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Chromatin remodelling beyond transcription: the INO80 and SWR1 complexes

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Abstract

Chromatin-modifying factors have essential roles in DNA processing pathways that dictate cellular functions. The ability of chromatin modifiers, including the INO80 and SWR1 chromatin-remodelling complexes, to regulate transcriptional processes is well established. However, recent studies reveal that the INO80 and SWR1 complexes have crucial functions in many other essential processes, including DNA repair, checkpoint regulation, DNA replication, telomere maintenance and chromosome segregation. During these diverse nuclear processes, the INO80 and SWR1 complexes function cooperatively with their histone substrates, γ -H2AX and H2AZ. This research reveals that INO80 and SWR1 ATP-dependent chromatin remodelling is an integral component of pathways that maintain genomic integrity.

The structure of chromatin is inherently stable. Therefore, to allow DNA processing and metabolism, chromatin-modifying factors are needed to create a dynamic chromatin environment that facilitates these activities. The modification of chromatin can occur through several mechanisms, including histone post-translational modification by histone-modifying enzymes as well as variation of nucleosome composition and positioning by ATP-dependent chromatin-remodelling complexes.

The ATPase subunits of chromatin-remodelling complexes belong to the SWI/SNF family¹, which is part of a large superfamily of helicases and translocases called superfamily 2 (SF2). The SWI/SNF family is named after the first identified chromatin-remodelling complex^{2,3}. Members of the SWI/SNF chromatin-remodelling family include the SWI/SNF, ISWI, CHD and INO80 subfamilies in *Saccharomyces cerevisiae* and have similarities in their DEAD/H

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DATABASES

BioGRID — Repository for Interaction Datasets: www.thebiogrid.org INO80 | SWR1 | SRCAP

Entrez Gene: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene><http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene> *PHO5* | *PHO84*

Human Protein Reference Database: www.hprd.org BAF53A | RUVBL1 | RUVBL2 | SRCAP | UCH37 | YY1

Saccharomyces Genome Database: www.yeastgenome.org Arp4 | Arp6 | *aRP8* / Ctf18 | Ies3 | Ies4 | *INO80* / Ku70 | Mec1 | Nhp10 | Rvb1 | Rvb2 | Swc2 | Swc6 | Swr1 | Tel1 | *TOF1*

UniProtKB: <http://www.uniprot.org> ATM | ATR | Htz1 | Ku80 | Pleiohomeotic | Pontin | Reptin | RuvB
FUrthEr inFormation

Xueting Shen's homepage: http://gsbs.uth.tmc.edu/tutorial/shen_x.html

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box-containing ATPase subunits. However, they also have divergent characteristics that further distinguish them into different subfamilies. The INO80 subfamily is the most recent addition to the SWI/SNF family of chromatin remodellers, and ATPase orthologues and homologues of Ino80 have been identified in yeast⁴⁻⁷, flies^{8,9}, plants^{10,11} and mammals¹²⁻¹⁴ (TABLE 1). The chromatin-remodelling complexes of the INO80 subfamily are: **INO80** and **SWR1** in *S. cerevisiae*; INO80, Snf2-related CBP activator protein (**SRCAP**) and p400 in mammals; and INO80 and p400 in *Drosophila melanogaster*. The INO80 subfamily seems to be the most evolutionarily conserved of all of the chromatin -remodelling subfamilies owing to the high degree of homology in the ATPase subunit (both in the ATPase domain and the surrounding sequences), the presence of a large number of orthologous sub-units in many organisms and the relatively conserved composition of individual complexes.

Like most chromatin-remodelling complexes, INO80 subfamily complexes have been identified as transcriptional regulators. The ability of the *S. cerevisiae* **INO80** gene product to regulate inositol-responsive gene expression was the reason for its initial discovery¹⁵. Since their characterization, INO80 subfamily complexes have been found to directly regulate the expression of genes in yeast^{4-7,16}, mammals^{17,18}, flies⁹ and plants^{10,11}. The effect of the INO80 complex on transcription is undoubtedly linked to the function of the transcription factors yin yang 1 (**YY1**; in mammals)¹⁷ and **Pleiohomeotic** (in *D. melanogaster*)⁹, which are found in INO80 complexes (TABLE 1). These trans-cription factors, which are involved in cell proliferation, differentiation and embryonic development, can serve to specify the genes that are targeted for INO80-mediated chromatin remodelling. Unlike genes that are regulated by the INO80 complex, SWR1-regulated genes in *S. cerevisiae* are enriched near telomeres, suggesting that the chromatin-remodelling activity of the SWR1 complex might be needed to regulate transcription in particularly heterochromatic chromosomal regions^{5,6}. In addition, the chromatin-remodelling activity of homologous SWR1 and SRCAP complexes results in increased expression of genes in plants and mammals^{10,18}.

The purified *S. cerevisiae* INO80 and SWR1 complexes contain 15 and 14 subunits (TABLE 1), respectively, and are approximately 1.2–1.5 MDa each in mass⁴⁻⁶. A distinguishing characteristic of the INO80 subfamily, including the INO80 and SWR1 complexes, is the presence of RuvB-like helicases in the complexes^{4,5,14}. The RuvB helicase is a DNA repair factor in bacteria^{19,20}, and thus the presence of RuvB-like subunits in the complexes suggests a role for the INO80 subfamily in DNA damage responses. Indeed, recent research shows that DNA damage responses are impaired when components of the INO80 subfamily are mutated in yeast²¹⁻²³, plants¹¹, flies⁸ and mammals^{14,24}. These findings changed the perception of chromatin-remodelling complexes, which were typically considered to be transcriptional regulators, and initiated pioneering research that has revealed multiple roles for chromatin-remodelling complexes in additional genome stability pathways, including cell cycle checkpoint activation, DNA replication, telomere regulation, centromere stability and chromosome segregation.

The activity of homologous INO80 and SWR1 complexes in these diverse nuclear processes is a composite of the function of several subunits in these complexes. essential subunits that form the catalytic core include the ATPase (INO80, Swr1 and SRCAP), RuvB-like proteins and the actin-related protein (Arp) subunits (TABLE 1). Other subunits have regulatory

functions that are specific to particular processes, such as the yeast INO80 complex components non-histone protein 10 (Nhp10; an HMG-like protein) in DNA repair²², INO80 subunit 4 (Ies4) in the DNA damage checkpoint response²⁵ and Ies3 in telomere regulation²⁶ (TABLE 1). One function of the regulatory subunits is to facilitate the association of unique chromatin substrates with the INO80, SWR1 and SRCAP complexes. Interestingly, complexes of the INO80 subfamily have a prominent and distinct affinity for the histone variants γ -H2AX and H2AZ. (Phosphorylated H2AX is often referred to as γ -H2AX and will be used in this article for consistent nomenclature.) γ -H2AX and H2AZ are not found in canonical nucleosomes and function to direct the activities of the INO80 subfamily in specific processes, such as DNA repair and DNA damage checkpoint responses^{5,8,21–23}.

In this Review, we discuss the roles of homologous INO80 and SWR1 chromatin-remodelling complexes beyond transcription, and elaborate on their roles in pathways that maintain genomic stability, such as DNA repair, cell cycle checkpoint regulation, DNA replication, chromosome segregation and telomere maintenance. Moreover, using the INO80 and SWR1 complexes as examples, we aim to show that the major pathways of chromatin modification, such as chromatin remodelling, histone post-translational modification and histone variant deposition are connected. Furthermore, INO80 and SWR1 also exemplify the distinct mechanisms that regulate chromatin-remodelling complexes. Other chromatin-remodelling complexes, including the INO80 subfamily member and SRCAP paralogue p400 (of the TIP60, or p400, complex), are not mentioned. However, we discuss the regulatory mechanisms that direct the activities of these complexes in such varied nuclear processes, such as the functional relationship between histone substrates and the INO80, SWR1 and SRCAP complexes.

Unique components of the INO80 subfamily

The ATPase subunits of the INO80 subfamily are distinguished from other ATPases in the ISWI, SWI/SNF and CHD subfamilies owing to the presence of a spacer region that splits the conserved ATPase domain (FIG. 1a,b). Deletion of this spacer region in *S. cerevisiae* Swr1 ATPase results in loss of the association of several subunits from the SWR1 complex, including the RuvB-like Rvb1 and Rvb2 subunits²⁷. Rvb1 and Rvb2 are also present in the *S. cerevisiae* INO80 complex⁴ and are homologous to human RUVBL1 and RUVBL2 and *D. melanogaster* Reptin and Pontin, which are also present in other INO80 subfamily complexes (TABLE 1).

The RuvB-like proteins found in homologous INO80 and SWR1 complexes are essential for viability in eukaryotes^{28,29} and are functionally related to the bacterial RuvB helicase, which forms a double hexamer and mediates Holliday junction migration during homologous recombination in double-strand break (DSB) repair³⁰. Interestingly, these RuvB-like proteins are each found at a 1:6 stoichiometry in the INO80 subfamily complexes^{4,5}, which is reminiscent of the bacterial RuvB hexameric ring surrounding a Holliday junction, and is suggestive of a role for the INO80 subfamily in DSB repair.

Remodelling mechanisms and substrates

Homologous INO80 and SWR1 complexes have distinctive features that are indicative of specialized chromatin-remodelling activities. In this section, we discuss the activities of homologous INO80 and SWR1 complexes, with emphasis on their chromatin substrates. Notably, these complexes associate with histone variants (BOX 1) and this association is evolutionarily conserved and distinct from other chromatin-remodelling subfamilies. These unique chromatin substrates have important roles in specifying the chromatin-remodelling activities of homologous INO80 and SWR1 complexes.

Chromatin-remodelling mechanisms of the INO80 complex.

Most of the chromatin-remodelling complexes in the SWI/SNF family have helicase domains in their respective ATPase subunits but do not exhibit helicase activity. However, the *S. cerevisiae* INO80 complex is unique because it does exhibit *in vitro* ATP-dependent DNA helicase activity⁴. The mammalian INO80 complex preferentially binds two specialized DNA structures *in vitro* — a four-way junction that mimics a Holliday junction and a three-way junction that resembles a replication fork²⁴.

The *in vitro* ATPase activity of INO80 is stimulated not only by DNA but also by nucleosomes^{4,31}. Furthermore, chromatin-remodelling assays show that the INO80 complex repositions (or slides) nucleosomes *in vitro* on a reconstituted chromatin template^{4,31,32} (FIG. 1c). *In vivo*, INO80 influences nucleosome eviction^{33,34}, a rather dramatic chromatin-remodelling event in which the nucleosomes are completely removed from the DNA, thereby leaving the DNA accessible to participate in nuclear functions without the presence of histones. INO80-mediated nucleosome sliding might precede the resulting nucleosome eviction that is observed *in vivo*, thereby linking these two mechanisms in the same process. However, if distinct, these activities might functionally facilitate different DNA processing events. For instance, nucleosome sliding can reposition the nucleosome to expose or mask a specific DNA sequence to regulate its recognition to a DNA-binding factor, such as a transcription factor. Alternatively, histone eviction might be necessary when the presence of nucleosomes severely impedes the DNA processing event, such as DNA repair and replication.

The chromatin-remodelling activity of the *S. cerevisiae* INO80 and SWR1 complexes is dependent on the function of actin and Arps^{27,31,35,36} (TABLE 1). Studies in *S. cerevisiae* show that the evolutionarily conserved helicase-SANT-associated domain (HSA domain) in the ATPase subunits of the INO80 subfamily complexes are required for the binding of Arps and actin components to the complex³⁶. Mutants of Arps in *S. cerevisiae* diminish the chromatin-remodelling activity of the INO80 complex, as these factors mediate interactions between the nucleosome and chromatin-remodelling complexes^{21,31,37}. Therefore, Arps and actin provide a conserved functional module that links the chromatin-remodelling enzyme and its substrate (FIG. 1b,c).

Chromatin-remodelling mechanisms of the SWR1 complex.

The *S. cerevisiae* SWR1 complex co-purifies with the histone variant Htz1 (H2AZ in mammals)⁵ (BOX 1). Histone variants are often incorporated into nucleosomes at site-specific locations to accommodate cellular functions, such as transcription and replication, that require particular chromatin templates. The SWR1 and SRCAP complexes facilitate ATP-dependent histone replacement of canonical H2A with the H2AZ variant in the nucleosome^{5,6,10,12}. H2AZ has essential functions in a range of cellular processes, such as transcriptional regulation⁵, heterochromatin establishment^{38,39}, chromosome segregation^{40,41}, cell cycle progression⁴² and DNA damage responses^{34,43}. A clue to the function of H2AZ in these diverse processes might be found in the structural analyses of this histone variant. Analyses of chromatin fibres *in vitro* suggest that H2AZ promotes different conformational states of the nucleosome that might facilitate varied chromatin functions⁴⁴. Specifically, the crystal structure of H2AZ-containing nucleosomes suggests that the nucleosome is destabilized by a region that includes the carboxyl-terminal α -helix of H2AZ, which contains a high degree of sequence divergence from H2A⁴⁵ (BOX 1). Loss of this H2AZ C-terminal region results in poor survival in yeast²⁷ and impaired development in *D. melanogaster*⁴⁶. Importantly, this region of H2AZ is also essential for recognition by the SWR1 chromatin-remodelling complex for histone exchange²⁷.

This H2AZ histone exchange mechanism is a multistep process that uses the function of the SWR1 complex 2 (Swc2), Swc6 and Arp6 subunits of the complex. These are responsible for binding to the histone variant, associating with the nucleosome and facilitating histone exchange²⁷. In particular, the conserved Swc2 subunit that binds the histone variant contains clusters of acidic residues, a feature that is reminiscent of other histone chaperones²⁷ (FIG. 1c). This H2AZ histone exchange process is specific to the SWR1 and SRCAP complexes and requires unique subunits that are found only in these homologous complexes. However, there are some similarities between the *S. cerevisiae* SWR1 and INO80 complexes in that the *in vitro* remodelling activity of both complexes is dependent on their Arps and actin subunits^{27,31,36} (FIG. 1b,c). Therefore, both common and distinct mechanisms of chromatin remodelling exist among the different members of the INO80 subfamily.

Regulation of the INO80 complex

The function of the chromatin-remodelling complexes can be modulated by multiple mechanisms in response to cell stimuli and signalling pathways. One mechanism for regulating the function of the INO80 complex is the posttranslational modification of specific subunits of the complex. For instance, in response to activation of DNA damage response pathways, the Ies4 subunit of the *S. cerevisiae* INO80 complex is phosphorylated by the ataxia-telangiectasia (A-T) mutated (ATM) and A-T and RAD3-related (ATR) kinases *in vivo* and *in vitro*²⁵. The ATM and ATR kinases (Tel1 and Mec1 in yeast) are essential regulators of the DNA damage responses⁴⁷, as mutations in these genes in humans result in disorders that are characterized by DNA damage sensitivity and cancer predisposition^{48,49}. Phosphorylation of Ies4 modulates the cellular response to DNA-damaging agents but does not alter the composition of the complex or its ability to localize to sites of DNA damage. Although not formally proven, the chromatin-remodelling activity of the INO80 complex at

sites of DNA damage might be modified by Ies4 phosphorylation. Indeed, a similar scenario has been identified for the chromatin-remodelling activities of SWI/SNF in humans, which are inactivated in a cell cycle-dependent manner following phosphorylation⁵⁰.

The activities of the INO80 complex are also regulated by the inositol signalling pathway. Inositol lipids and inositol polyphosphates modulate the activities of chromatin-remodelling complexes of the INO80, ISWI and SWI/SNF subfamilies^{51–53}. Inositol signalling is initiated by a range of external stimuli, such as growth factors and hormones, and regulates a number of crucial cellular functions, including cell growth, apoptosis and differentiation⁵⁴. By an unknown mechanism, the inositol polyphosphate kinase Arg82 (also known as Ipk2) promotes the *in vivo* association of the *S. cerevisiae* INO80 complex to the promoters of the phosphate responsive genes PHO5 and PHO84 (REF. 52). Decreased binding of the INO80 complex to these promoters in *arg82* mutant cells results in reduced chromatin remodelling and reduced expression of these genes. Furthermore, inositol hexakisphosphate (InsP6) inhibits the ATP-dependent nucleosome sliding activity of the *S. cerevisiae* INO80 complex *in vitro*⁵¹. Thus, small signalling molecules can modulate the activity of the INO80 complex.

Remodelling beyond transcription

Many of the chromatin-remodelling mechanisms that facilitate the roles of the INO80, SWR1 and SRCAP complexes beyond transcription are unknown. However, the functional relationship between the complexes and their chromatin substrates, such as γ -H2AX and H2AZ histone variants, is emerging in some cases. As previously mentioned, the INO80 subfamily prominently and specifically associates with γ -H2AX and H2AZ, which have important roles in specifying the functions of homologous INO80 and SWR1 complexes in processes that maintain genome stability.

γ -H2AX is a substrate of INO80 and SWR1.

The histone variant H2AX is phosphorylated on its C terminus by ATM and ATR (or Tel1 and Mec1) in chromatin regions that surround damaged DNA^{55,56} (BOX 1). γ -H2AX is also a crucial component of DNA damage responses, as defects in the regulation of H2AX phosphorylation lead to alterations in the DNA damage checkpoint, genomic instability and cancer predisposition in mice^{57–60}. γ -H2AX participates in the maintenance of genome integrity by serving as docking sites for several DNA damage response proteins^{61–64}, such as the INO80 and SWR1 complexes, thereby focusing the activity of these factors to regions that are proximal to the damage site.

Two *S. cerevisiae* INO80 subfamily components, Nhp10 and Arp4, have been implicated in conferring an association of the complex with γ -H2AX. Deletion of the Nhp10 subunit greatly reduces the association of the INO80 subunit Ies3 and γ -H2AX with the complex, and eliminates recruitment of the *S. cerevisiae* INO80 complex to DSBs²². Nhp10 and Ies3 are unique to the INO80 complex, demonstrating that this chromatin-remodelling complex has specialized components that facilitate its activity in DNA damage response pathways through association with γ -H2AX. Additionally, Arp4 (BRG1-associated factor 53a (BAF53A) in mammals), a subunit of the INO80, SWR1 and SRCAP complexes, binds to γ -

H2AX *in vitro* and its deletion reduces recruitment of Rvb- containing complexes, such as INO80 and SWR1, to DSBs in yeast²¹.

INO80 and SWR1 assist DSB repair.

DSBs caused by genotoxic stress are particularly dangerous lesions that can result in mutations owing to error-prone repair or cell death if left unrepaired. The major pathways of DSB repair include homologous recombination (HR) and non-homologous end joining (NHEJ)⁶⁵. The Mre11–Rad50– Xrs2 (MRX) complex, which contains exonuclease activity, collaborates with other factors to promote the production of single-stranded DNA, a process known as resection⁶⁶. Repair and checkpoint factors, such as the Mec1 kinase, then localize to break sites. During HR, *RAD52* epistasis group proteins (Rad50, Rad51, Rad52, Rad54 and Rad55) promote homology search, strand invasion and synapsis between the invading recipient strand and donor DNA, leading to the formation of Holliday junctions. DNA repair is complete once DNA synthesis has finished and Holliday junctions have been resolved. Alternatively, during NHEJ, the Ku70–Ku80 complex facilitates tethering and ligation of the broken DNA ends.

As previously mentioned, *S. cerevisiae* INO80 and SWR1 complexes bind directly to sites of DNA DSBs through their association with γ -H2AX^{22,23,34}. In particular, these complexes are required for the proper processing of the DNA ends that are involved in the DSB (FIG. 2). Specifically, the *S. cerevisiae* INO80 complex influences the proximal eviction of nucleosomes surrounding DSBs, including nucleosomes that contain γ -H2AX and H2AZ. Deletion of ARP8, which reduces the *in vitro* chromatin-remodelling activity of the INO80 complex³¹, or deletion of NHP10, which decreases the recruitment of the INO80 complex to DSB²², result in defective nucleosome eviction in regions proximal to the DSB^{33,34,67} and in chromatin of the homologous donor locus⁶⁷.

Impaired nucleosome eviction seems to alter the subsequent steps that facilitate the DNA damage response owing to the reduced association of repair and checkpoint factors with the site of the DSB. Thus, this suggests that the presence of nucleosomes at repair sites impedes the association of proteins that facilitate these processes. For example, mutants of the INO80 complex in *S. cerevisiae* have defects in the association of the Mre11 nuclease with DSBs, and defects in the Mre11 -mediated promotion of single-stranded DNA, which is a prerequisite for repair through HR^{23,25,34}. The finding that the INO80 complex directly influences single-stranded DNA resection is controversial — a separate study did not observe this defect in single-stranded DNA production³³. Moreover, another study has questioned whether nucleosome eviction is a determinant or a consequence of single-stranded DNA production because these two events are tightly linked and are difficult to separate experimentally⁶⁸. Nevertheless, a downstream event of DNA resection, namely the invasion of the single-stranded DNA into the homologous donor locus, is impaired in an *arp8* mutant⁶⁷. The association of other DNA damage response factors, such as Mec1 and Rad51, is also decreased in this *arp8* mutant^{33,34,67}.

Conversely, the yeast SWR1 complex does not affect nucleosome eviction at DSBs³⁴. However, deletion of its chromatin substrate *HTZ1*, which is transiently enriched at DSB sites, results in decreased production of single stranded DNA and reduced association of

Rad51 to DSB proximal regions⁶⁹. The SWR1 complex is also needed for efficient recruitment of Mec1 and Ku80 to DSBs, which are required for NHEJ34 (FIG. 2). In addition, deletion of HTZ1 results in the inability of a persistent DSB to local-ize to the nuclear periphery⁶⁹, a rather enigmatic event that promotes DNA repair⁷⁰.

Defects in the chromatin-remodelling activity of the INO80 subfamily complexes ultimately result in deficient DNA repair. For instance, mutants of the Arp subunits in the *S. cerevisiae* INO80 complex have defects in NHEJ^{23,34} as well as the HR pathway⁷¹. In arp8 mutants, when HR repair does occur, gene conversion often consists of large and discontinuous DNA tracts that might result from unstable heteroduplex DNA that forms during strand invasion and branch migration⁶⁷. Indeed, mutants of the INO80 complex in plants and mammals also display defects in DSB repair^{11,24}, suggesting conserved mechanisms for the INO80 complex in this pathway. By contrast, the *S. cerevisiae* Swr1 ATPase subunit does not seem to function in HR, but rather participates in the error-free NHEJ pathway^{34,71}. These results show that different complexes in the INO80 sub-family can contribute to distinct repair mechanisms, in part owing to the function of specialized subunits in each complex.

INO80 and SWR1 influence checkpoint pathways.

Checkpoint pathways function cooperatively with DNA repair pathways by altering cell cycle kinetics, which allows for repair of damaged DNA and re-entry into the cell cycle^{72,73}. For example, the production of singlestranded DNA during DNA repair is required for the recruitment and activation of the checkpoint Mec1 kinase^{74–76}. Mec1 then activates downstream effector kinases that target proteins to arrest the cell cycle⁷⁷. Additional checkpoint proteins, such as *S. cerevisiae* Rad9 (53BP1 in mammals), bind to dam-age sites in a γ -H2AX-dependent manner and also assist in the activation of downstream checkpoint signalling components^{56,61,62,78}.

The Ies4 subunit of the INO80 complex is phosphorylated by the Tel1 and Mec1 kinases to modulate DNA replication checkpoint responses without altering DSB repair processes²⁵. Activation of the S phasecheckpoint delays replication origin firing, and cells that carry mutations that mimic phosphorylated Ies4 display inappropriately elevated S phase checkpoint activation. This results in decreased viability when exposed to DNA-damaging agents. In cells that have mutations that prevent Ies4 phosphorylation, deletion of the *TOF1* checkpoint factor (which mediates the DNA damage checkpoint response during exposure to replication stress^{79,80}) causes dramatic defects in the ability to resume the progression of the cell cycle when the replication stress is removed. These results show redundant or compensating roles between Tof1 and phosphorylated Ies4 as components of the cell cycle checkpoint pathway. Thus, the INO80 complex is capable of many distinct activities in DNA damage response pathways, such as the repair of DSBs and the regulation of the replication checkpoint, in part by using specific subunits, such as Nhp10 and Ies4 (FIG. 3).

Although the precise mechanisms of INO80 subfamily-mediated checkpoint regulation are unknown, evidence suggests that the roles of INO80 and SWR1 complexes in checkpoint pathways are directly linked to the function of the H2AZ and H2AX histone variants.

Both INO80 and SWR1 complexes in *S. cerevisiae* regulate the abundance of H2A variants in chromatin following exposure to DNA-damaging agents⁴³, and this influences checkpoint adaptation — a particularly rare occurrence in which the cell survives despite the presence of a persistently unrepaired DSB⁴³. Moreover, a recent report shows that deletion of *SWR1* or the *HTZI* histone variant in *S. cerevisiae* results in delayed checkpoint activation in response to a single persistent DSB⁶⁹.

Chromatin-remodelling activities that alter the levels of γ -H2AX might indirectly regulate the abundance of DNA damage proteins that bind to γ -H2AX and activate cell cycle checkpoints at sites of DNA damage, as well as the subsequent dissociation of these proteins to facilitate checkpoint recovery. Alternatively, the chromatin-remodelling activity of the INO80 subfamily complexes might produce DNA substrates that activate checkpoint factors. Indeed, mutants of the INO80 subfamily in *S. cerevisiae* that have reduced single-stranded DNA also have decreased recruitment of the checkpoint factor Mec1 to DSBs along with delayed checkpoint activation³⁴.

The INO80 complex participates in DNA replication.

Chromatin modulation is a crucial step in DNA replication processes, particularly when challenged with replicative stress that impedes the progression of the replication fork⁸¹. Local chromatin structure influences the function of the replication origin^{82,83} as well as DNA damage responses during replication stress^{68,84}. Stalled replication forks arise when the replication machinery encounters a DNA lesion or when nucleotide levels are low. If the damage is left unrepaired, or if nucleotide levels are not restored, disassembly of the replication machinery might occur at the same time as replication fork collapse, and this can result in DNA breaks⁷². The S phase DNA damage response attempts to resolve the DNA lesion by activating cell cycle checkpoint arrest and assembling repair proteins at the DNA lesion.

Checkpoint alterations occur in mutants of the yeast INO80 complex in response to replication stress, such as low dNTP levels and DNA crosslinks caused by genotoxic agents^{16,25,43}. As previously described, phosphorylated Ies4 specifically influences S phase checkpoint responses²⁵. Furthermore, global genetic screens in *S. cerevisiae* implicate both INO80 and SWR1 complexes in the maintenance of DNA integrity, including replicative damage response pathways^{85,86}.

Recent reports show that the *S. cerevisiae* INO80 complex is enriched at replication origins^{16,87–89}. This enrichment is further increased at stalled replication forks that are under replicative stress, a pattern that is similar for other S phase DNA damage response factors at these sites^{16,87,88,90}. Specifically, the INO80 complex is needed for sustained replication and survival of yeast cells that are transiently exposed to agents that cause stalling of the replication fork^{16,87,88}. Mutation of the *INO80* ATPase results in replisome integrity defects, as components of the replication machinery dissociate from the stalled replication fork⁸⁷. This defect in recovery of DNA replication after replication stress is also accompanied by an increase and persistent accumulation of checkpoint and repair protein foci, which is indicative of elevated DNA damage levels¹⁶. As a result, mutants of the INO80 complex, such as *ies4*, *arp8*, *arp5* and *ino80* mutants, have defects in checkpoint recovery and

decreased viability in the presence of replication stress^{16,25,87} (FIG. 4). SWR1 is not enriched at replication origins¹⁶ and *swr1* mutants do not have decreased viability when exposed to replication stress⁵. Therefore, the role of the SWR1 complex in DNA replication is distinct from that of the *S. cerevisiae* INO80 complex.

Research on the roles of the INO80 and SWR1 complexes in DNA replication is in its infancy, and recent studies present conflicting information on the role of the INO80 complex during DNA replication^{16,87}. The precise mechanisms and pathways through which these complexes influence DNA replication are unknown. Moreover, additional research is needed to determine if the function of the INO80 subfamily is dependent on an interaction with its H2A histone variant substrates. It should be noted that mutants of γ -H2AX and H2AZ in yeast display decreased viability when exposed to genotoxic agents that impede replication^{5,21}, and deletion of *HTZ1* in *S. cerevisiae* results in slower kinetics of S phase progression compared with wild type⁴². Furthermore, replication processes are dramatically impaired when the Nhp10 subunit of INO80 complex, which confers an association of the complex with γ -H2AX²², and the ATPase of the ISW2 chromatin-remodelling complex are both mutated in *S. cerevisiae*⁸⁸. These results suggest that multiple chromatin-remodelling complexes from different subfamilies, as well as histone variants, cooperatively facilitate chromatin modulation during DNA replication. Alternatively, it might be possible that a particular DNA structure stimulates the activity of the INO80 complex (for example, a three-way junction that mimics a stalled replication fork and has been shown to associate with the INO80 complex²⁴).

The INO80 complex is needed for telomere regulation.

Telomeres are chromosomal loci at the ends of chromosomes that contain repetitive DNA sequences, as well as specialized protein and DNA structures that stabilize the chromosome and avoid recognition by the DNA repair machinery of the chromosome end as a DNA DSB⁹¹. The telomerase enzyme adds repetitive DNA sequences on to the ends of chromosomes, and these are progressively lost during each DNA replication cycle as a result of the incomplete replication of linear chromosomes.

Genetic screens implicate both INO80 and SWR1 complexes in the process of telomere length regulation^{26,86}. Subunits of the *S. cerevisiae* INO80 and SWR1 complexes, including Ino80, Arp4, Nhp10 and Ies3, associate with yeast telomeric regions^{26,92}. Specifically, the Ies3 subunit of the INO80 complex interacts with the telomerase complex²⁶. Subunits of the INO80 complex, including Ies3, Arp8 and Nhp10, regulate telomere length in cells that contain active telomerase. Inactivation of telomerase and deletion of Ies3 results in delayed growth of surviving cells, as well as severely impaired genomic stability in these survivors, such as the fusion of telomere ends between two chromosomes²⁶. These results show that specific subunits of the INO80 subfamily are specialized in regulating telomere structure and function.

The DNA damage response is intricately involved in telomere regulation, as both repair and cell cycle checkpoint factors associate with telomere ends to facilitate DNA end processing as well as telomere protection mechanisms⁹¹. For instance, the ATM and ATR kinases (and Tel1 and Mec1) and γ -H2AX are present on telomeres of normal length^{93–95}. The presence

of these kinases on telomeres influences the recruitment of the telomerase and presumably regulates telomere length during normal replication^{94,96}. ATM and ATR kinases and γ -H2AX become further enriched at crucially shortening telomeres in an attempt to repair the telomere end that resembles a DSB⁹⁷. As previously discussed, the subunits of the INO80 subfamily that mediate the interaction between the chromatin-remodelling complexes and γ -H2AX to localize to DSBs in *S. cerevisiae* — Arp4 of both INO80 and SWR1 complexes and Nhp10 of the INO80 complex — are enriched at telomeres^{26,92}. Furthermore, deletion of *S. cerevisiae NHP10* results in altered lengthening of telomeres²⁶. In *D. melanogaster*, loss of the histone variant H2Av, which is homologous to both H2AX and H2AZ in other organisms (BOX 1), results in telomere fusions and decreased association of telomere capping proteins that prevent the recognition of a telomere end as a DSB⁹⁸. These observations raise the interesting possibility that the INO80 subfamily might use a common mechanism of associating with modified histone variants, such as γ -H2AX and H2AZ, to accumulate at both DSBs and telomeres. As such, the INO80 subfamily might function at telomeres in a manner similar to that of DSBs, such as the regulation of DNA repair and recombination. Alternatively, specific subunits that have not been found to affect DSB repair, such as Ies3, might facilitate specialized activities of the INO80 complex that are unique to telomere regulation.

Centromere stability and chromosome segregation.

Proper chromosome segregation during mitosis ensures the faithful transmission of genetic information to daughter cells. Chromosome segregation occurs through a rather elaborate process that includes accurate sister chromatid cohesion, attachment of micro tubules to chromosomes through the kinetochore complex, and separation of the replicated chromosomes. Global genetic screens in *S. cerevisiae* show that the INO80 and SWR1 complexes are involved in chromosome stability mechanisms through a role in chromosome segregation^{40,99,100}. Subunits of the *S. cerevisiae* INO80 and SWR1 complexes, such as Arp4 and the Ino80 and Swr1 ATPases, bind directly to centromeres⁹². Mutation of *ARP4* in *S. cerevisiae* causes defects in the assembly of kinetochore components, such as the centromeric histone H3 variant chromosome segregation protein 4 (Cse4), resulting in mitotic cell cycle arrest⁹². Overexpression of *ARP4* partially suppresses the increase in chromosomal ploidy owing to the defects in chromosome segregation that are observed in histone H2A yeast mutant strains¹⁰¹. In addition, *ARP8* deletion in the *S. cerevisiae* INO80 complex results in decreased association of the sister chromatid cohesion component Ctf18 (chromosome transmission fidelity 18) to chromatin and increased rates of sister chromatid separation during mitosis compared with wild-type cells⁹⁰.

The chromatin-remodelling activities of the INO80 and SWR1 complexes that facilitate centromere stability and chromosome segregation are unknown. However, it might be possible that the function of these complexes in chromosome segregation is directly linked to the role of histone H2A variants, as both yeast and mammalian Htz1 and H2AZ variants participate in establishing the specialized chromatin structures in centromeric chromosomal regions^{40,41,102}.

Conclusions and perspectives

Chromatin-remodelling complexes contribute to many essential cellular processes beyond their roles in transcription. Specifically, the roles of INO80 and SWR1 complexes in nuclear activities are quite diverse and range from DSB repair to chromosome segregation. The involvement of these complexes in such varied processes suggests that they might function in different and specialized chromatin-remodelling activities in each process. If so, sophisticated regulatory mechanisms must exist to manage and facilitate the chromatinremodelling activity of each complex. Potential modes of regulation include the targeting of the complex to specific genes by transcription factors, association with different histone and DNA substrates, the participation of specialized subunits in the diverse processes¹⁰³ and the regulation of the complex in signalling pathways by post-translational modification. Additional modes of regulation include swapping of functional subunits and modulation by small molecules, such as inositol lipids and inositol polyphosphates (FIG. 5). Taken together, a single chromatin-remodelling complex can be regulated by multiple mechanisms to generate considerable functional diversity.

The precise chromatin-remodelling mechanisms of the INO80 and SWR1 complexes in diverse nuclear processes are largely unknown. However, both the INO80 and SWR1 complexes associate with histone variants *in vivo* and specialized DNA structures *in vitro*^{21–24}. In certain instances, the association of these specific substrates with the INO80 and SWR1 complexes recruits their activity to a specific nuclear process, such as DNA repair^{22,23}. An interesting possibility is that these substrates also stimulate different chromatin-remodelling activities of the complexes, such as nucleosome sliding or helicase activity. Additionally, it is likely that future research will expand the number of known chromatin substrates to which the INO80 subfamily complexes associate. For instance, it might be possible that acetylated and methylated residues on histones also direct the recruitment and/or activity of the complex to facilitate distinct nuclear processes¹⁰⁴. As exemplified by the INO80 subfamily of chromatinremodelling complexes, the three major mechanisms of chromatin modification — post-translationally modified histones, ATP-dependent chromatin remodeling and histone variants — are intimately and specifically connected. Such connections are expanding, for instance the WICH chromatin-remodelling complex in the ISWI subfamily has recently been linked to a modified histone variant (H2AX with phosphorylated Tyr142) to regulate DNA damage responses¹⁰⁵.

Studies discussed in this Review show that the participation of specific subunits in the function of the complex is dynamic, with different subunits influencing particular processes in which the complex is involved, such as Nhp10 of the *S. cerevisiae* INO80 complex in mediating an interaction with γ -H2AX²² and Ies4 in influencing checkpoint responses. Recent studies reveal that the deubiquitylating enzyme ubiquitin C-terminal hydrolase 37 (UCH37), a component of the 19S regulatory particle of the proteasome, is also present in the mammalian INO80 complex^{106,107}. The transient association of the INO80 complex with UCH37 regulates the deubiquitylating activity of this subunit. As both the INO80 complex and ubiquitylated histones are involved in transcription and repair processes¹⁰⁸, it is possible that chromatin components are the substrates of the deubiquitylation-associated activity of INO80 in these pathways. Thus, for each nuclear process that requires chromatin

remodelling, a functional hierarchy of subunits, including core subunits and regulatory subunits, might be invoked to regulate the activities of that complex.

Currently, most research investigating the role of the INO80 and SWR1 complexes in DNA repair processes has focused on DSB repair. Recent research also implicates the INO80 subfamily in other repair pathways in both yeast and mammals, such as repair of ultraviolet-induced lesions through nucleotide excision repair^{4,5,24,109}. Additional research is needed to determine the exact chromatin-remodelling mechanisms that are required for these different DNA repair processes. Indeed, it might be possible that each different DNA damage pathway elicits the function of specific chromatin-remodelling subunits, or chromatin substrates, to facilitate certain mechanisms of DNA repair.

The roles of INO80 and SWR1 complexes outside of transcription are largely found in genome stability pathways, such as DNA repair, replication, telomere regulation and centromere stability. The consequences of alterations in these chromatin-remodelling complexes are only beginning to be investigated. Gross chromosomal defects have been found in mutants of the yeast INO80 complex¹¹⁰ and it will be interesting to see if these defects contribute to diseases, such as cancer, in mammals. A precedent for the designation of a chromatin-remodelling complex as a tumour suppressor has been previously demonstrated, as haploin sufficiency of the mammalian TIP60 complex accelerates oncogene-induced tumorigenesis¹¹¹ and mutation of the SWI/SNF chromatin-remodelling complex results in carcinogenesis¹¹². Interestingly, like the SWI/SNF complex, the mammalian INO80 complex also contributes to chromosomal polyploidy when mutated^{24,113}. Indeed, the role of the INO80 subfamily in health and human disease has been largely unexplored. As research investigating the function of the INO80 chromatin-remodelling subfamily emerges, it is becoming clear that mechanisms of DNA integrity maintenance rely on the activity of these complexes to regulate chromatin architecture.

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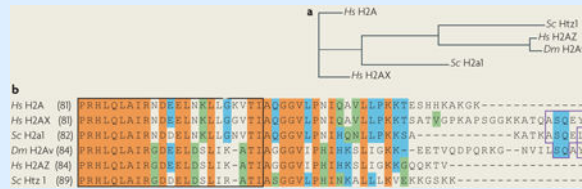
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Box 1 |

Histone H2a variants are substrates of the INO80 subfamily

Of the four core histones, variants of histone H2A are the most common¹¹⁴ and can be incorporated into the nucleosome to signal for specific DNA processing events, such as DNA repair and transcription. Members of the INO80 subfamily bind to H2A variants to facilitate chromatin remodelling. H2AZ is a highly conserved histone variant that has been found in a range of organisms, including protozoans, fungi and metazoans (see the figure, part **a**, which shows the phylogeny of histone H2A variants in *Homo sapiens* (Hs), *Saccharomyces cerevisiae* (Sc) and *Drosophila melanogaster* (Dm)). These H2AZ-like variants are more homologous to each other across species than to canonical H2A, which suggests that they arose relatively early during evolution and have specialized conserved functions¹¹⁴. Mammalian histone H2AX, as well as the *D. melanogaster* homologue H2Av, is a variant found in approximately 10% of nucleosomes throughout the genome^{115,116}. H2a1 and H2a2 (only H2a1 is shown), the predominant canonical histones in yeast, are found in most nucleosomes and are orthologous to the mammalian H2AX variant. Unlike H2AZ-like histones, the H2AX-like histone variants have a large degree of homology with canonical human H2A, with the main sequence deviation located in their carboxyl termini. During the activation of DNA damage responses, ataxia telangiectasia (A-T) mutated (ATM) and A-T and RAD3-related (ATR) kinases (Tel1 and Mec1 in yeast) phosphorylate the H2AX-like histones on the Ser of the C-terminal (S/T)Q consensus motif^{55,56} (see the figure, part **b**). In addition to being homologous to human H2AZ, *D. melanogaster* H2Av is also phosphorylated by ATM and ATR on its C terminus consensus sequences. Thus, H2Av is a unique hybrid that contains similarities to both H2AX and H2AZ. Identical amino acids are shown in orange, conserved amino acids in blue, similar amino acids in green and unique amino acids are not shaded. Amino acids in the core histone domain are boxed with a black line and C terminus residues that contain phosphorylation sites are highlighted in purple. The numbers in parentheses indicate the position of amino acids in the sequence.



Helicase

An enzyme that unwinds double-stranded nucleic acids in an energy-dependent manner.

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DEAD/H box

An evolutionarily conserved domain found in proteins that are a part of the super family 2 helicases, which are essential for RNA metabolism and processing.

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RuvB

A bacterial ATP-dependent DNA helicase that forms a ring-shaped double hexamer complex around a Holliday junction and promotes its migration during homologous recombination.

Centromere

Region of a chromosome that is attached to the spindle during cell division.

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HMG

(High mobility group). A large protein family of small, non-histone components of chromatin that function in chromatin structure

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Holliday junction

A mobile junction that contains four strands of DNA and is generated during the synaptic phase of homologous recombination.

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Homologous recombination

A DNA recombination pathway, which includes the repair of double-strand DNA breaks, that uses a homologous double-stranded DNA as a template for the repair of the broken DNA.

Helicase-SANT-associated domain

The region in the ATPase subunit of the INO80 and SWI/SNF subfamilies that serves as the primary binding site for nuclear actin and actin-related proteins within the chromatin-remodelling complex.

Heterochromatin

Dense chromatin that is less transcriptionally active than euchromatin. Heterochromatin includes structural regions of the chromosome, such as centromeres and telomeres (constitutive heterochromatin), as well as genes that are silenced in a given cell type (facultative heterochromatin).

Non-homologous end joining

(NHEJ). A DNA repair pathway for double-strand breaks that is often error-prone because it leads to the joining of breaks without a template.

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Mre11 nuclease

A subunit of the Mre11–Rad50–Xrs2 (MRX) complex that has 3' to 5' exonuclease activity and assists in resecting the DNA ends of a double-strand break.

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Replication origin

A site where replication is initiated during S phase.

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Replisome

A multiprotein complex at the junction of the DNA replication fork that contains all the enzymes that are required for DNA replication.

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Kinetochores

A multiprotein complex that assembles on centromeric DNA and mediates the attachment and movement of chromosomes along the microtubules of the mitotic spindle.

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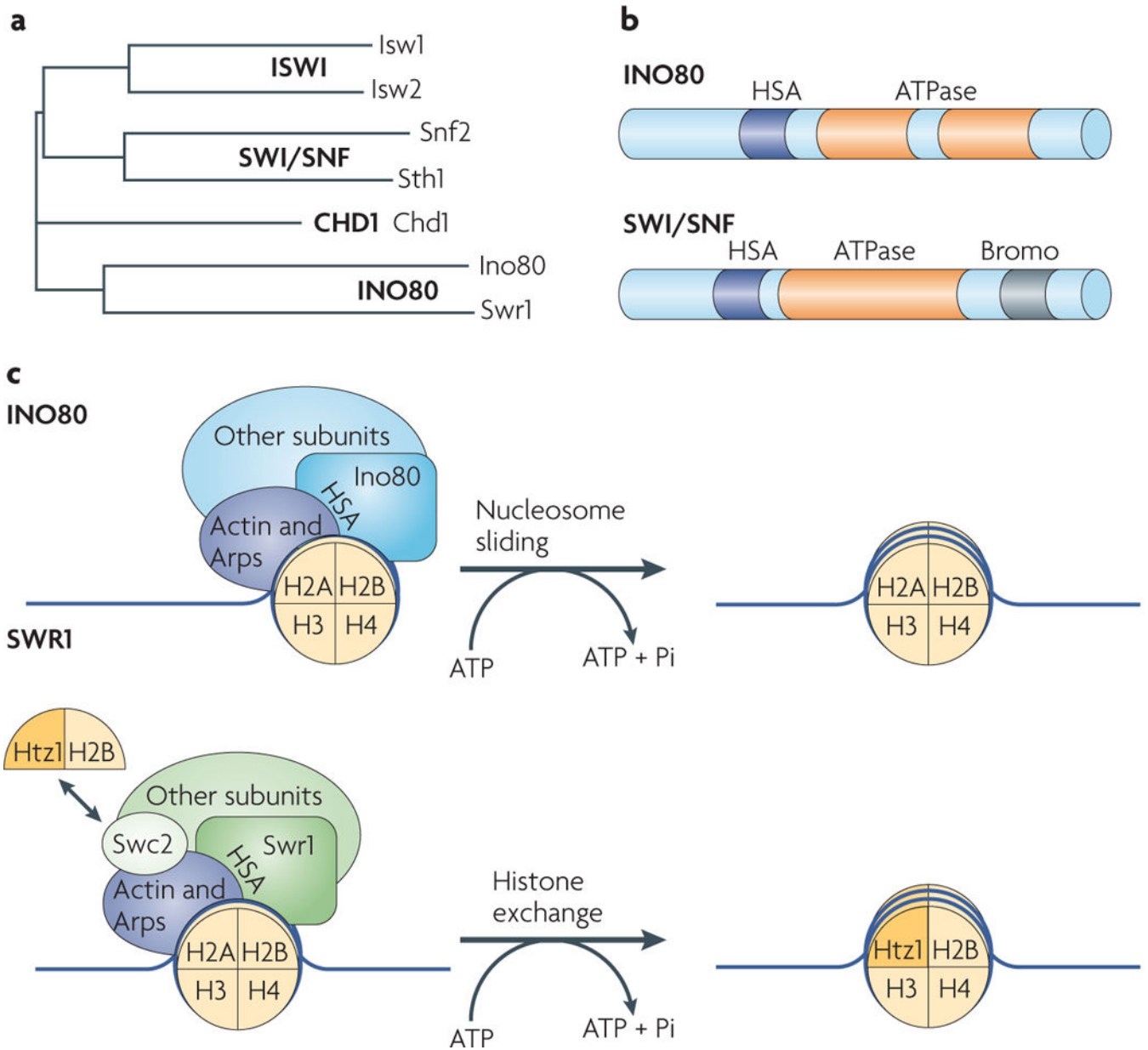


Figure 1 | Chromatin-remodelling mechanisms of the INO80 and SWR1 complexes.

a | Phylogeny of *Saccharomyces cerevisiae* chromatin-remodelling ATPase subunits.

Members of the ISWI, SWI/SNF, CHD1 and INO80 subfamilies are shown. **b** | ATPase subunits of the INO80 and SWI/SNF subfamilies are shown. The ATPase domain of the INO80 subfamily is split in the middle by a spacer region. The SWI/SNF ATPase subunit contains a bromodomain (Bromo), which binds to acetylated histones. Both subunits contain a helicase-SANT-associated (HSA) domain that mediates the association of the subunit with actin and actin-related proteins (Arps). **c** | Distinct ATP-dependent chromatinremodelling mechanisms of INO80 and SWR1 complexes. The INO80 complex repositions nucleosomes to a central position from the end of the DNA. The SWR1 complex incorporates the histone

variant Htz1 into the nucleosome. Both mechanisms require ATP hydrolysis and the function of actin and Arp subunits in the complexes.

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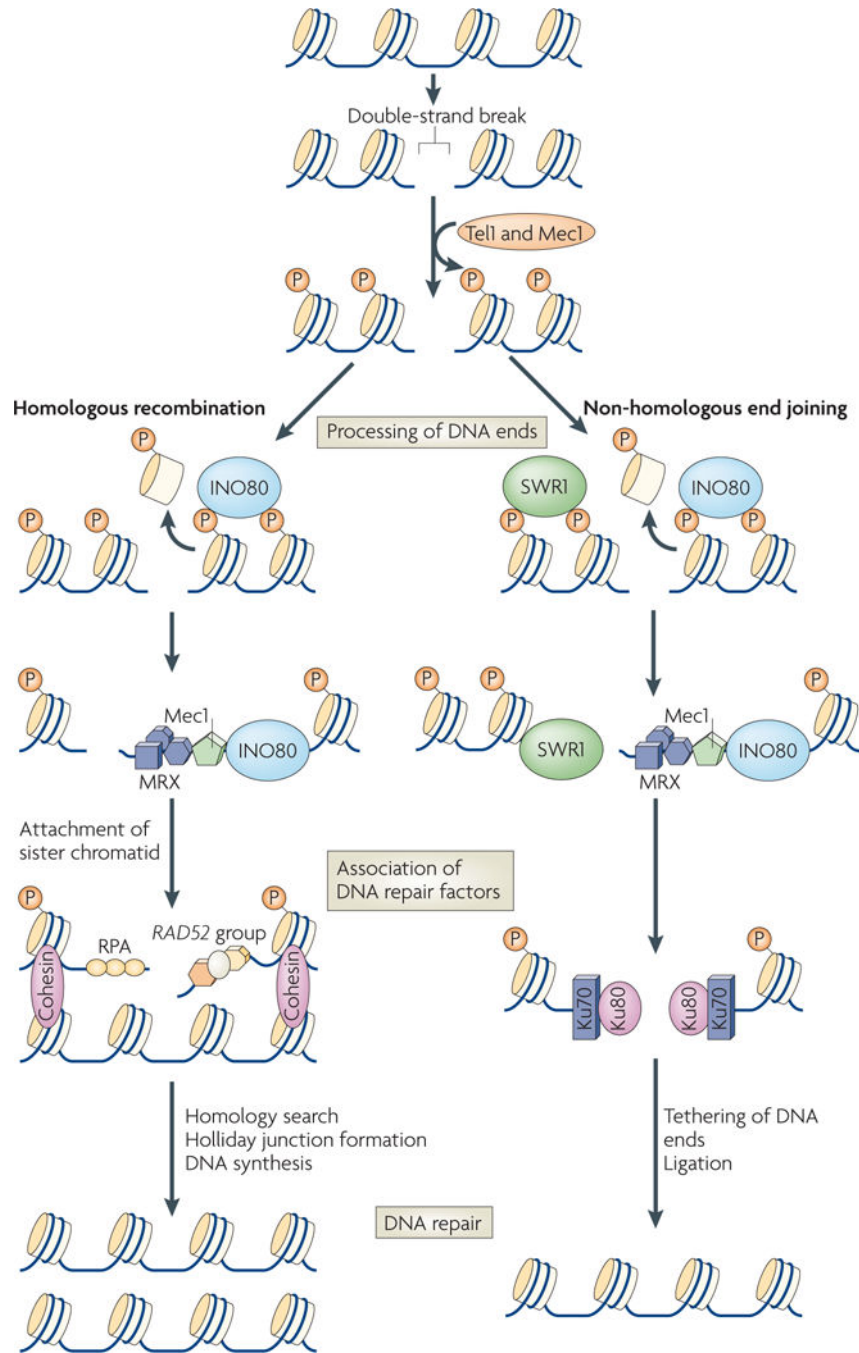


Figure 2 | INO80 and SWR1 complexes regulate double-strand break repair. The *Saccharomyces cerevisiae* kinases Tel1 and Mec1 (ataxia telangiectasia (A-T) mutated (ATM) and A-T and RAD3-related (ATR) in mammals) phosphorylate H2AX after the creation of a double-strand break, which can be repaired by homologous recombination (HR) or non-homologous end joining (NHEJ). During HR and NHEJ, the INO80 and SWR1 complexes bind to phosphorylated H2AX. The INO80 complex is involved in nucleosome eviction proximal to the break site. The DNA ends are then recognized by the Mre11–Rad50–Xrs2 (MRX) complex. The Mre11 nuclease is involved in the production of single-

stranded DNA. During HR, the single-stranded DNA-binding protein replication protein A (RPA) and the Mec1 checkpoint kinase bind to resected DNA. The cohesin complex assists in holding the sister chromatids together^{64,117}. The *Rad52* epistasis group, which includes Rad51, Rad52 and Rad54, facilitate the search for and synapsis of homologous DNA sequences. A Holliday junction is formed between the two DNA strands, followed by DNA synthesis and resolution of the junction. During NHEJ, the SWR1 complex promotes the association of Ku80 to the DNA ends, a component of the Ku70–Ku80 complex that is required for NHEJ. Repair is then completed following ligation of the DNA ends. Mutants of the INO80 complex have defects in HR and NHEJ, whereas mutants of the SWR1 complex have defects in error-free NHEJ.

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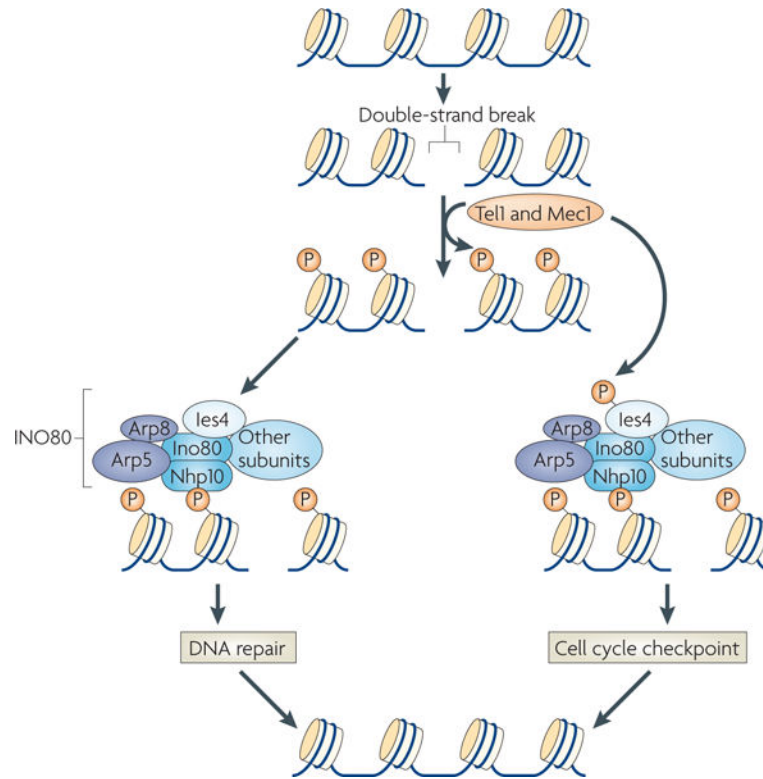


Figure 3 |. The INO80 complex is a component of the Tel1 and Mec1 pathway.

Following the creation of a double-strand break, the *Saccharomyces cerevisiae* kinases Tel1 and Mec1 (ataxia telangiectasia (A-T) mutated (ATM) and A-T and RAD3-related (ATR) in mammals) phosphorylate H2AX. The non-histone protein 10 (Nhp10) subunit of the INO80 complex is needed for the complex to associate with phosphorylated H2AX (γ -H2AX). Once localized to the DNA break site, core catalytic subunits, such as actin-related protein 5 (Arp5) and Arp8, participate in DNA repair processes. The Tel1 and Mec1 kinases also phosphorylate INO80 subunit 4 (Ies4) to regulate the cell cycle checkpoint response. Therefore, Tel1 and Mec1 regulate two aspects of the INO80 complex when cells are exposed to DNA-damaging agents: the phosphorylation of H2AX, leading to the recruitment of the INO80 complex at DNA damage sites, and phosphorylation of the Ies4 subunit to influence the cell cycle checkpoint response.

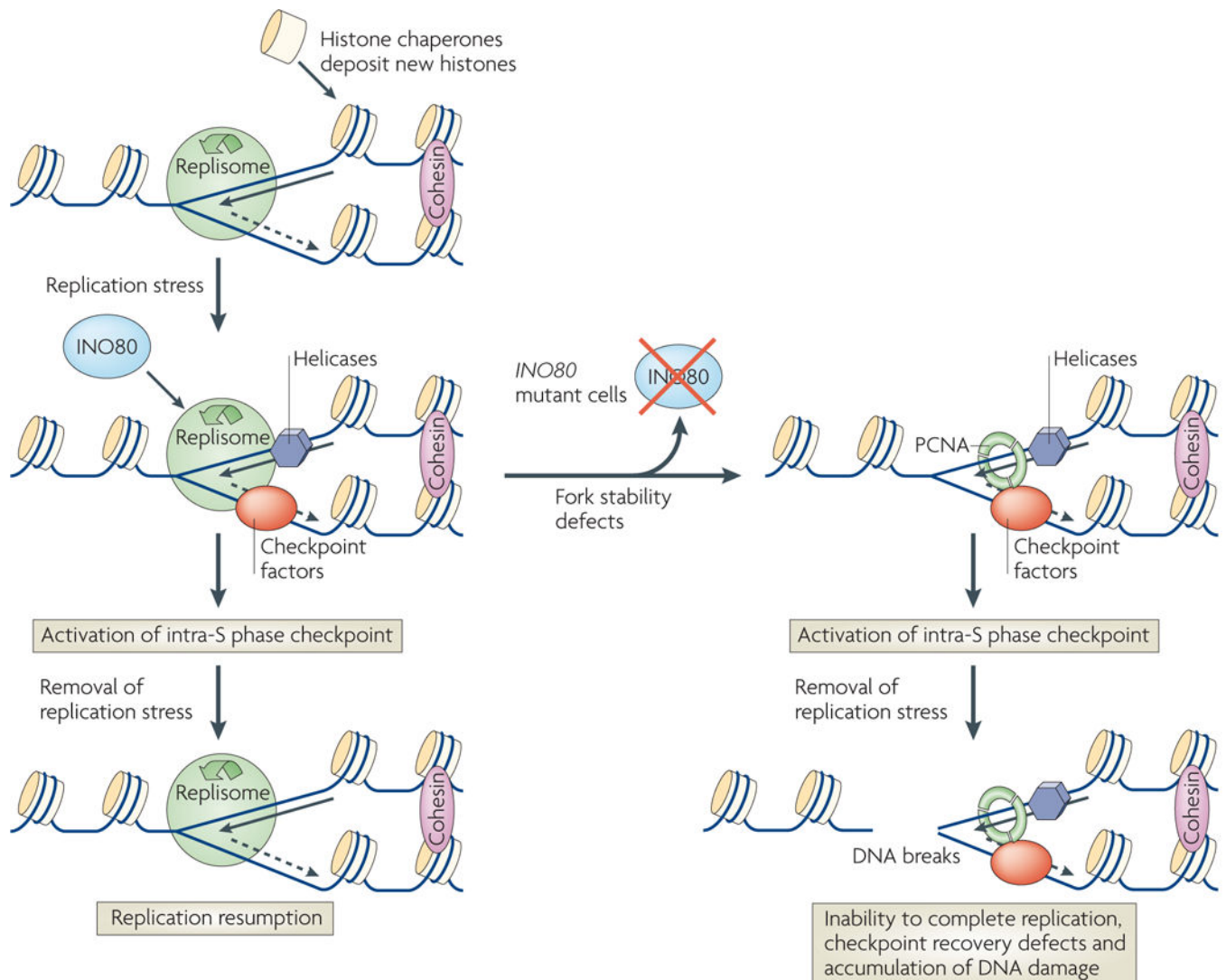


Figure 4 | The INO80 complex promotes recovery of stalled replication forks.

During replication, DNA synthesis is catalysed by the replisome, which contains polymerases, primases and helicases¹¹⁸. Histone chaperones deposit histones on to newly synthesized DNA. Replication forks stall when exposed to replication stress, such as depleted dNTP pools. When this happens, the replisome is stabilized by DNA damage response factors, such as the *Saccharomyces cerevisiae* INO80 complex and the Tof1 and Mrc1 checkpoint factors, which activate the intra-S phase checkpoint to prevent replication origin firing. On the removal of replication stress, the replication fork recovers and DNA synthesis resumes. In the absence of the INO80 complex, fork stability defects occur as the replisome is destabilized and some of its components dissociate, leaving others, such as proliferating cell nuclear antigen (PCNA), at the replication fork. In this case, replication does not restart following the removal of replication stress. Accordingly, checkpoint recovery is delayed and DNA damage accumulates.

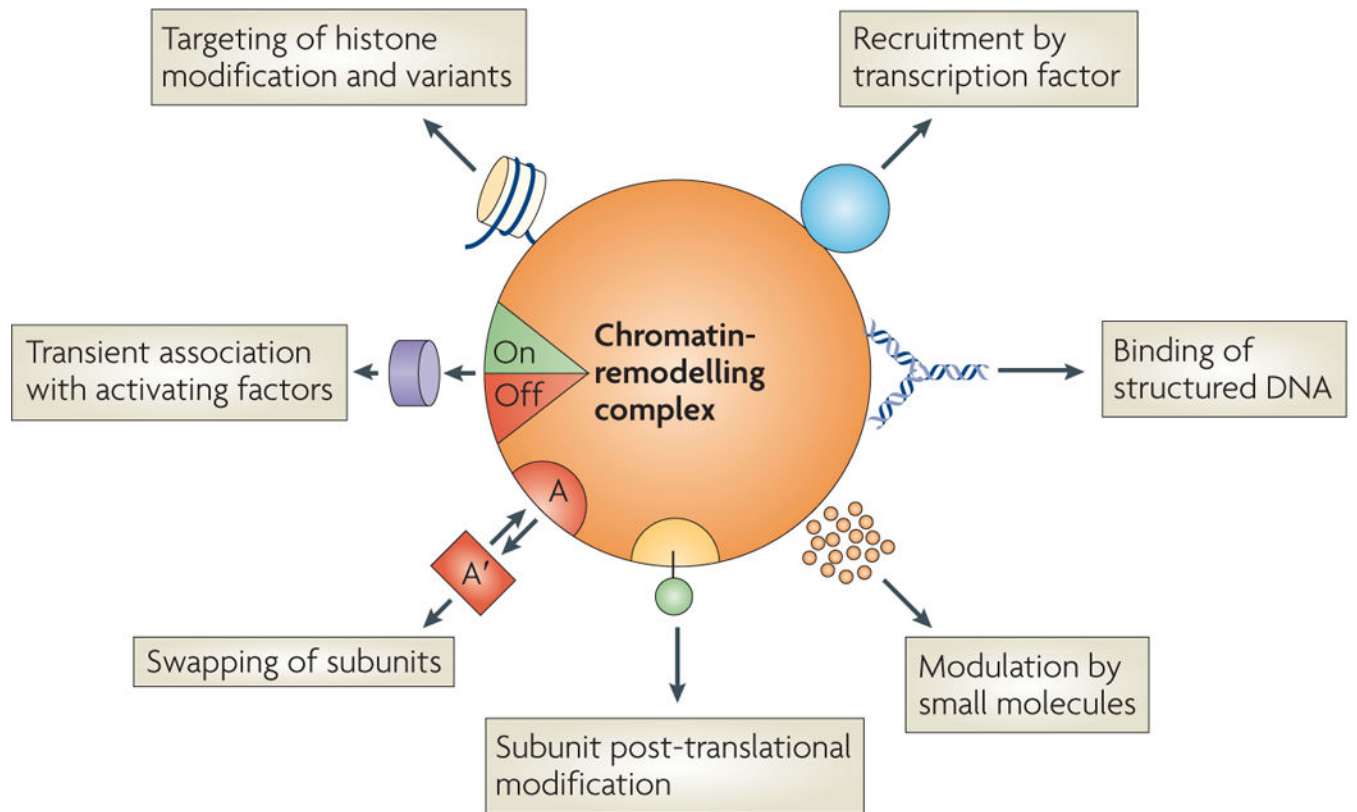


Figure 5 |. Regulation of aTP-dependent chromatin remodelling.

Seven distinct mechanisms in combination can generate numerous structural and functional diversities for a single chromatin-remodelling complex. Transcription factors can target the complex for recruitment to specific target genes. The binding of structured DNA, such as three-way and four-way junctions that represent DNA replication and repair intermediates, can also recruit and potentially alter the activity of the complex. Small molecules, such as inositol polyphosphates and phosphoinositides, can modulate the activity of the complex. Additionally, subunits in the complex can be post-translationally modified or exchanged (swapped)¹¹⁹ to alter the function of the complex. The activity of specific subunits can also be regulated by transient association of the complex with activating factors, such as the activation of the deubiquitylating enzyme ubiquitin carboxy-terminal hydrolase 37 (UCH37) following association of this 19S proteasome component to the INO80 complex. Finally, the association of unique chromatin substrates, such as histone variants and post-translationally modified histones, can further specify the chromatin-remodelling mechanisms of the complex.

Table 1 |

Homologous INO80, SWR1 and SRCAP chromatin-remodelling complexes

Subunit type	INO80 complex			SWR1 and SRCAP complexes	
	<i>Saccharomyces cerevisiae</i>	<i>Homo sapiens</i>	<i>Drosophila melanogaster</i>	<i>Saccharomyces cerevisiae</i>	<i>Homo sapiens</i>
ATPase	Ino80	INO80	INO80	Swr1	SRCAP
RuvB-like	Rvb1 and Rvb2	RUVBL1 and RUVBL2	Reptin and Pontin	Rvb1 and Rvb2	RUVBL1 and RUVBL2
Actin	Act1	β -Actin	Actin	Act1	β -Actin
Actin-related protein	Arp4, Arp5 and Arp8	BAF53A, ARP5 and ARP8	ARP5 and ARP8	Arp4 and Arp6	BAF53A and ARP6
YEATS protein	Taf14	Not known	Not known	Yaf9	GAS41
Non-conserved subunits*	Ies1, Ies2, Ies3, Ies4, Ies5, Ies6 and Nhp10	Amida, CCDC95, FLJ20309, IES2, IES6, MCRS1, NFRKB, UCH37 and YY1	Pleiohomeotic	Bdf1, Swc2, Swc3, Swc4, Swc5, Swc6 and Swc7	DMAP1, GAS41, tubulin, XPG, YL1 and ZnF-HIT1

* Subunits in all other rows of this table are conserved. Act, actin; Arp, actin-related protein; BAF53A, BRG1-associated factor 53A; Bdf1, bromodomain factor; CCDC95, coiled-coil domain-containing 95; DMAP1, DNA methyltransferase 1-associated protein 1; GAS41, glioma amplified sequence 41; Ies, INO80 subunit; MCRS1, microspherule protein 1; NFRKB, nuclear factor related to κ B-binding protein; Nhp10, non-histone protein 10; Rvb, RuvB-like; RUVBL, RuvB-like; SRCAP, SNF2-related CBP activator protein; Swc, SWR1 complex; Taf14, TBP-associated factor 14; UCH37, ubiquitin C-terminal hydrolase 37; XPG, xeroderma pigmentosa group G; Yaf9, yeast AF9; YEATS, Yaf9, ENL, AF9, Taf14, Sas5; YY1, yin yang 1; Znf-HIT1, zinc finger-His triad protein 1.