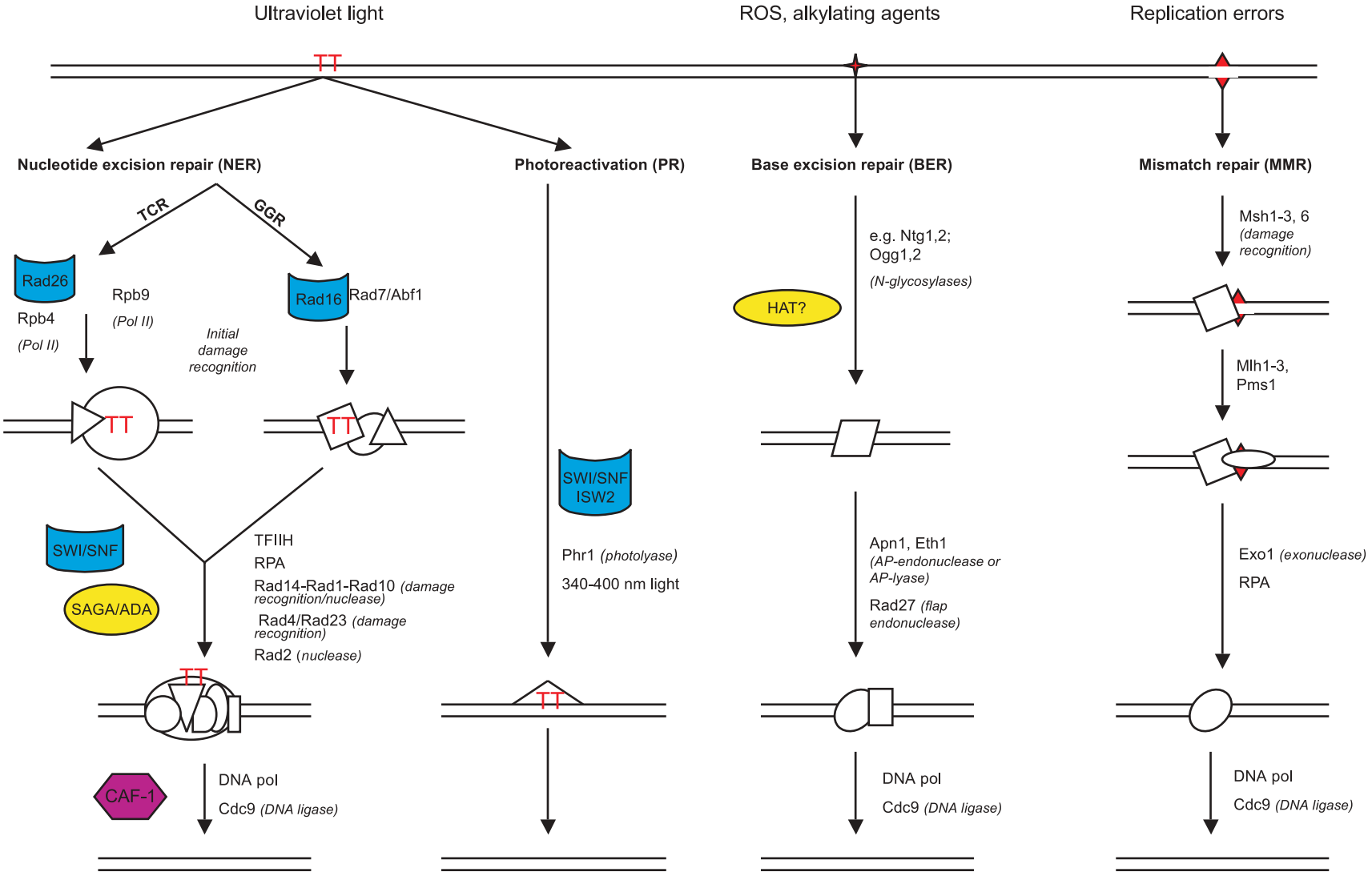
Nucleotide excision repair

The NER pathway is specifically responsible for removing DNA lesions that distort the DNA helix, such as UV-induced 6-4 photoproducts (6-4PPs) and cyclobutane pyrimidine dimers (CPDs) (Thoma 1999). Chromatin plays a role in both the spectrum of damage formation and repair of the lesions. For example, CPDs are mainly found in the minor groove of DNA facing away from the histone surface, and 6-4PPs are preferentially formed in linker DNA but can also be seen throughout the histone core region (Wuebbles and Jones 2004). This indicates that nucleosomes can actually confer partial protection against this type of DNA damage. All UV-induced photoproducts result in an abnormal DNA structure that signals the lesion. Studies in yeast clearly show the inhibitory effect of chromatin structure on repair, since both CPDs and 6-4PPs are repaired at faster rates in nucleosome-free regions and in the linker DNA than in the nucleosome core (Smerdon and Thoma 1990; Tanaka et al. 1996; Wellinger and Thoma 1997). Similar results were also reported in the case of the yeast genomic copy of the *URA3* gene (Tijsterman et al. 1999), as well as for CPD repair in *MET16* (Ferreiro et al. 2004), the *MET17* promoter (Powell et al. 2003), the *GAL1–10* promoter region (Li and Smerdon 2002*a*; Li and Smerdon 2004), and in rDNA (Conconi et al. 2005). The role of chromatin structure for DNA repair in NER has also been addressed recently in several excellent review articles (Conconi 2005; Gong et al. 2005; Reed 2005; Thoma 2005).

Once the damage is recognized, it can be repaired either by direct reversal of damage or via an excision repair pathway (Fig. 1, left). In yeast, UV-induced CPDs and 6-4PPs can be repaired directly by DNA photolyases through photoreactivation (PR) (Sancar 2000). Photolyases bind to CPDs, flip damaged bases out of the DNA helix, and bury them in a deep active site (Fuxreiter et al. 2002). Upon excitation by 340–400 nm light, photolyases cleave the link between adjacent pyrimidines and restore monomeric bases without cutting the phosphodiester backbone of DNA. Following repair, the nucleotides move out of the cavity, and the enzyme dissociates from DNA. The yeast photolyase Phr1 preferentially reverses CPDs in the nontranscribed strand of active genes (Aboussekhra and Thoma 1998); however, it is inhibited by RNA polymerase II (Pol II) stalled at DNA lesions, which leads to slow repair of the transcribed strand (Livingstone-Zatchej et al. 1997). Gaillard et al. (2003) showed that yeast ATP dependent remodelers SWI/SNF and ISW2 remodel the damaged nucleosome to facilitate the repair of CPDs through the PR repair pathway in vitro. SWI/SNF destabilizes UV-damaged nucleosomes so that photolyase can access the lesion, and ISW2 moves the position of a nucleosome on UV-damaged DNA by nucleosome sliding, resulting in the repositioning of CPDs in the more accessible linker DNA. These results show that ATP-dependent remodeling activities can clearly facilitate direct repair of UV damage. It remains to be seen which remodeler(s) facilitate photolyase access in vivo.

The other mechanism for repair of UV damage is the NER pathway, which requires a large number of repair proteins that assemble at the sites of DNA damage in a sequential manner (Guzder et al. 1996*a*; van Hoffen et al. 2003) (Fig. 1, left). DNA damage in the nontranscribed strand of active genes or unexpressed regions of the genome is removed by global genome repair (GGR), whereas lesions in the transcribed strands are targeted for removal by transcription-coupled repair (TCR) (Tornaletti et al. 1999; Svejstrup 2002; Li and Smerdon 2004). These two NER pathways are modulated by chromatin structure and transcription, and utilize the same core set of proteins, but rely upon different proteins that recognize the lesions. In *Saccharomyces cerevisiae*, damage recognition in the GGR pathway depends on a complex composed of Rad16/Rad7/Abf1 proteins (Reed et al. 1999), and the TCR pathway on Rad26 and the Pol II subunit Rpb9 (Li and Smerdon 2002*b*). It has been shown that UV-induced DNA damage is repaired more rapidly in

Fig. 1. Excision repair pathways in the context of chromatin. Cartoon illustrating the 3 major excision repair pathways in yeast: nucleotide excision repair (left), base excision repair (center), and mismatch repair (right). Key repair factors for each pathway are indicated, and factors that influence chromatin structure are color-coded: ATP-dependent remodelers, blue; histone modifying enzymes, yellow; chromatin assembly factors, magenta. In the NER pathway, the ATP-dependent remodeling enzymes provide damage recognition and increased accessibility to the damaged site, as well as recruitment of histone-modifying enzymes. Chromatin assembly is required to restore chromatin structure. See text for full discussion.



the transcribed strands of expressed genes than in the inactive DNA strand (Smerdon and Thoma 1990; Sweder and Hanawalt 1992).

The most challenging step in NER is the recognition of DNA lesions in their chromatin context. Nucleosomes on damaged DNA inhibit efficient NER, and there is a functional connection between chromatin remodeling and the initiation steps of NER, as well as DNA repair efficiency (Ura et al. 2001). CPDs comprise a covalent joining of 2 adjacent thymine residues in the same DNA chain, which acts as an obstacle to DNA replication or transcription, since it blocks both DNA polymerase and RNA polymerase (Pol) elongation in the transcribed strands of expressed genes (Tornaletti et al. 1999). It is generally believed that RNA Pol II blockage is the first signal that initiates and recruits the NER machinery to remove the transcription-blocking lesion in the TCR pathway (Selby and Sancar 1993; Svejstrup 2002).

Several studies have indicated that Rad26 plays a role in RNA Pol II transcription elongation in yeast cells, and that it is involved in the preferential repair of UV lesions on the transcribed strand in NER (Guzder et al. 1996*b*; Lee et al. 2001). Rad26 enables RNA Pol II to transcribe through damaged bases, thus freeing the lesion from stalled RNA Pol and making DNA lesions accessible to repair enzymes (Lee et al. 2002). However, it was suggested that this transcription promotion by Rad26 might be independent of more direct roles in repair. Rad26, the yeast homolog of the Cockayne Syndrome B (CSB) protein, is a member of the Swi2/Snf2 family of DNA-dependent ATPases (Eisen et al. 1995; Fyodorov and Kadonaga 2001). Recently, it was reported that increased expression of Rad26 results in an increase in repair of both the transcribed and nontranscribed strands of genes (Bucheli and Sweder 2004).

Besides the Rad26-mediated TCR subpathway in yeast, Li and Smerdon (2002*b*) identified another TCR subpathway which is mediated by RNA Pol II via its Rpb9 subunit. *Saccharomyces cerevisiae* RNA Pol II is composed of 12 subunits designated Rpb1–12; Rpb9 protein regulates transcription initiation and elongation (Hemming et al. 2000). Li and Smerdon showed that the Rpb9-mediated TCR subpathway operates primarily in the coding region of the transcribed gene, whereas the Rad26-mediated pathway repairs lesions both in the coding region and in regions upstream of the transcription start site. Rpb4, another subunit of RNA Pol II, simultaneously suppresses the Rpb9-dependent subpathway and facilitates the Rad26-dependent pathway. The authors suggest that the role of Rpb9 might be to either affect chromatin remodeling during transcription or to enable RNA Pol II to resume transcription after being stopped at the site of UV damage.

A recent report showed that Rad26 is essential for TCR during the G1 phase in yeast haploid cells, but not in G2/M, since there is also a Rad26-independent pathway which involves homologous recombination (HR) proteins (Aboussekhra and Al-Sharif 2005; discussed further below). In addition, it was found that HR is involved in UV repair in diploid cells. These findings indicate that homologous recombination may represent a significant alternative pathway for repair of UV damage, either during the G2/M phase in haploid cells, when exchange between sister chromatids can take place, or in diploid cells, when recombination with a homologous chromosome is possible.

The yeast Rad7–Rad16 complex is involved in the initial recognition of DNA damage in the nontranscribed strand of active genes, and it functions specifically in the GGR pathway (Mueller and Smerdon 1995). Rad16 is also a member of the SWI2/SNF2 superfamily, and shows DNA-dependent ATPase activity (Prakash et al. 1993), which is implicated in chromatin remodeling and an increased accessibility to the DNA lesion. The Rad7–Rad16 complex moves along DNA in an ATP-dependent manner (Guzder et al. 1997); however, this ATPase activity is inhibited by the presence of UV-damage. The end result is stable binding of this complex to the lesion, and recruitment of the other NER factors (Guzder et al. 1998). The Rad7–Rad16 complex is also involved in the incision of damaged DNA (Reed et al. 1998). A study of purified Rad7–Rad16 complex revealed the presence of a tightly bound third member of the complex, Abf1 protein (Reed et al. 1999), which facilitates the excision of oligonucleotides containing sites of base damage during NER in yeast. Recent work in Reed's laboratory (Yu et al. 2004) reported that the ATPase activity of Rad16 leads to the generation of superhelical torsion in the nontranscribed strand of damaged DNA, and that generated torsion by the Rad7/Rad16/Abf1 complex is necessary for removal or excision of DNA base damage by the GGR pathway of NER.

In addition to Rad26 and the Rad7–Rad16 complex in yeast, the major damage-binding factors are the basal transcription factor complex TFIIH, replication protein A (RPA), Rad14, and the Rad4–Rad23 complex. The ATP-dependent helicase activity of TFIIH has a role in opening the dsDNA in both NER pathways, providing NER factors with the necessary access to the lesion (Sung et al. 1987; Guzder et al. 1994). RPA is an ssDNA-binding protein (He et al. 1995; Lao et al. 2000), which is needed by TFIIH for the full opening of the DNA helix at the damage site (Evans et al. 1997; Mu et al. 1997). Rad14 is a damage binding protein that shows a high affinity for UV-damaged DNA (Guzder et al. 1993). The Rad4–Rad23 complex is required for both TCR and GGR pathways; however, it should be noted that majority of the yeast genome is transcriptionally active (Holstege et al. 1998). Rad23 protein participates directly in NER by stimulating the binding activity of Rad4 on damaged DNA, as well as by stabilizing the levels of Rad4 protein during NER (Lommel et al. 2002; Xie et al. 2004).

In yeast, TFIIH, RPA, Rad14, the Rad4–Rad23 complex, the Rad7–Rad16 complex, Rad2, and the Rad1–Rad10 complex are all involved in the dual incision of UV-damaged DNA (Guzder et al. 1995, 2006), which results in the removal of a DNA fragment of 25–30 nucleotides long (Huang et al. 1992). Both yeast Rad2 and the Rad1–Rad10 complex exhibit ssDNA endonuclease activity for dual incisions of the UV-damaged lesion (Tomkinson et al. 1993; Sung et al. 1993; Habraken et al. 1993). In addition, these complexes are also involved in the proper assembly of the NER factors at the damage site (Mu et al. 1995).

After removal of the DNA lesion, and completion of new DNA synthesis by DNA polymerase and DNA ligase, the original structure of chromatin is restored with the help of chromatin assembly factor 1 (CAF-1) (Green and Almouzni 2002). The recruitment of mammalian CAF-1 is restricted to damage sites and depends on NER, binding concomitantly with repair synthesis (Green and Almouzni 2003), and yeast

CAF-1 has also been shown to be required for survival of UV damage (Kaufman et al. 1997). It is interesting to note that yeast cells devoid of NER show a significant elevation of chromosome gain in both haploid and diploid strains (Howlett and Schiestl 2004), suggesting that NER is also involved in normal chromosome disjunction.

In vitro studies on the influence of chromatin structure on NER and direct links between nucleosome positioning and chromatin accessibility to repair factors show that overall repair of CPDs by NER is less efficient in reconstituted nucleosomes than in naked DNA, confirming that the presence of nucleosomes on damaged DNA inhibits the activity of NER repair factors (Ura et al. 2001). In addition, it was reported that in vitro, NER is slow or nonexistent on the nucleosomal surface (Thoma 1999; Ura et al. 2001); however, in vivo, there is relatively efficient repair of lesions by NER in repressive chromatin (Verhage et al. 1994; Teng et al. 1997). Since it is clear that chromatin at the lesion must be disrupted during repair, the concerted action of chromatin modifiers results in unfolding-access-refolding during NER, in which UV irradiation results in both global and local changes in chromatin structure; thus, the damaged DNA becomes more accessible to repair proteins (Teng et al. 2002; Yu et al. 2005).

Chromatin remodeling via histone modification and ATP-dependent remodelers can provide NER machinery with access to DNA damage sites. The histone acetyltransferease Gcn5 is involved in the removal of CPDs from nucleosomal DNA in the transcriptionally active *MFA2* gene (Teng et al. 2002). It was reported in yeast that hyperacetylation of histone H3 at the repressed *MFA2* promoter, as well as a general increase in global H3 and H4 acetylation, occurred within minutes of UV irradiation, even in the absence of critical NER factors (Yu et al. 2005; Yu and Waters 2005). This result shows that certain chromatin modifications can occur independently or upstream of NER, and that a general increase in histone acetylation can be part of the cellular response to DNA damage, since it can facilitate the access of repair proteins to the damage site, or act as a signal for recruitment of chromatin remodeling factors and repair proteins. Repair of UV damage at the *MET16* gene has been shown to require subunits of both the SAGA and ADA complexes, Gcn5 and Ada2 (Ferreiro et al. 2006). The full transcriptional induction of *MET16* also requires SAGA/ADA, and repair efficiency is proportional to the transcription level, so it is not yet possible to tease apart the separate roles of SAGA/ADA in increased transcription (thereby increasing access overall) and specifically, in influencing NER.

Several ATP-dependent remodelers have been implicated in the repair of UV damage. As mentioned above, Gaillard et al. (2003) showed that yeast SWI/SNF and Isw2 complexes facilitate the accessibility of photolyases to CPDs in reconstituted nucleosomes. SWI/SNF also appears to act in vivo during NER, where it is at least partially responsible for increasing DNA accessibility in the *MFA2* promoter following UV treatment (Yu et al. 2005; Teng et al. 2005). However, deletion of the *SWI2* subunit of SWI/SNF does not significantly inhibit overall repair at *MFA2*, suggesting that other chromatin remodelers (such as Rad26) may be required to provide essential remodeling activity. Taken together, these results demonstrate that both ATP-dependent remodeling activities and histone modifications play an active role in NER within nucleosomal DNA.

Base excision repair

DNA lesions that do not significantly distort the DNA backbone to stall replication forks or stop transcription elongation are corrected by the BER pathway (Lindahl 2000). Damaged DNA bases recognized by BER can be introduced chemically by oxidation or alkylation. Reactive oxygen species (ROS) cause DNA oxidative damage, such as modified bases or single-strand breaks (Cadet et al. 1997). ROS are formed in the cell as by-products of normal aerobic respiration in mitochondria, or due to chemical mutagens, such as hydrogen peroxide. Among oxidative DNA lesions, the most mutagenic is the oxidized guanine (G) 8-oxo-G, which can base pair with cytosine (C) or adenine (A), leading to incorporation of A or C upon replication (G:C → T:A transversions), thus generating mutations (Girard and Boiteux 1997). The most abundant lesions produced by simple alkylating agents, such as methylmethane sulfonate, are *N*-methylpurines.

A specific *N*-glycosylase that recognizes a particular damaged base initiates BER (Fig. 1, center). *N*-glycosylase binds to the altered nucleotide and cleaves the *N*-glycosylic bond between the base and the sugar, producing an apurinic/apyrimidinic (AP) or abasic site. The AP site is processed by an AP endonuclease or glycosylase-associated AP-lyase, in which the phosphate backbone adjacent to the AP site is cleaved to generate a base gap, a single-strand nick, or nucleotide overhang(s) when more than one nucleotide is involved, at the lesion. DNA polymerase inserts the correct base(s), and DNA ligase seals the nick, thereby repairing the damage (Bogenhagen et al. 2001). A study of the interaction of glycosylases in complex with their DNA lesion has shown that the binding of glycosylases causes DNA bending, and that the damaged DNA base is flipped out into the active site of the enzyme (Bruner et al. 2000). The enzyme then cleaves the bond between the mismatched base and deoxyribose in the DNA backbone.

Two distinct pathways can repair the AP site generated by a DNA glycosylase: the short-patch pathway involves a single nucleotide replacement followed by ligation, and the long-patch pathway involves DNA synthesis of multiple nucleotides (usually 2–6) and removal of displaced nucleotide overhang by an endonuclease (Hoeijmakers 2001). Each pathway is composed of numerous variations that are specific for a different type of incorrect base(s), and specificity of each pathway and its variations depends on the DNA *N*-glycosylases. In yeast, a number of glycosylases that catalyze the excision of damaged bases have been identified, such as Ntg1, Ntg2, Ogg1, Ogg2, Ung1, and Mag proteins. The AP lesions in yeast are processed by AP endonucleases Apn1, Apn2, or Eth1. Additional factors in yeast include the flap endonuclease Rad27 for flap removal in the long-patch pathway; several DNA polymerases that can perform DNA synthesis; and the Cdc9 DNA ligase (Memisoglu and Samson 2000, Boiteux and Guillet 2004).

In general, the effect of chromatin structure on the BER pathway has not received much attention, particularly in yeast, and most of our understanding comes from in vitro

studies using purified mammalian repair factors. However, it appears that both histone-modifying enzymes and ATP-dependent remodelers play a role in facilitating access to lesions in this DNA repair pathway. A recent in vivo study linked histone acetylation with the repair of DNA lesions by BER (Tini et al. 2002). It was shown in mammalian cells that the HAT CBP/p300 interacts with thymine DNA glycosylase (TDG), and can acetylate both histones and TDG itself in this context, suggesting a direct link between chromatin-modifying activity and DNA repair. A similar role for yeast HATs has not been tested.

In another study, the short-patch BER pathway in chromatin was tested using an in vitro system that used human BER enzymes and rotationally positioned DNA containing a single uracil (U) associated with a nucleosome. It was reported that BER enzymes (U DNA glycosylase and AP endonuclease) showed a 90% reduction in activity when repairing G:U base pairs (the most common mismatch) in nucleosomes versus naked DNA (Beard et al. 2003), confirming the expected inhibitory effect of nucleosomes on the BER pathway. The effect of histone tails on BER of G:U mismatches was also tested in vitro, using nucleosomes with and without tails. This study showed that repair was not enhanced in the absence of histone tails (Beard et al. 2005). However, this study did not directly address either specific modifications of histone tails or the requirement of tails for recruitment of chromatin remodeling activities, leaving open the question of the role of histone modifications in vivo. This clearly represents a wide-open field for future studies.

Mismatch repair

DNA MMR is involved in mutation avoidance and replication fidelity, and it targets mismatches that arise during replication and homologous recombination, such as base–base mismatches and insertion/deletion loops (Marra and Schar 1999; Hsieh 2001). In addition, mismatches can result from DNA damage arising from modification by a variety of genotoxic agents (e.g., alkylating agents).

The MMR system is best understood in *Escherichia coli,* in which the MutS protein recognizes and binds to the mismatch or loop on a newly replicated daughter strand. This binding triggers an ATP-dependent conformational change that results in the recruitment of MutL. Together, and in the presence of ATP, they activate the MutH endonuclease that cleaves the unmethylated strand. The nick created by MutH serves as a point of entry for single-stranded DNA binding protein (SSB) and DNA helicase to displace the error-containing strand. The daughter strand is degraded by an exonuclease, followed by DNA polymerase, SSB, and DNA ligase, which carry out repair synthesis (Hsieh 2001; Schofield and Hsieh 2003).

In budding yeast, multiple factors that are involved in MMR have been identified (Fig. 1, right): 4 MutS homologs, Msh1–Msh3 and Msh6; 4 MutL homologs, Mlh1–Mlh3 and Pms1; the exonuclease ExoI; the ssDNA binding protein RPA; DNA polymerase; and DNA ligase. Currently, there is no known homolog for MutH in any eukaryote. Msh1 is thought to function in MMR in mitochondrial DNA, while Msh2, Msh3, and Msh6 appear to function in the nucleus. Two other MutS homologs, Msh4 and Msh5, are not involved in MMR; they function specifically in meiosis (Schofield and Hsieh 2003).

It has been suggested that MMR might act as a backup repair mechanism for BER in the repair of oxidative damage in both nuclear and mitochondrial DNA in budding yeast (Earley and Crouse 1998; Dzierzbicki et al. 2004). Experiments by Hawk et al. (2005) indicate that the efficiency of MMR varies in different regions of the yeast genome, and suggest that this variable DNA repair efficiency is due to local differences in chromatin structure.

Studies in human cells have revealed a role for the high mobility group box 1 protein (HMGB1), a nonhistone chromatin protein, in MMR (Yuan et al. 2004). HMGB1 binds directly to the human MutS α complex and promotes mismatch repair in vitro. However, there is surprisingly little else known about mismatch repair in the context of chromatin. This pathway of repair clearly represents another area in need of study by chromatin biologists.

Double-strand break repair pathways

DNA double-strand breaks (DSBs), the most damaging lesions in the genome, can occur as a result of multiple damaging agents, such as ionizing radiation or chemical exposure. Two major conserved repair pathways for DSBs are nonhomologous end joining (NHEJ) and HR. NHEJ involves the ligation of 2 broken DNA ends with no or minimal homology, and it can be error prone because no intact DNA template is involved. In HR, the information contained in a homologous sequence is used as a template for repair, and it is error free. HR is a major pathway for DSB repair in all eukaryotes; however, if a homologous DNA donor is not present or cannot be found, the NHEJ pathway is used. In both cases, repair has to occur within the context of the chromatin structure present at the lesion, as well as at any homologous donor sequences. The DNA DSB repair pathways are the most extensively studied pathways of DNA repair with respect to the role of chromatin remodeling enzymes (for recent reviews see Cairns 2005; Downs and Cote 2005; Huang et al. 2005; Lydall and Whitehall 2005; Moore and Krebs 2004; Morrison and Shen 2005; van Attikum and Gasser 2005*a*).

Several studies demonstrated that one of the first events following DSB is the phosphorylation of histone H2A at serine 129 (H2AX S139 in mammals; Rogakou et al. 1999; Downs et al. 2000), resulting in a phosphorylated chromatin domain that extends up to 50 kb around a DSB in yeast (Downs et al. 2004; Shroff et al. 2004; Unal et al. 2004). Phosphorylated H2A is involved in the recruitment of multiple chromatin-modifying complexes at the site of DNA damage, where they are able to change the chromatin structure to allow repair factors to gain access to, and repair, the lesion. The chromatin modifiers involved in DSB repair include numerous HATs and ATP-dependent remodelers, as well as histone kinases, phosphatases, and deacetylases. Since several of these chromatin modifiers have been shown to facilitate DNA accessibility and repair in both DSB repair pathways (HR and NHEJ), we will briefly review what is known about their recruitment mechanisms; however, their detailed roles and functions will be discussed separately with respect to each DSB repair pathway.

Phosphorylation of H2A is one of the earliest events to occur at the site of a double-strand break, so it is perhaps not surprising that phosphorylated H2A (PhosphoH2A) appears to serve as a major means for recruiting other necessary factors to the DSB. PhosphoH2A recruits the HAT NuA4, via its Arp4 (actin-related protein 4) subunit, to the DSB site. Once at the lesion, NuA4 acetylates the N-terminal tail of histone H4 (Bird et al. 2002; Downs et al. 2004). Assembly of chromatin modifiers continues with the recruitment of the ATP-dependent remodeling complexes INO80 and SWR1 (Downs et al. 2004; Morrison et al. 2004; van Attikum et al. 2004). Both of these chromatin remodelers also contain the Arp4 subunit, and it had been previously reported that the Arps interact with histones (Shen et al. 2003). Recruitment of the remodelers to the lesions depends on PhosphoH2A, which creates a binding site for Arp4, the common subunit in the NuA4 HAT complex, and the SWR1 and INO80 remodeling complexes. A recent study showed that mutations in *ESA1* (the catalytic subunit of NuA4) reduced recruitment of INO80 and SWR1 (Downs et al. 2004), suggesting that histone H2A phosphorylation and H4 acetylation are both important for the recruitment of the chromatin remodelers to the DSBs.

In addition to serine 129 in the H2A C-terminal tail, H2A serine 122 was also recently shown to be involved in mediating cell survival after several types of DNA damage had occurred. Although serine 122 can be phosphorylated in vivo and is located in close proximity to S129, its function in repair is independent from that of S129 (Wyatt et al. 2003; Harvey et al. 2005; J.D. Moore, O. Yazgan, Y. Ataian, and J.E. Krebs, unpublished results).

Taken together, it is clear that histone modifications play a complicated role in DSB repair. In addition to their effects on the structure of nucleosomes, histone modifications act as a marker to facilitate the recruitment of repair factors, and are a prerequisite for nucleosome remodeling by certain ATPases at the site of DNA damage. For DSB repair, the ability of PhosphoH2A to recruit a HAT and multiple distinct ATP-dependent remodelers to the lesion site emphasizes crucial role of chromatin remodeling, even before a repair pathway is chosen.

Homologous recombination

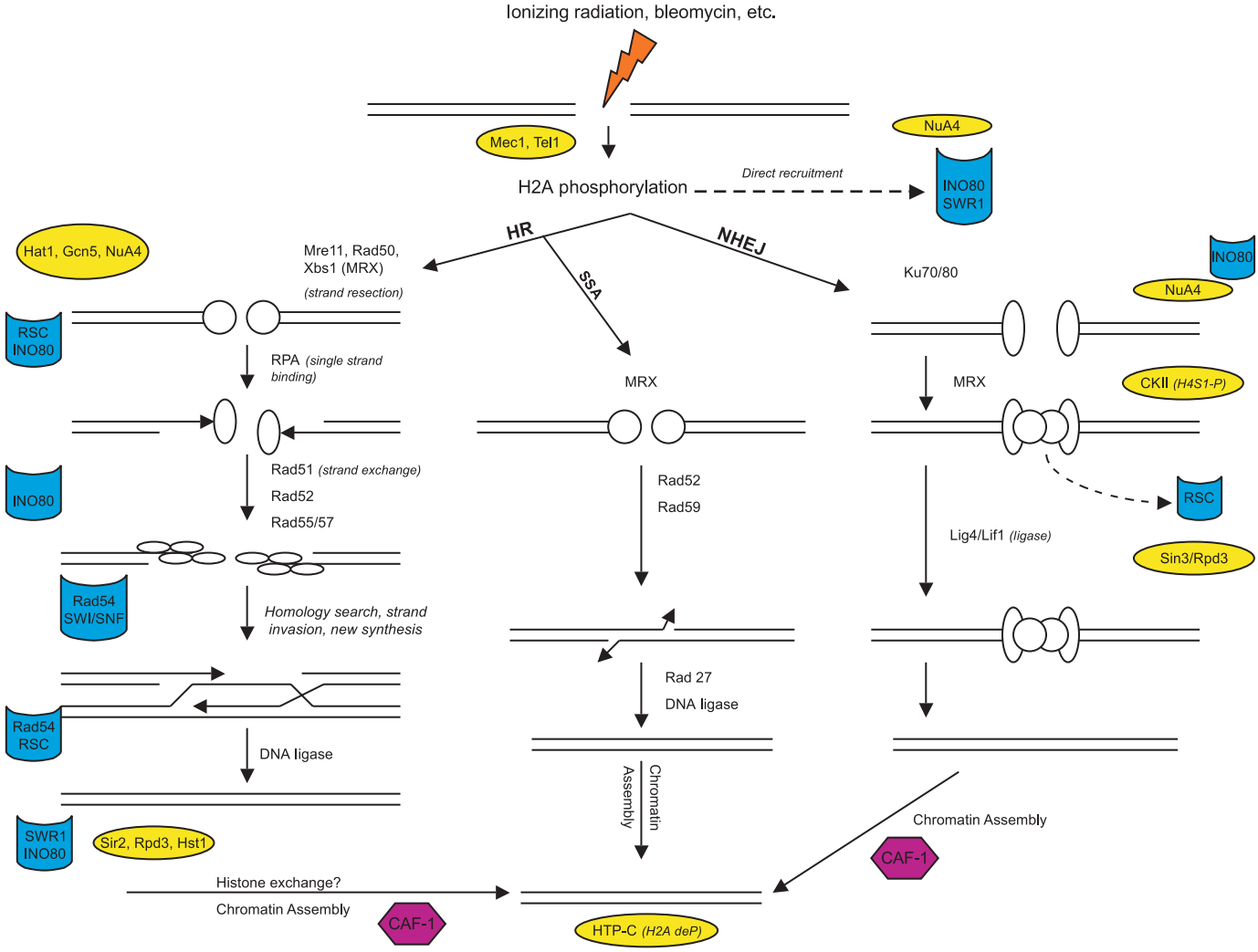
HR repair is the preferred mechanism for repair of DSBs in yeast, since the reliance on an intact homologous region ensures that no essential sequence information is lost. In haploid cells, this requires the presence of a sister chromatid or another source of homology other than a homologous chromosome. HR requires genes in the *RAD52* epistasis group, which includes *RAD50*, *RAD51*, *RAD52, RAD54, RAD55, RAD57, RAD59, MRE11*, and *XRS2* (recently reviewed in Aylon and Kupiec 2004; Dudas and Chovanec 2004; Fig. 2, left). Upon formation of a DSB, the broken ends are recognized and processed by the Rad50/Mre11/Xrs2 (MRX) exonuclease complex, which resects 1 strand of the broken end from 5′ to 3′. The result is 3′ ssDNA overhangs (Haber 2000; Dudas and Chovanec 2004). The ssDNA-binding protein, RPA, binds to these ssDNA overhangs. Recruitment of Rad52, Rad54, and the Rad55/Rad57 heterodimer mediate the replacement of RPA with Rad51, creating a Rad51 filament that can participate in the search for and invasion of a homologous sequence (Sung et al. 2000; Symington 2002; Wolner et al. 2003). Rad55 and Rad57 assist Rad51 in initiating strand exchange (Sung 1997). Following priming by the invading 3′ ends and replication of the homologous template by DNA polymerase, the resulting intertwined chromosome structure is resolved and the DNA is ligated.

An alternative HR repair pathway is single-strand annealing (SSA) (Fig. 2, center), which can occur when a homologous donor cannot be found. The SSA pathway requires the MRX exonuclease complex, as well as the Rad52, Rad59, and Rad27 proteins. SSA also appears to require some NER factors, including the nuclease complex Rad1–Rad10. SSA relies on the annealing of complementary repeated sequences close to the break, and the efficiency of repair is directly related to the length of homology, with approximately 200 bp giving the optimum result (Sugawara et al. 2000). This repair pathway requires a homology search, but not a strand invasion step, which may explain why this pathway is independent of Rad51. SSA uses Rad52 to search for homologous sequences on the 3′ ends, and Rad59 enhances the activity of Rad52 in SSA (Davis and Symington 2001). The Rad27 flap endonuclease removes the unpaired DNA ends after the homology search is finished (Wu et al. 1999). This is followed by synthesis of new DNA and ligation, which produces 2 continuous strands. In yeast, the SSA pathway competes with error-free HR, but repair by SSA always results in DNA sequence deletion (Sugawara et al. 2000).

It was recently reported that the ATP-dependent chromatin remodeling complex RSC is present at the site of a DSB (Chai et al. 2005; Shim et al. 2005). RSC is recruited by the MRX complex through an interaction between Mre11 and RSC. The recruitment of RSC seems to precede that of other remodelers (e.g., INO80), and RSC appears to play a broad role in the repair of DSBs. The mechanism(s) by which RSC is directed to either the HR or the NHEJ repair pathway is not fully understood. It has been shown that the RSC and SWI/SNF chromatin remodeling complexes are involved in HR (Chai et al. 2005; Huang et al. 2005), and can be detected both at the site of the DSB and at donor sequences when homologous donors are available. The data suggest that SWI/SNF is recruited to the donor sequence before the strand invasion step to expose nucleosomal DNA to the homology-searching complex, and SWI/SNF appears to be required for synapsis between the damage site and donor sequence. Intriguingly, while RSC is recruited to a DSB prior to SWI/SNF, RSC's essential role in HR is required after synapsis, suggesting that its remodeling activity might function to dissociate the invading and donor DNA before the final ligation step.

The relative timing of recruitment and activity of other remodelers is not entirely clear. The related SWR1 and INO80 complexes are both recruited by phosphoH2A via their Arp4 subunits (Downs et al. 2004; Morrison et al. 2004; van Attikum et al. 2004). Chromatin remodeling activity of the INO80 complex alters nucleosome positioning to facilitate the processing of newly broken DNA ends, which enables the conversion of dsDNA ends into 3′ ssDNA overhangs by the MRX complex (Morrison et al. 2004; van Attikum et al. 2004). It has been shown that transcription factor access to chromatin can be achieved through the active ejection of nu-

Fig. 2. Double-strand break repair pathways in the context of chromatin. Cartoon illustrating the major double strand break (DSB) repair pathways in yeast: homologous recombination (HR; left), the HR subpathway single strand annealing (SSA, center), and nonhomologous end joining (NHEJ, right). Key repair factors for each pathway are indicated, and factors that influence chromatin structure are color coded: ATP-dependent remodelers, blue; histone modifying enzymes, yellow; chromatin assembly factors, magenta. Phosphorylation of H2A surrounding a DSB allows binding of several chromatin remodeling and modifying enzymes, as well as recruitment of DNA repair factors. These remodelers/modifiers facilitate Rad51 homology search and strand invasion process in HR, and ligation of broken ends in NHEJ. Positioning of chromatin-modifying factors in these pathways is approximate, based on data describing the relative time of recruitment or functional data on the role at a particular step in the pathway, when available. See text for detailed discussion.



cleosomes, and that this ejection might involve the chromatin assembly factor Asf1 (Reinke and Horz 2003; Boeger et al. 2004; Adkins et al. 2004; Linger and Tyler 2005). Recently, it was found that, although INO80 is recruited by PhosphoH2A, it exhibits ATP-dependent nucleosome displacement, or histone eviction, at DSBs that depends on the MRX complex (Tsukuda et al. 2005). Nucleosome eviction by the INO80 chromatin remodeler controls the rate at which Rad51 displaces RPA during HR, suggesting a very early role for this complex.

An alternative to nucleosome eviction is the exchange of individual histones in the nucleosome. Recent studies have shown that ATP-dependent chromatin remodeling activities can change the histone composition of nucleosomes (for recent reviews, see Korber and Horz 2004; Cairns 2005; Jin et al. 2005; van Attikum and Gasser 2005*a*). The yeast SWR1 chromatin remodeler associates with Htz1 (the yeast homolog of the histone H2A variant H2AZ). In vivo, SWR1 is responsible for depositing Htz1 into chromatin in specific locations throughout the genome (Li et al. 2005; Zhang et al. 2005);in vitro, it catalyzes the replacement of H2A/H2B with Htz1/H2B dimers by breaking H2A/H2B-DNA contacts using the energy of ATP hydrolysis (Krogan et al. 2003; Mizuguchi et al. 2004; Kobor et al. 2004). During DSB repair, the *Drosophila* HAT and exchange factor dTip60 has been shown to acetylate and then replace phosphorylated H2Av (the *Drosophila* H2AX homolog) with an unmodified H2Av (Kusch et al. 2004). Recent data suggest that yeast SWI1 may act analogously to replace PhosphoH2A with Htz1 after successful repair, while INO80 may in fact prevent or reverse

this exchange to prevent premature cessation of repair activities in the absence of complete repair (M. Papamichos-Chronakis, J.E. Krebs, and C.L. Peterson, unpublished).

A chromatin remodeler with a unique role in HR is Rad54, another member of the SWI2/SNF2 superfamily. Rad54 has ATPase activity that is needed to remove nucleosomes and other DNA-binding proteins to enhance accessibility of nucleosomal DNA during recombination (Wolner and Peterson 2005). Rad54 physically interacts with and assists Rad51 during the homology search and strand invasion at the homologous donor by binding to both Rad51 and ssDNA (Sugawara et al. 2003; Wolner et al. 2003; Mazin et al. 2003). As proposed for RSC, Rad54 might also be involved in facilitating the dissociation of Rad51 from the postsynaptic complex (Solinger et al. 2002). It is suggested that Rad54 uses the energy of ATP hydrolysis to move along DNA 1 nucleotide at a time, generating superhelical torsion in the DNA. This torsion may enhance the accessibility of DNA within nucleosomes at potential donor sequences, thereby facilitating the homology search by Rad51 (Jaskelioff et al. 2003).

In addition to the various activities of ATP-dependent remodelers, and the extensively characterized roles of H2A phosphorylation, many histone modifications have been reported to be important for DNA repair by HR (reviewed in van Attikum and Gasser 2005*b*), such as acetylation of lysine residues in the N-terminal tail of histone H3 by the Hat1 acetyltransferase (Qin and Parthun 2002). In a recent study, dynamic changes in acetylation of the N-terminal tails of histones H3 and H4 were identified during repair of a DSB (Tamburini and Tyler 2005). The HATs Gcn5 and Esa1, as well as the histone deacetylases Sir2, Rpd3, and Hst1, were all shown to be recruited to the DSB, suggesting that the interplay of these factors are what controls these waves of histone modifications during HR. These authors proposed that histone modifications might be involved in increasing the accessibility of nucleosomal DNA, recruitment of chromatin remodelers, or acting as signals to turn off damage checkpoints so the cell can proceed through the cell cycle.

Nonhomologous end joining

NHEJ repair in yeast requires the DNA end-binding heterodimer Ku70/Ku80, the Lig4/Lif1 ligase complex, and the MRX complex (recently reviewed in Dudasova et al. 2004; Daley et al. 2005; Fig. 2, right). During NHEJ, the ends of a DSB are detected and bound by the Ku70/Ku80 heterodimer. It is thought that this binding protects the broken ends from degradation and marks the damage site. Binding of Ku70/Ku80 heterodimer recruits the MRX complex to the site of damage. This complex has end-bridging activity, facilitating the contact between the 2 broken ends (Dudasova et al. 2004). It is speculated that the nuclease activity of the MRX complex may promote end alignment and end processing of nonblunt ends (Hefferin and Tomkinson 2005). Finally, the Ku70/Ku80 heterodimer and MRX complex together recruit the Lig4–Lif1 complex to the lesion site to ligate the broken DNA ends.

In addition to these specific repair factors, a number of chromatin-modifying factors have been shown to play specific roles in NHEJ. In yeast, the Sin3p/Rpd3p histone deacetylase complex is required for deacetylation of histone H4 (lysine 16), which is involved in efficient repair in the NHEJ pathway but not in HR (Jazayeri et al. 2004). It was proposed that deacetylation of H4 is not required for recruitment of NHEJ repair proteins, but rather for generating a region in chromatin that facilitates synapsis of the broken ends (Fernandez-Capetillo and Nussenzweig 2004). It has also been shown that the N-terminal tail of histone H4 is phosphorylated at serine in response to DSBs, and this modification appears to be important for the NHEJ repair pathway (Cheung et al. 2005). This phosphorylation inhibits H4 acetylation by NuA4; however, it was found that histone phosphorylation occurs much later than acetylation of histone H4 (lysine 16) by NuA4, and that it is associated with deacetylation of H4 by Sin3p/Rpd3p deacetylases (Utley et al. 2005). Taken together, these data suggest that NuA4 acetylation may act early to relax chromatin structure around the DNA lesion. Subsequently, this acetylation is removed by Sin3p/Rpd3p deacetylases, which may be required for late stages of repair, or may play a role in chromatin reestablishment. Deacetylase activity is followed by H4 S1 phosphorylation, which inhibits re-acetylation of H4 by NuA4 and may also function in chromatin restoration after repair is completed.

A recent study on the role of the RSC remodeling complex in NHEJ reported the detection of physical interactions between RSC and the Mre11 and Ku80 proteins. In addition, the absence of Mre11 or Ku70 abolishes RSC recruitment to a double-strand break (Shim et al. 2005). It is speculated that ATPase remodeling activity of RSC may serve to facilitate access for proteins involved in NHEJ, or assist the end-joining reaction in the context of chromatin by facilitating cohesion loading, which could contribute to holding the DSB ends together. van Attikum et al. (2004) showed that the INO80 complex is also required for efficient repair by NHEJ, though its role in this pathway has not been defined.

Chromatin resetting after DSB repair

The final stages of all DNA repair pathways entail reassembly of nucleosomes in newly replicated regions, as well as the restoration of the local epigenetic state of the chromatin. Myung et al. (2003) have shown a role for both CAF-1 and replication-coupling assembly factor in DNA repair. Defects in either factor result in the accumulation of DNA damage, particularly genome rearrangements such as translocations and major deletions, consistent with a particular role in DSB repair. The CAF-1 chromatin assembly factor has subsequently been shown to be required for both the HR and NHEJ pathways of DSB repair (Linger and Tyler 2005), while the Asf1 histone chaperone does not appear to have an essential function in DSB repair itself (Ramey et al. 2004).

In addition to the need to reassemble chromatin as a result of nucleosome displacement during repair, the repair process generates many nucleosomes bearing damage-specific modifications. Removal of damage-specific histone modifications, such as phosphorylation of H2A, can be accomplished by 2 general mechanisms. One is direct removal/exchange of the modified histones, as described above. However, it also seems reasonable that the damage-specific modifications could be reversed, either in situ at the site of damage, or on the exchanged histones, which could then be recycled. Recently, Keogh et al. (2006) reported the identification of

HTP-C (histone H2A phosphatase complex) in yeast, a complex containing the phosphatase Pph3, which specifically dephosphorylates PhosphoH2A after its displacement from a DSB. Similarly, the PP2A phosphatase was shown to be involved in the loss of H2AX phosphorylation following DSB repair in mammalian cells, though whether this dephosphorylation occurs in situ or after displacement is not known (Chowdhury et al. 2005).

Concluding remarks

The interplay between histone modifications and ATP-dependent remodeling activities along different pathways of DNA repair is amazingly complex. The emerging picture in this field of research shows multiple interdependencies between the 2 classes of enzymes that modify chromatin structure and the variety of repair factors that must access damage in chromatin. Histone modifications can serve to mark the specific positions of DNA damage and provide novel landing platforms for repair machineries. Specific patterns of histone modification might be used to signal the damage type, thereby regulating the recruitment of the correct subset of DNA repair factors, as appears to be the case for modifications of histone H2A/H2AX. Histone modifications can also direct the recruitment of ATP-dependent chromatin remodeling complexes required for DNA repair. For example, histone acetylation is involved in recruiting SWR1 and INO80 to sites of DNA lesions, delivering nucleosome remodeling and histone exchange activities to facilitate the repair process.

It is clear that we have only begun to scratch the surface in our understanding of DNA repair in the context of chromatin, and further work is needed to elucidate both the individual functions and the coordinated activities of chromatin remodeling and repair enzymes in all of the different DNA repair pathways. As we realize the multifunctional role of chromatin-remodeling complexes, more questions are raised as to the mechanism by which the damage is sensed by the cell, the choice of a particular repair pathway, the role and impact of other histone modifications and remodeling activities on DNA damage signaling and checkpoint activation, the mechanism(s) by which specific chromatin remodelers are directed to a specific repair pathway, and last but not least, the mechanisms by which chromatin reassembly and resetting takes place. The answers to these questions and to many others that will arise as a result of new discoveries will provide exciting insights into the dynamic nature of chromatin remodeling and its influence on the processes of DNA repair.

Considering the array of available tools brought to bear on the study of chromatin in the repair of double-strand break repair pathways, rapid progress has been made in this field in the past few years. It is hoped that similar intensive study can also be turned to the excision repair pathways and the roles of chromatin modification in these modes of repair.

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