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Chromatin remodeling in DNA double-strand break repair

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ATP-dependent chromatin remodeling complexes use ATP hydrolysis to remodel nucleosomes and have well-established functions in transcription. However, emerging lines of evidence suggest that chromatin remodeling complexes are important players in DNA double-strand break (DSB) repair as well. The INO80 and SWI2 subfamilies of chromatin remodeling complexes have been found to be recruited to the double-strand lesions and to function directly in both homologous recombination and non-homologous end-joining, the two major conserved DSB repair pathways. Improperly repaired DSBs are implicated in cancer development in higher organisms. Understanding how chromatin remodeling complexes contribute to DSB repair should provide new insights into the mechanisms of carcinogenesis and might suggest new targets for cancer treatment.

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Current Opinion in Genetics & Development 2007, 17:126–131

This review comes from a themed issue on
Chromosomes and expression mechanisms
Edited by Tom Misteli and Abby Dernburg

Available online 22nd February 2007

0959-437X/\$ – see front matter

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DOI [10.1016/j.gde.2007.02.010](https://doi.org/10.1016/j.gde.2007.02.010)

Introduction

Eukaryotic genomes are packaged into chromatin, which creates a natural barrier against access to DNA during transcription, replication, repair and recombination. Extensive studies have revealed that the basic unit of chromatin, the nucleosome, is reconfigured dynamically during transcription by histone modification, histone variant incorporation, and ATP-dependent chromatin remodeling. Recently, all of these mechanisms have been implicated in chromatin alterations in response to DNA double-strand breaks (DSBs).

DSBs are the most genotoxic lesions because unrepaired or improperly repaired DSBs can lead to chromosomal truncations and translocations, which can contribute to cancer in higher eukaryotic organisms. Two major conserved mechanisms have evolved to repair the DSBs in eukaryotic cells. Homologous recombination uses sister chromatids as a template to rejoin DSBs and is a high-fidelity break repair

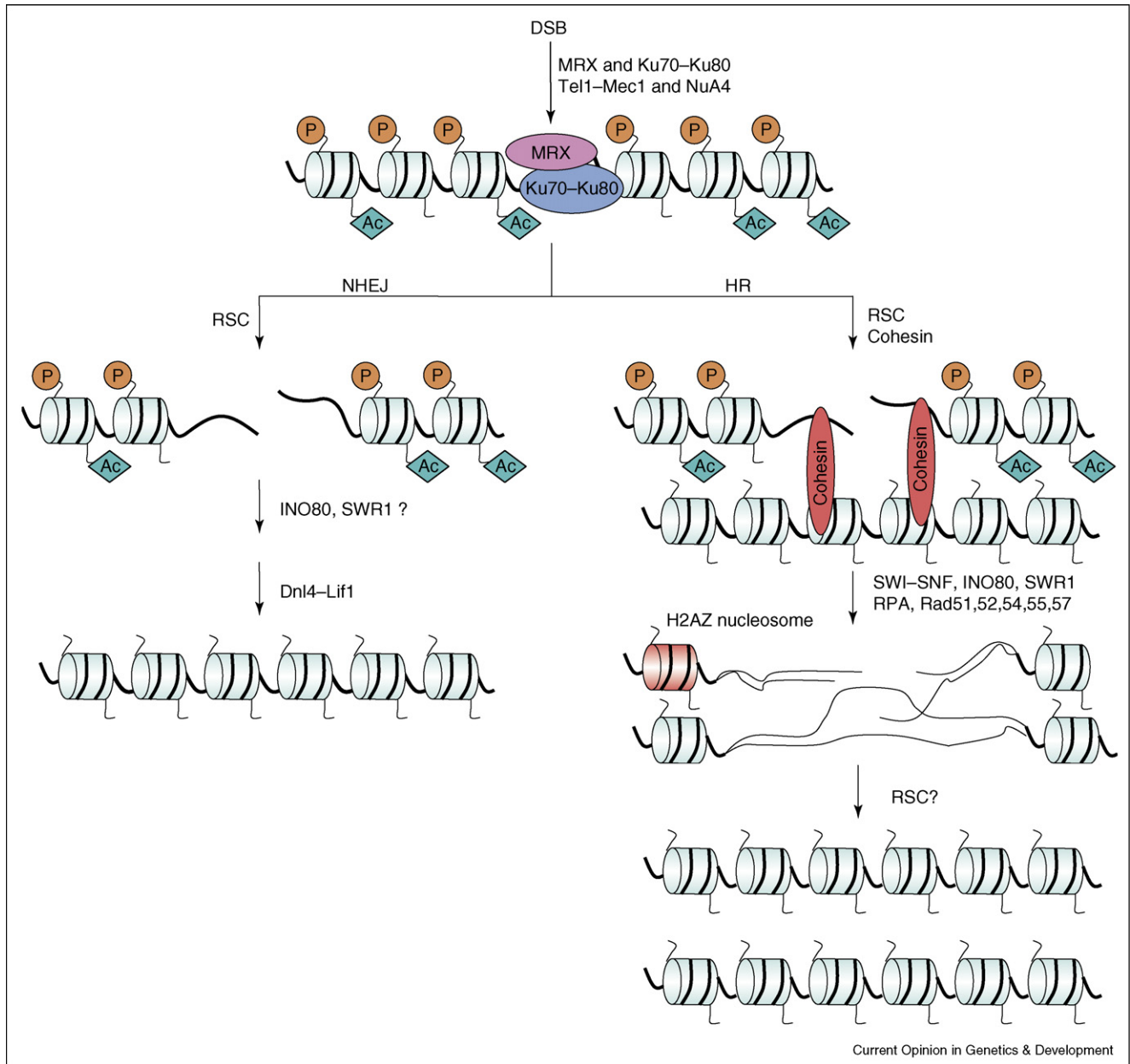
process. By contrast, non-homologous end-joining is often an error-prone process in which the broken ends can be re-ligated directly.

ATP-dependent chromatin remodelers are large multi-protein complexes containing an ATPase subunit that belongs to the SWI2–SNF2 (switching–sucrose non-fermenting) subfamily. These complexes use ATP hydrolysis to remove histones or to reconfigure the nucleosomes, increasing the accessibility of DNA elements to the regulatory proteins. SWI2, ISWI, CHD (chromo-ATPase–helicase–DNA-binding protein) and INO80 constitute the four best-studied subfamilies of ATP-dependent chromatin remodeling complexes. Several members of the INO80 and SWI2 subfamilies have been found to be recruited to the DSB lesions. This review begins with an overview of DSB repair and explores recent advances in our understanding of how these remodelers are recruited to DSB sites, and function directly in both homologous recombination and non-homologous end-joining repair pathways. For more comprehensive overviews of chromatin alterations upon DNA damage, readers are directed to two recent reviews [1,2].

Overview of DSB repair

DSBs can form in response to environmental stress or endogenously programmed events, such as ionizing radiation, V(D)J recombination, and stalling of DNA replication forks. In eukaryotic cells, the DSB damage response occurs swiftly and accurately to convey the damage signal to many cellular machineries that conduct DNA repair, cell cycle regulation, apoptosis, and so on. Non-homologous end-joining takes place throughout the cell cycle and is the predominant DSB repair mechanism in G₁ phase. In this pathway, the DSB lesion is recognized and bound by the Ku70–Ku80 heterodimer (associated with DNA-dependent protein kinase [DNA-PK] in mammals), and then the end-to-end ligation is accomplished by the Lig4–Lif1 complex (Lig4–XRCC4 in mammals) [3,4]. Homologous recombination functions in late S–G₂ phase, using a sister homologue as a template. In this pathway, the MRX (Mre11–Rad50–Xrs2) complex (or MRN [Mre11–Rad50–Nbs1] in higher eukaryotic cells) is the sensor for DSB and is recruited to the break to generate single-strand DNA (ssDNA) ends by resection. This is followed by formation of ssDNA–Rad51 nucleoprotein filaments, strand invasion, formation of Holliday junctions, repair DNA synthesis, branch migration, ligation of the broken ends, and resolution of the heteroduplex (Figure 1) [4]. The key signal transducers in the DSB damage response are several members from the phosphatidylinositol 3-kinase-like family of kinases,

Figure 1



A model for the functions of chromatin remodeling complexes at DNA double-strand breaks in budding yeast. Following DNA double-strand break formation, the Mre11–Rad50–Xrs2 (MRX) complex and the Ku70–Ku80 heterodimer are recruited to the DNA ends. Thereafter, Tel1 and Mec1 are recruited and phosphorylate H2A Ser 129 over a ~50 kb region. NuA4 HAT complex is also recruited to acetylate H2A and H4 histone tails. RSC is recruited to DSBs by interaction with Mre11. In the homologous recombination pathway, RSC can remodel chromatin around DSBs to promote loading of cohesin, which holds the sister chromatids together to facilitate strand invasion and Holliday junction formation during homologous recombination. INO80 is recruited by phosphorylated H2A and promotes the formation of the presynaptic filament by control the loading of Rad51 on the recipient DNA. SWR1 complex might be recruited to the DSBs, in concert with NuA4 complex, to exchange γ -H2AX with H2AZ, which might further alter the local chromatin structure and facilitate the process of DNA repair. SWI-SNF is recruited to DSBs and is required for synapsis between donor and recipient DNA by removing nucleosomes on the donor sequences. RSC is also required at a later postsynaptic step of homologous recombination repair. RSC, INO80 and probably SWR1 might also be involved in different steps of non-homologous end-joining pathway with unknown mechanisms.

including ATM (ataxia telangiectasia-mutated; Tel1 in budding yeast), ATR (ataxia telangiectasia-related; Mec1 in budding yeast), and DNA-PK. ATM and ATR are responsible for the rapid and extensive phosphorylation of histone H2AX on serine 139 (serine 129 of H2A in yeast) over a megabase domain around the DSB site. This phosphorylated H2AX (γ -H2AX) is crucial for the accurate repair of DNA lesions, because H2AX deficiency results in genomic instability and cancer predisposition [5,6].

Role of INO80 and SWR1 (TIP60) complexes in DSB repair

The yeast INO80 remodeling complex contains 15 subunits, including Ino80, actin, Arp4, Arp5, Arp8, Nhp10, Rvb1 and Rvb2 [7,8]. It has been shown that *ino80*, *arp5* and *arp8* mutants are each hypersensitive to DNA damage agents [7,9,10^{••}]. Recently published studies further demonstrated that Ino80, Arp8 and Rvbs are recruited to the homothallic switching (HO) endonuclease-induced DSB at the *MAT* locus, suggesting that the INO80 complex functions directly in DSB repair [10^{••}–12^{••}]. The INO80 complex is recruited to a 1.6 kb region around the double-strand break within 30–60 minutes after it has formed. Interestingly, both *in vitro* and *in vivo* assays revealed that γ -H2AX was necessary for the recruitment of the INO80 complex [10^{••}–12^{••}]. Although the Arp4 subunit (shared by both the INO80 and the NuA4 histone acetyltransferase [HAT] complexes) has been proposed to interact with γ -H2AX [12^{••}], Nhp10 (and/or Ies3) might play a more significant role in the recruitment of INO80 at DSB, because deletion of Nhp10, but not the lack of Arp4, results in the loss of γ -H2AX interaction with the INO80 complex *in vitro* and the loss of INO80 recruitment *in vivo* [11^{••}].

Several lines of evidence indicate that INO80 functions in both the non-homologous end-joining and the homologous recombination repair pathways. It has been shown that *arp5* Δ and *arp8* Δ mutants display hypersensitivity to DSB agents or HO-induced DSB when the homologous recombination pathway is disrupted, suggesting an important role for INO80 in the non-homologous end-joining pathway [10^{••},11^{••},13^{••}]. By contrast, INO80 has been implicated in the homologous recombination pathway in yeast as well as in plants [10^{••},14[•]]. To address the function of INO80 in homologous recombination, the Gasser group [10^{••}] monitored the formation of ssDNA at DSBs and found that both *arp8* and nonphosphorylatable H2A mutants had reduced ssDNA production, indicating that INO80 facilitates ssDNA formation, a crucial step in homologous recombination. Recently, it was shown by Tsukuda *et al.* [13^{••}] that the INO80 remodeling activity is probably required for histone eviction near DSBs, and that defects in histone loss result in a delayed recruitment of the Rad51 repair protein [13^{••}]. Taken together, these data suggest that INO80 participates in the homologous recombination

pathway by removing nucleosomes around the DSB site to facilitate ssDNA formation and subsequent repair events (Figure 1).

In addition, removal of γ -H2AX is another potential role of INO80 remodeling activity at DSB sites. It was recently suggested that in yeast these dissociated γ -H2AX–H2B dimers can be dephosphorylated by the protein phosphatase Pph3 before DNA repair is completed [15]. Notably, protein phosphatase 2A (PP2A) was identified as the enzyme that dephosphorylates chromatin-associated γ -H2AX in mammalian cells [16]. However, it remains unclear whether a PP2A-like activity exists in yeast. INO80 remodeling activity might promote exchange of γ -H2AX, which is required for recovery from G₂–M DNA damage checkpoint arrest [15]. It should be noted that INO80 has not been shown to be able to exchange histones *in vitro*, an activity which has been observed for the SWR1 complex.

The yeast SWR1 remodeling complex, another member of the INO80 subfamily, contains 14 components [8,17]. Among these SWR1 subunits, actin, Arp4, Rvb1 and Rvb2 are subunits shared with INO80, whereas actin, Arp4, Swc4 and Yaf9 are also present in the NuA4 HAT complex, which acetylates nucleosomal histones H2A and H4 [7,18]. Interestingly, Tip60 complex, the homolog of SWR1 complex in higher eukaryotic cells, appears to be a fusion of the yeast SWR1 and NuA4 complexes [18,19]. In a similar manner to the INO80 complex, several lines of evidence suggest that the SWR1 complex is also involved in DSB repair. First, *swr1* mutants display increased sensitivities to DNA damage-inducing agents (e.g. MMS, UV light and hydroxyurea) [8,20]. Second, the SWR1 complex also associates with γ -H2AX, although the amount of γ -H2AX in SWR1 is less than that in INO80 complex [11^{••}]. Third, it was demonstrated recently that purified SWR1 complex specifically binds to γ -H2AX peptides *in vitro*, and that a Rvb1-containing complex, which might be an INO80 and/or SWR1 family complex, is recruited to DSB sites *in vivo* [12^{••}].

By contrast, the HAT activity of the NuA4 and Tip60 complex has been implicated in DNA repair as well [18,21]. For example, it was found that Esa1, the HAT of the NuA4 complex, is required for repair of DSBs *in vivo* [22]. In addition, a recent study indicated that Tip60 HAT activity is responsible for rapid acetylation and activation of ATM following DNA damage [23^{••}]. Growing evidence suggests that SWR1 and NuA4 work together to regulate H2AZ deposition and DSB repair. It has been found that SWR1 specifically deposits the histone variant dimer H2AZ–H2B onto nucleosomes by replacing the pre-existing H2A–H2B dimer [8,20,24]. Furthermore, genome-wide studies revealed that both NuA4 and Gcn5 (HAT for histones H2B and H3) are required for efficient recruitment of Htz1, suggesting that

specific histone acetylation patterns are necessary for proper H2AZ deposition [20]. Bdf1, the shared component of the SWR1 and TFIID complexes bearing two bromodomains, might mediate recruitment of SWR1 to chromatin, because it selectively binds acetylated forms of histone H4 and is required for efficient H2AZ deposition [25–27]. Recently, several groups found that the deposited H2AZ is acetylated by the NuA4 complex and that the acetylated H2AZ plays an important role in blocking the spread of heterochromatin into euchromatin [28–30]. Interestingly, a report by Kusch *et al.* [31**] demonstrated that *Drosophila* Tip60 complex is required for acetylation of phospho-H2Av (the equivalent of γ -H2AX) at DNA lesions and subsequent replacement with unmodified H2Av (the equivalent of H2AZ). Taken together, the emerging data suggest that the SWR1 complex is recruited to DSBs, in concert with the NuA4 complex, to exchange γ -H2AX with H2AZ, which might further alter the local chromatin structure and facilitate the process of DNA repair. The acetylation of H2AZ and/or ATM by NuA4–TIP60 might serve as important regulatory steps during these histone exchanges (Figure 1).

Interestingly, a recent study by the Peterson group [32**] linked INO80 and SWR1 together with cell cycle checkpoint adaptation in response to DSB. It was shown that Ino80 is required for escape from an extended cell cycle checkpoint arrest, and that the absence of a functional Ino80 — the first 900 base pairs of the *ino80* open reading frame was deleted — leads to decreased levels of γ -H2AX and increased incorporation of H2AZ adjacent to a DSB. Moreover, the *ino80;swr1* double mutant studies showed that inactivation of Swr1 eliminates H2AZ and restores γ -H2AX in chromatin surrounding a DSB, and alleviates the checkpoint adaptation defect of the *ino80* Δ strain. These results suggest that INO80 and SWR1 function antagonistically in regulating H2AZ and γ -H2AX dynamics around DSBs during cell cycle checkpoint adaptation [32**]. The mechanisms of such regulation remain to be studied.

Role of SWI–SNF and RSC complexes in DSB repair

The SWI–SNF and RSC complexes belong to the SWI2 subfamily of chromatin remodelers in budding yeast. It has been well established that the SWI–SNF complex plays important roles in transcriptional regulation [33], whereas the essential RSC complex has been linked to a variety of cellular activities, such as gene expression regulation, cell wall integrity pathway and cohesion of sister chromatid arms [34,35,36*]. Recent progress suggests that both of these chromatin remodelers also participate in DSB repair directly.

One report shows that both RSC and SWI–SNF play important roles in DSB repair, specifically in the

homologous recombination pathway [37**]. It was found that *rsc* and *swi–snf* single mutants are hypersensitive to genotoxic agents and are unable to repair DSBs by homologous recombination [37**]. Second, they revealed that both RSC and SWI–SNF are recruited to a DSB site *in vivo*, but with distinct kinetics. Their results further suggest that SW–SNF is required at or just preceding strand invasion, whereas RSC can participate in both the early step and the postsynaptic step of homologous recombination [37**]. Furthermore, both RSC and SWI–SNF were recruited to the homologous donor sequence within a time-frame preceding the appearance of the primer extension product, suggesting that nucleosomes on the donor sequence are cleared by these remodelers to expose DNA sequence to the homology-searching complex (Figure 1) [37**].

In S phase, newly replicated sister chromatids are held together by the cohesin complex. Interestingly, emerging evidence indicates that cohesin is recruited to DSBs [38,39]. It has been proposed that cohesin holds sister chromatids together at DSBs to enable strand invasion and Holliday junction formation during homologous recombination. Notably, a study by Huang *et al.* [36*] demonstrated that RSC associates specifically with chromosome arm cohesin-binding sites in a cell cycle-regulated manner and interacts physically and genetically with components of cohesin. Moreover, they found that mutant RSC specifically blocks the recruitment of cohesin to chromosomal arms [36*]. Consistently, another study also determined that RSC is required for the establishment of sister chromatid cohesion [40]. Thus, one of RSC's functions in DSB repair might be remodeling chromatin around DSBs to promote loading of cohesin, which further holds the sister chromatids together during homologous recombination (Figure 1). Interestingly, a genetic screen has also linked RSC to the non-homologous end-joining pathway of DSB [41*]. It was further revealed that RSC is rapidly recruited to an *in vivo* DSB site and physically interacts with the core non-homologous end-joining protein Ku80 [41*] (see also Update). However, it remains unclear how RSC regulates non-homologous end-joining.

Recently, a study by Park *et al.* [42**] linked mammalian SWI–SNF to DSB repair and γ -H2AX induction. It was shown that inactivation of SWI–SNF results in a large defect in γ -H2AX formation and inefficient DSB repair, and this is not due to misregulation of DSB repair genes, DNA damage checkpoints, or ATM expression and/or activation. Furthermore, they found that SWI–SNF is recruited rapidly to chromatin around DSB through interaction with γ -H2AX. These results suggest that SWI–SNF reconfigures chromatin around DSB sites and promotes H2AX phosphorylation to facilitate DNA repair (Figure 1) [42**]. This study highlights that the SWI–SNF subfamily of remodelers are widely involved in DSB repair from yeast to higher organisms.

Conclusions

In eukaryotic cells, DNA DSB damage response consists of a series of fast and complex cellular events, including DSB repair and cell cycle arrest. It is becoming clear that the evolutionally conserved SWI2 and INO80 subfamilies of ATP-dependent chromatin remodeling complexes are new players in DSB damage response and that they play important roles in distinct steps and/or different types of DSB repair pathways through multiple mechanisms. Given the well-established roles of chromatin remodelers in other nuclear processes, such as transcription, an important question that needs to be addressed is how the remodeling complexes are regulated and directed to different nuclear processes. Additionally, it remains to be examined whether and how other remodelers, such as the ISWI and Mi-2 subfamilies of remodeling factors, function in DSB repair. It is also important to test if remodelers also take part in other types of DNA damage response, such as UV damage repair. For example, SWI-SNF has recently been linked to the nucleotide excision repair pathway by both *in vitro* and *in vivo* studies [43,44]. Despite the emerging picture, many details of how chromatin remodelers integrate within the DSB repair pathways are unknown. Systematic studies using models such as the HO-induced DSB in yeast will probably provide insights to these questions. Unrepaired or improperly repaired DSBs can contribute to cancer development in higher organisms. Understanding how chromatin remodeling complexes function in DSB repair should provide new insights into the mechanisms of carcinogenesis and might lead to new targets for cancer treatment.

Update

Recent work showed that chromatin remodeling and loading of Mre11 and YKu protein at the HO endonuclease-induced DSB is reduced significantly when Sth1 (the ATPase of RSC) or Rsc2 is depleted from budding yeast, suggesting that RSC remodels nucleosomes at the DSB site to facilitate loading of repair machinery [45**].

Acknowledgements

YB is supported by the Odyssey Program and the H-E-B Award for Scientific Achievement at The University of Texas, MD Anderson Cancer Center; XS is supported by the National Cancer Institute and the American Cancer Society. We apologize to colleagues whose relevant studies were not cited, owing to space limitation.

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