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MINI-REVIEW

# Regulation of ISWI chromatin remodelling activity

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**Abstract** The packaging of the eukaryotic genome into chromatin facilitates the storage of the genetic information within the nucleus, but prevents the access to the underlying DNA sequences. Structural changes in chromatin are mediated by several mechanisms. Among them, ATP-dependent remodelling complexes belonging to ISWI family provides one of the best examples that eukaryotic cells evolved to finely regulate these changes. ISWI-containing complexes use the energy derived from ATP hydrolysis to rearrange nucleosomes on chromatin in order to favour specific nuclear reactions. The combination of regulatory nuclear factors associated with the ATPase subunit as well as its modulation by specific histone modifications, specializes the nuclear function of each ISWI-containing complex. Here we review the different ways by which ISWI enzymatic activity can be modulated and regulated in the nucleus of eukaryotic cells.

**Keywords** ISWI · Nucleosome · Chromatin remodelling · Histone

## Introduction

Eukaryotic cells store their genetic information in the form of chromatin, a complex of DNA packed with structural and regulatory proteins. The functional repeating unit of chromatin is the nucleosome core, consisting of 147 bp of DNA wrapped around an octamer of histone proteins. While this packaging provides the cell with the obvious benefit of organizing a large and complex genome in the nucleus, it can also block the access to DNA sequences. Nuclear reactions therefore depend on factors that modulate the accessibility of DNA within the context of chromatin. Indeed, ATP-dependent chromatin remodelling and covalent modification of histones, play central roles in determining chromatin accessibility (Martens and Winston 2003; Iizuka and Smith 2003; Becker and Horz 2002). These reactions are catalyzed by evolutionarily conserved multi-subunit complexes that directly alter chromatin structure to regulate gene expression and other nuclear functions (Martens and Winston 2003; Iizuka and Smith 2003; Becker and Horz 2002; van Vugt et al. 2007).

ISWI is a component of several ATP-dependent chromatin remodelling complexes conserved in composition and function across species (Dirscherl and Krebs 2004; Corona and Tamkun 2004b) (Fig. 1). In higher eukaryotes, ISWI is an abundant and ubiquitously expressed protein that is essential for cell viability (Deuring et al. 2000; Stopka and Skoultchi 2003). ISWI chromatin remodellers are involved in important nuclear functions such as DNA replication, DNA repair, transcriptional regulation and chromosome structure maintenance (Corona and Tamkun 2004a; Yadon and Tsukiyama 2011). In order to modulate these essential biological processes, ISWI activity needs to be finely regulated. To date, work conducted in several model systems has revealed a multitude of ways by which ISWI-chromatin remodelling activity can be regulated in the eukaryotic cell.

Due to the broad spectrum of functions played by ISWI, many factors influence its enzymatic activity in order to integrate nucleosome remodelling reactions in different physiological contexts in vivo. Indeed, nucleosome spacing reactions catalyzed by ISWI can be regulated (1) in *cis*, by intrinsic ISWI domains (Fig. 2), (2) by its associated subunits and chromatin factors (Fig. 3), (3) by ISWI post-translational modification or by its associated nucleosomal substrate (Fig. 4) and finally (4) by specific DNA and RNA sequence features (Fig. 5). Here, we present a review of the different

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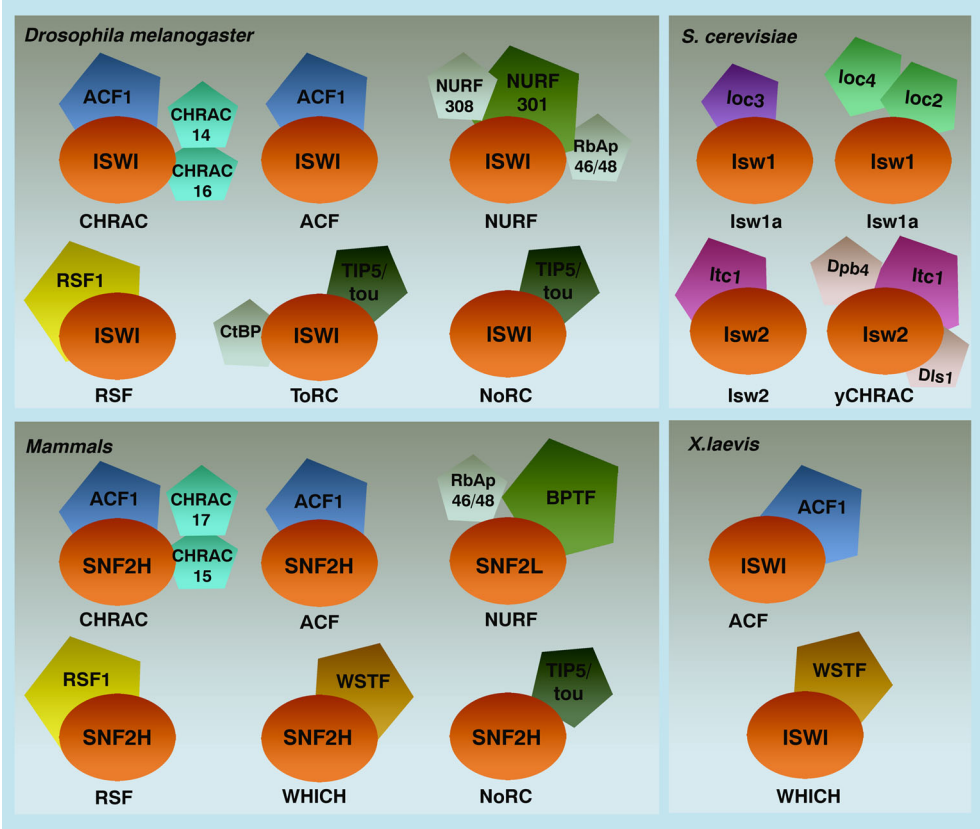


**Fig. 1** ISWI containing complexes and their associated subunits. The ISWI (*Imitation SWItch*) chromatin remodelling ATPase, identified for the first time in *Drosophila*, exists in all eukaryotes and constitutes an important subfamily within the SNF2 superfamily of ATPase. The ISWI protein is represented by *orange ovals* while the accessory subunits are shown as *pentagons*. Homologous proteins belonging to different complexes in different species are all indicated with the same color code

mechanisms by which ISWI enzymatic activity could be modulated across species.

## Regulation through structural and functional ISWI domains

Regulation of ISWI targeting and activity on nucleosomal substrates is essential to gain knowledge on chromatin dynamics. Since their discovery, different levels of regulation of ISWI chromatin remodelling activity have emerged (Erdel et al. 2011). Recent works have shed light into the function of ISWI intrinsic domains. Interestingly, studies conducted in vitro, demonstrated that the conserved ATPase domain has autonomous nucleosome remodelling activity, while domains adjacent to the ATPase module have regulatory function (Mueller-Planitz et al. 2013; Hota et al. 2013; Clapier and Cairns 2012).

ISWI contains a highly conserved ATPase core domain located at the N-terminal half of the protein and a characteristic set of HAND–SANT–SLIDE (HSS) domains with DNA-binding function, at the C-terminal portion (Fig. 2) (Boyer et al. 2004; Grune et al. 2003b; Hota and Bartholomew 2011). Over the past few years, in vivo and in vitro studies have led to a broadly accepted model in which the HSS domain plays an integral part during the remodelling reaction (Boyer et al. 2004; Grune et al. 2003a; Boyer et al. 2002). Unexpectedly, a recent study conducted on *Drosophila* ISWI (*d*ISWI) showed that most of the fundamental regulatory aspects of nucleosome remodelling are contained around the compact ATPase module (Mueller-Planitz et al. 2013). In this work the authors found that ISWI lacking its HSS domain can still remodel nucleosomes, with an intrinsic ability to bind nucleosomes and to interact with histone H4 N terminus, revealing a positive role for the HSS domain in increasing the affinity and specificity of ISWI ATPase for nucleosome (Fig. 2) (Mueller-Planitz et al. 2013). Similarly, another study showed a regulatory function for the SLIDE domain of *Saccharomyces cerevisiae* Isw2 subunit to help maintaining the directionality of DNA movement into nucleosomes (Hota et al. 2013). Altogether, these data underline that the accessory domains of ISWI may have evolved to optimize catalysis and modulate the outcome of the remodelling reaction.

This idea has been recently supported by the identification of two new conserved and separate negative regulatory regions of the *d*ISWI ATPase, defined as AutoN and NegC (Fig. 2) (Clapier and Cairns 2012). The AutoN is located within the N terminus of ISWI ATPase and its conserved sequence resembles the basic patch of histone H4 tail. On the other hand, the NegC module is located between the ATPase core and the HSS DNA-binding domain. AutoN inhibits the ATP hydrolysis rate, working as a brake that

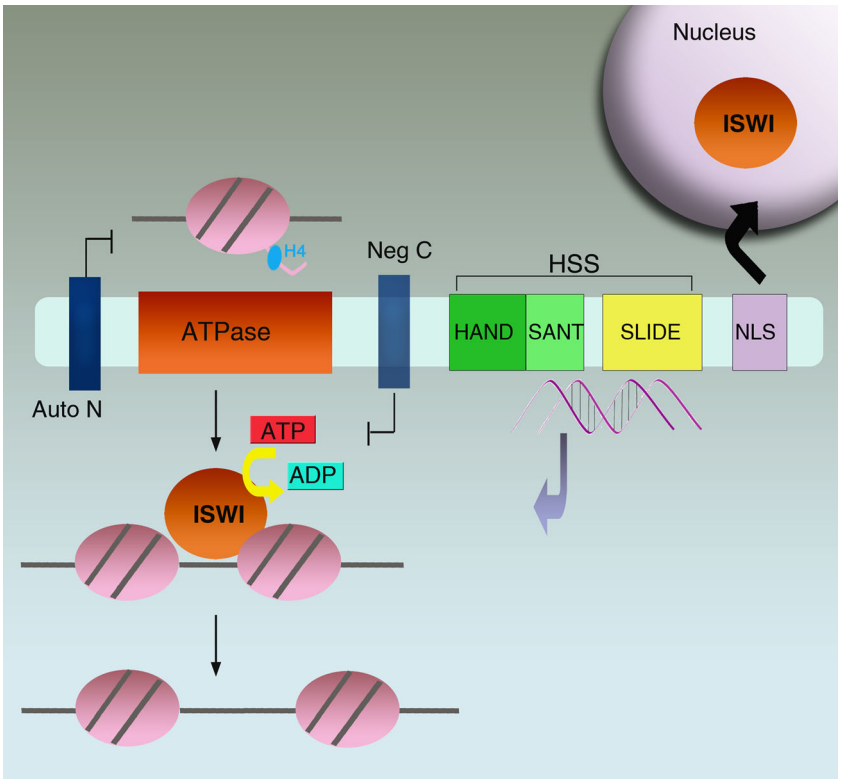


**Fig. 2** Structure and function of ISWI domains. ISWI domains are showed as *rectangles*. The ISWI ATPase domain (*orange color*) with an intrinsic ability to bind nucleosomes, is flanked by two functional domains Auto N (*dark blue*) and Neg C (*light blue*) with inhibitory roles. ISWI C-terminal portion contains the HAND (*dark green*), SANT (*light green*), SLIDE (*yellow*) with DNA-binding function and the NLS (*purple*) domain important for nuclear localization

constrains the catalytic activity of ISWI by making contact with the ATPase lobes. Instead, NegC locks the ATPase lobes in a conformation that inhibits ATPase coupling to DNA translocation. Mutation of AutoN and NegC enables marked nucleosome sliding without the H4 basic patch, DNA linker, or the HSS domain, confirming that the ISWI ATPase core is an intrinsically active DNA translocase, flanked by specific regulatory modules that ensure remodelling only in the presence of proper nucleosomal epitopes (Clapier and Cairns 2012).

An integrated view of the above mentioned and other structural data obtained so far, imply that the chromatin-remodelling activity of ISWI is regulated by conformational changes, triggered by nucleosomal epitopes, which stabilize a permissive conformation of ISWI for DNA translocation. In particular, ATPase kinetic studies indicate that ISWI is present in two distinct conformations in absence of DNA. Indeed, the addition of DNA causes a dramatic ISWI protease hypersensitivity at level of residues adjacent to NegC and AutoN (Mueller-Planitz et al. 2013). On the basis of the characterization of AutoN and NegC inhibitory function, the conformational change triggered by nucleosomal epitopes binding probably involves the removal of both of these ATPase brakes (Manning and Peterson 2013).

Very recently, a novel role in the regulation of the nuclear import process of chromatin remodelling enzymes has emerged (Fig. 2). While it has been previously shown that the import of *human* ISWI (*h*SNF2H) (Yadon and Tsukiyama 2011) to the nucleus is controlled by the accessory subunits of the complex (Lan et al. 2010; Sheu et al. 2008), in a very recent study it has been highlighted that the nuclear import of *S. cerevisiae* Isw1 is mediated by a specific nuclear localization signal (NLS) located at the end of the C-terminal portion (a. a10079-1105) (Vasicova et al. 2013). Indeed, in vitro binding assay of *y*Isw1-NLS to importin-α revealed that the nuclear translocation of *y*Isw1 is mediated by the classical import pathway. Moreover, this mechanism was recognized as the unique regulator of chromatin remodeller nuclear translocation in vivo. Interestingly, similar nuclear localization motifs were identified in silico in ISWI higher eukaryote orthologues, suggesting that the C termini of the ISWI family proteins play a role in their nuclear import (Vasicova et al. 2013).

## ISWI chromatin remodellers regulation by protein–protein interaction

Since the discovery that ISWI, out of the context of its associated subunits, has nucleosome remodelling activity (Corona et al. 1999) at least two principal roles have been recognized for the complex subunits: (1) the modulation of nucleosome remodelling reactions and (2) the targeting of the remodelling complex to specific chromatin regions (Fig. 3).

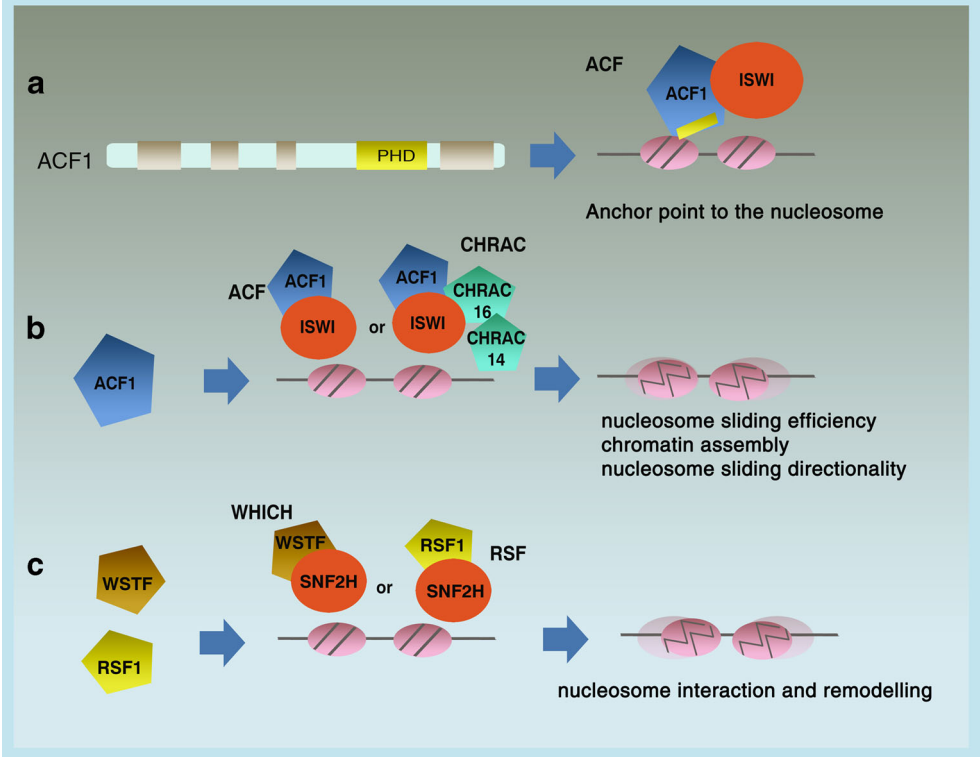


**Fig. 3** Regulation of ISWI activity by its non catalytic subunits. The associated ISWI subunits (*pentagons*) interacting with ISWI protein (*orange sphere*) are able to positively regulate ISWI chromatin assembly activity and nucleosome directionality. **a** The targeting of ISWI to DNA can be mediated by PHD motif (*yellow rectangle*) present in ISWI associated subunit, such as Acf1. **b** The association of ISWI with Acf1 subunit is able to increase the nucleosome assembly and sliding ability of ISWI. **c** The accessory subunits of *h*SNF2H complexes influence the ability of the remodeller to interact and remodel nucleosomes

The first identified subunits able to regulate ISWI nucleosome remodelling activity were *Drosophila* ACF1 and NURF301. Both ACF1 and NURF301 can modulate ISWI enzymatic functions via their Plant Homeo Domains (PHD). This protein domain provide an anchor point on the nucleosome substrate that enables efficient conversion of the force generated by ATP hydrolysis into disruption of DNA–histone interactions (Fig. 3a) (Aasland et al. 1995; Eberharter et al. 2004; Strohner et al. 2005; Wysocka et al. 2006). The ACF1 subunit of both ACF and CHRAC complexes strongly increases nucleosome sliding efficiency (Eberharter et al. 2001, 2004) and the ability of ISWI to assemble chromatin (Fig. 3b) (Ito et al. 1999). *h*CHRAC complex contains two additional histone-fold proteins which enhance sliding activity mediated by ACF, probably by binding and bending the DNA emerging from the nucleosome (Hartlepp et al. 2005; Kukimoto et al. 2004; McConnell et al. 2004). These functional interactions are conserved also in the *Drosophila* CHRAC complex wherein the histone-fold protein subunits, CHRAC 14 and CHRAC 16, acting as DNA chaperones, enhance nucleosome sliding, in striking analogy to what observed for HMGB1(Hartlepp et al. 2005) (Bonaldi et al. 2002). The high mobility group (HMG) proteins indeed, cooperate with ISWI chromatin remodelling complexes to increase their capacity to bind nucleosomal DNA thus enhancing their sliding activity (Bonaldi et al. 2002; Xiao et al. 2001).

The association of ISWI with ACF1 or NURF301 subunits can also influence the biochemical properties of the ACF/CHRAC and NURF complexes (Fig. 3b). In particular, while ISWI alone catalyses the movement of a nucleosome toward the end of a short DNA fragment, the ACF complex pushes the nucleosome toward the central portion of the same DNA fragment (Brehm et al. 2000; Eberharter et al. 2001; Langst et al. 1999). Similarly, in the NURF complex, the NURF301 subunit modifies the intrinsic nucleosome mobilization proprieties of ISWI and interacts with sequence-specific transcription factors, targeting NURF complex to specific genes (Xiao et al. 2001). In a similar way, the non-catalytic subunits associated with human *h*SNF2H complexes (*h*ACF, *h*RSF, *h*CHRAC and WHICH) regulate *h*SNF2H ATPase ability to interact and to remodel nucleosomes through their interaction with the linker DNA (Fig. 3c) (He et al. 2008).

The regulatory role played by the accessory subunit of ISWI complexes was recently also described for the evolutionary conserved *Drosophila* Toutatis-containing chromatin Remodelling Complex (ToRC). ToRC remodeller consists of three different subunits TIP5/tou, ISWI and CtBP (Fig. 1) that are required to stimulate the intrinsic weak chromatin assembly activity of ISWI (Emelyanov et al. 2012). The Emelyanov work not only supports the regulatory role of the ISWI associated subunit in ToRC, but also provides evidence for a NoRC complex in *Drosophila*. Emylyanov and colleagues identified, in *d*NoRC, a TIP5/tou C-terminally truncated protein that forms a CtBP-free complex localized in the nucleolus (Fig. 1). As in mammals, *d*NoRC complex is a nucleolar-specific SN2H-containing chromatin remodelling factor involved in the transcriptional silencing of rDNA repeats (Mayer et al. 2008).

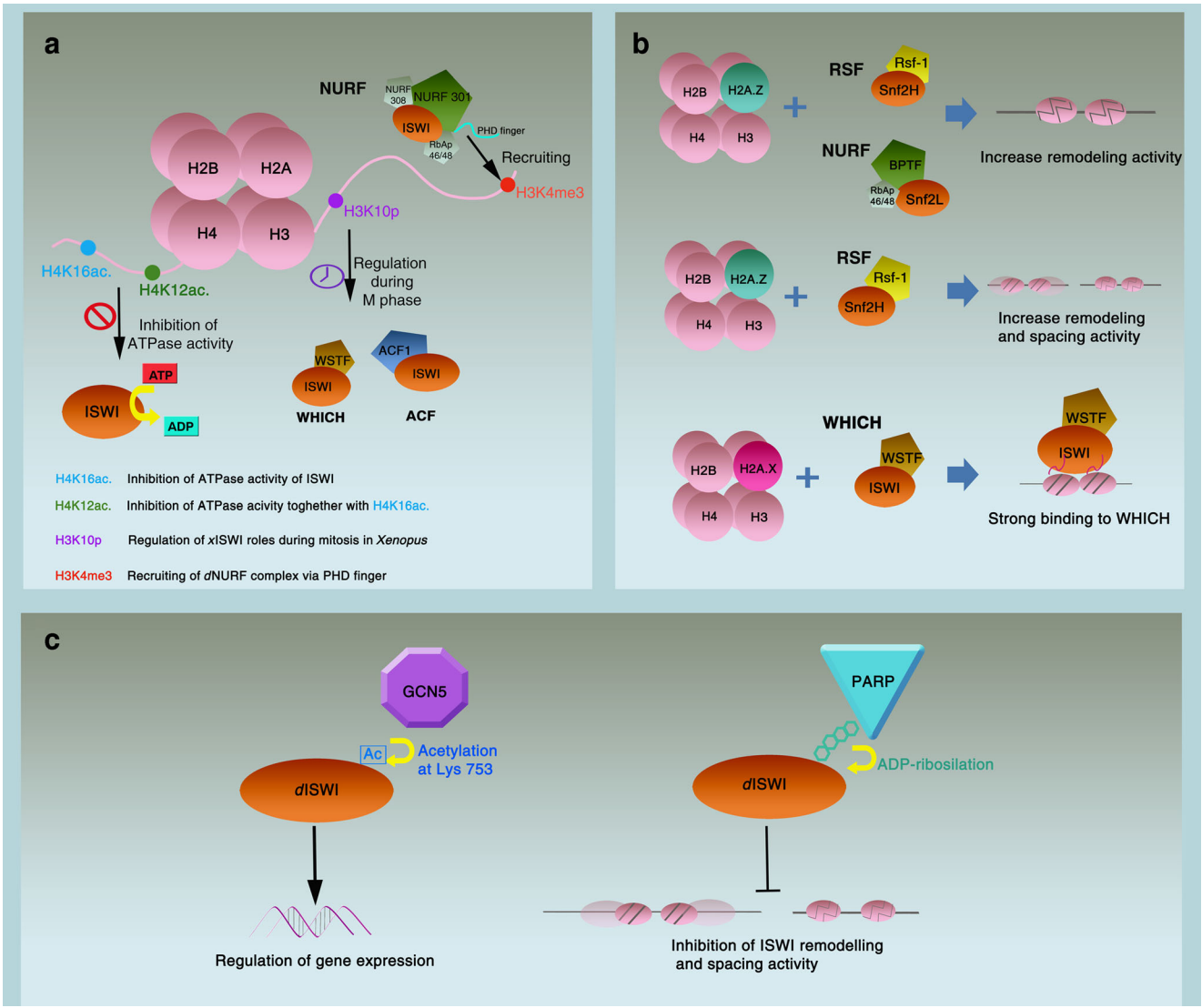


**Fig. 4** Regulation of ISWI chromatin remodellers by histones and post-translational modifications. **a** Histone proteins are indicated as pale pink spheres, from which H3 and H4 N-terminal tails are protruding. *Colored dots* indicate specific post translational modifications regulating ISWI activity. H4K16ac. (*blue dot*) is able to inhibit the catalytic activity of ISWI as well as H4K12ac. (*green dot*) in association with H4K16ac. H3K10p, indicated with a *purple dot*, was shown to interact with xWHICH and xACF during mitosis. H3K4me3 (*red dot*) can act as a platform to recruit the NURF complex, by the PHD finger. **b** Regulation by histone variants. Non-canonical forms of H2A known to influence the remodelling, spacing and targeting reaction of ISWI remodellers are represented by *colored spheres* within the histone octamer. H2A.Z (*light blue sphere*) increases the remodelling activity of NURF and RSF complexes in mammals. The same histone variant is able to positively affect both the remodelling and spacing reactions of the Drosophila counterpart of the human Rsf-1 subunit, while H2A.X (*pink sphere*) has been shown to bind strongly than canonical histones to ISWI subunit of WHICH complex. **c** Regulation by post-translational modifications of remodeller. The histone acetyl transferase GCN5 is represented as a *purple octagon*. This enzyme mediates the specific acetylation of K753 of *Drosophila* ISWI (*d*ISWI), probably regulating gene expression during development. The enzyme PARP, indicated as a light blue triangle, is known to mediate the ADP ribosylation of *d*ISWI. This modification was shown to counteract all ISWI functions in *Drosophila*

## Regulation by histones and post-translational modifications

### Histone modifications

Histone modifying enzymes not only directly regulate chromatin structure by changing the interactions between the octamer and the DNA, but most importantly they also regulate remodelling enzymes targeting (Strahl and Allis 2000) (Bannister and Kouzarides 2011; Berger 2002; Wu and Grunstein 2000). The ability to recognize histone modifications constitutes an integral part of all ATP-dependent chromatin complexes that may either help the targeting of the enzymes to particular genomic sites and/or modulate their activities. In particular, the ISWI ATPase and its regulatory subunits posses dedicated domains that specifically interact

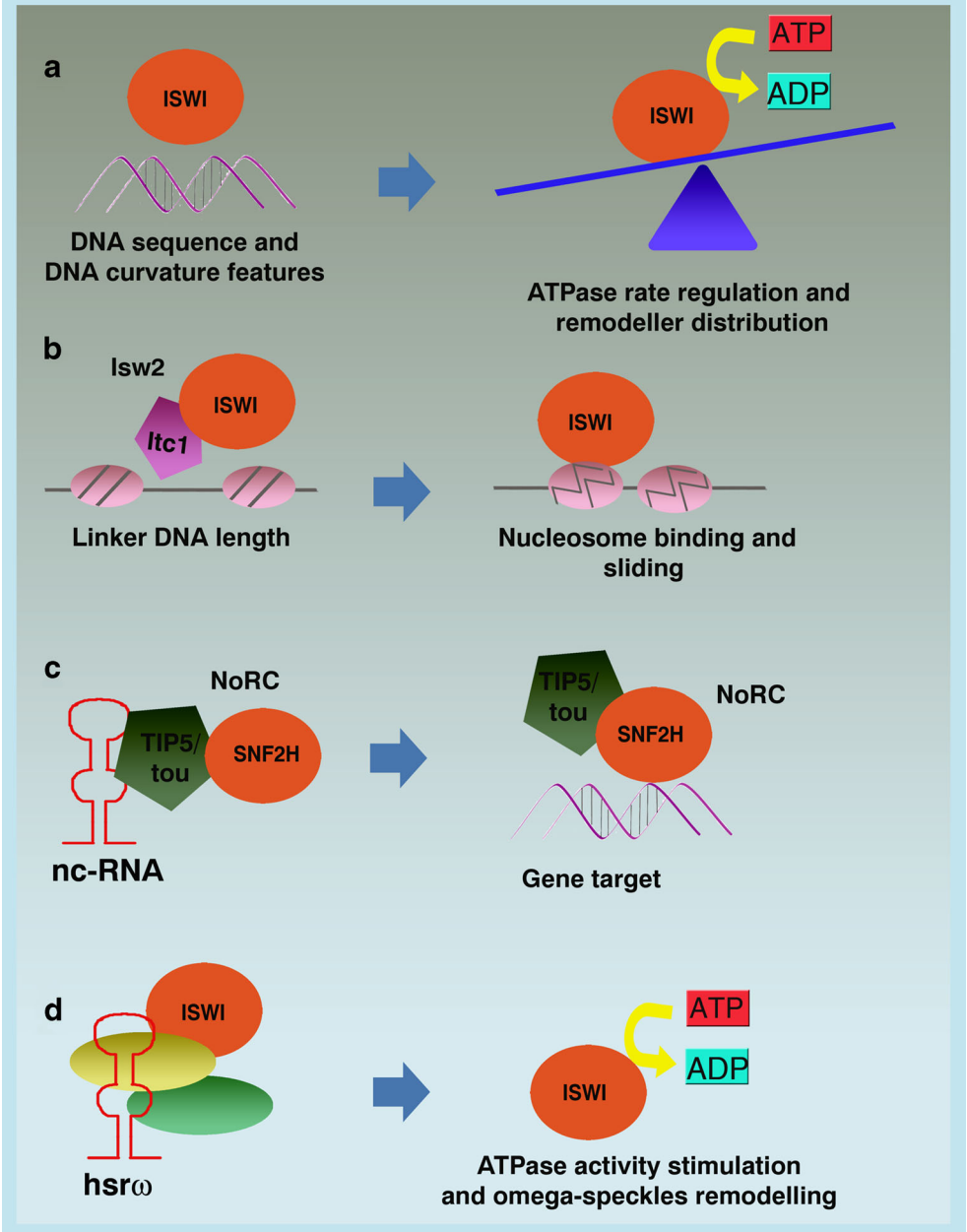


**Fig. 5** Regulation of ISWI by DNA and RNA. **a** ISWI ATPase hydrolysis rate can be directly influenced by specific DNA sequences and curvature. **b** The interaction between the accessory subunit Itc1 of the *y*Isw2 complex with linker DNA is able to orient the remodeller on nucleosomes, thus driving the nucleosome sliding reaction. **c** The interaction between a specific ncRNA (*red structure*) with the TIP5 subunit (*green pentagon*) of hNorC is sufficient to target the remodeller on specific target genes. **d** The ncRNA hsrω-containing omega speckles (*yellow and green ovals associated with red structure*) interaction with ISWI subunit is able to stimulate ISWI ATPase activity, thus triggering omega speckles remodelling

with unmodified and modified histone tails. One of the peculiarities of ISWI remodelling enzymes is that they require the binding of H4 tail for substrate recognition and efficient remodelling activity. Many studies in flies highlighted that the DNA-bound basic patch of H4 is an epitope specifically bound by ISWI SANT domain and that the state of acetylation of adjacent K12 and K16 lysine residues, can negatively influence the remodeller functions (Fig. 4a) (Clapier et al. 2001; Clapier et al. 2002; Corona et al. 2002; Hamiche et al. 2001). Moreover, in *yeast* it has been demonstrated that the remodelling activity of Iswi2 is influenced by the acetylation of H4K16. Indeed, this modification decreases the catalytic rate of ATP hydrolysis of ISWI, confirming that unmodified H4 tail acts as an allosteric activator (Ferreira et al. 2007a) important for both chromatin compaction as well as nucleosome remodelling activity (Zhou et al. 2012).

Furthermore, ISWI containing complexes can also recognize methylated histones, thanks to the PHD finger domain harboured in some ISWI associated subunits. For example, the trimethylation of H3K4 is a post-translational modification with a regulatory role in the recruitment of ISWI complexes (Fig. 4a). In particular, this modification recruits the PHD finger domain of the BPTF subunit of NURF complex (Wysocka et al. 2006). Also in *yeast*, it has been shown that di- or tri-methylation of the histone H3K4 is specifically required for the recruitment of Isw1 and for the correct

repositioning of RNA pol II in the coding regions (Santos-Rosa et al. 2003). In addition, regulatory roles regarding the phosphorylation of histones were also highlighted. In *Xenopus laevis*, there are evidences showing that *x*ISWI complexes regulation during mitosis is under the control of the INCENP-aurora B kinase through the phosphorylation of serine 10 of histone H3 (MacCallum et al. 2002) (Fig. 4a).

### Histone variants

ISWI chromatin remodelling reactions can be influenced not only by covalent modifications of histones, but also by their non-allelic isoforms, named histone variants (Konev et al. 2007; Mizuguchi et al. 2004; Okada et al. 2009; Perpelescu et al. 2009). To date, the majority of histone variants acting as regulators of chromatin remodellers are members of H2A family.

Many of the H2A variants are involved in the formation of higher-order chromatin structure (Pusarla and Bhargava 2005). H2A.Z proteins are essential for establishing proper chromatin structure in many organisms (Raisner and Madhani 2006). Mammalian H2A.Z contributes to the unique structure of centromere (Greaves et al. 2007) as well as to maintain genome integrity (Rangasamy et al. 2004). In plants, H2A.Z has been shown to be enriched in nucleosomes localized at transcriptional control regions and to regulate both silencing and activation (Coleman-Derr and Zilberman 2012). This non canonical form of H2A was found to generally increase, in vitro, the remodelling activity of all the human *h*ISWI complexes, either containing SNF2H or SNF2L subunits, probably influencing transcriptional control (Goldman et al. 2010) (Fig. 4b). A recent evidence supporting a mechanism of regulation of the human RSF chromatin remodeller by H2A.Z was provided in the paper of Hanai and colleagues. In this work, it is shown that the *Drosophila* orthologue of the human Rsf-1 subunit (*dRsf-1*) promotes histone H2A.Z replacement by physically interacting with the histone variant and its exchange machinery, known as Tip60, thus suggesting that RSF remodeller is involved in the pathway of silent chromatin formation (Hanai et al. 2008) (Fig. 4b).

Contradictory data exist about the regulation of chromatin remodelling activity by macroH2A histone proteins. macroH2A is found in diverse animal phyla with subtypes and splice variants present in ancestral animals and vertabrates, altrough lost in *Drosophila* and *Caenohabditis*. This protein, which is nearly three times the size of canonical histone H2A (Chadwick and Willard 2001), has been suggested to negatively influence the binding of chromatin remodelling complexes. Whereas some works demonstrated that this variant specifically interferes with ACF and SWI/SNF nucleosome remodelling (Angelov et al. 2003; Doyen et al. 2006), in a recent study it was shown that macroH2A has a negative effect on the recruitment and remodelling activity of only the SWI/SNF complex (Chang et al. 2008). An additional example of how histone variants can regulate ISWI activity is represented by H2A.X. This non-canonical histone, which is important for genome integrity maintenance, was shown to bind strongly the ISWI-containing complex WHICH (Fig. 1), thus regulating DNA damage response in mammalian cells (Xiao et al. 2009) (Fig. 4b).

### ISWI post-translational modifications

A further regulatory strategy of ISWI-containing chromatin remodelling complexes implies the direct post-translational modification of the catalytic subunit by specific enzymatic activities. It has been extensive documented that the Gcn5 protein acts as a histone acetyltransferase on H3K14 (Wang et al. 1997). The pioneering work of Ferreira and colleagues identified and characterized for the first time in vitro and in vivo the acetylation of *d*ISWI ATPase by Gcn5 at the conserved lysine 753 located in the HAND domain (Fig. 4c). This study and other unpublished observations mentioned within, suggested that the acetylation of ISWI is an early-development regulated process, probably linked to the expression of selected *Drosophila* genes (Ferreira et al. 2007b).

Interestingly, in vivo and in vitro studies demonstrated that *d*ISWI is also target of the PARP enzyme, an abundant nuclear protein that transfers ADP-ribose units to regulate proteins involved in DNA transcription, repair and chromatin structure. ISWI–PARP interaction was detected for the first time in an unbiased genetic screening aimed at the identification of factors modifying phenotypes caused by loss of ISWI function in flies. This screening provided the first genetic interaction map of potential regulators of ISWI in the higher eukaryote *Drosophila melanogaster* (Arancio et al. 2010; Burgio et al. 2008). Poly-ADP-ribosylated *d*ISWI displays a reduction in both nucleosome binding affinity as well as ATPase activity (Fig. 4c). Furthermore, poly-ADP-ribosylated ISWI tends to dissociate from its chromatin target sites, suggesting that poly-ADP-ribosylation counteracts ISWI functions, in vitro and in vivo (Sala et al. 2008).

While the phosphorylation of ATPase subunit of the *h*SWI/SNF remodelling complex was the first example of phospho-regulation of a remodeller to have been documented, a regulation of ISWI-type chromatin remodelling complex by phosphorylation has not yet been highlighted.

## Regulation of ISWI chromatin remodelling activity by nucleic acids

### DNA

As highlighted earlier in this review (Fig. 2), the interaction between remodeller and chromatin is mediated by DNA-

binding domains harboured either in the ATPase or in the accessory subunits (Figs. 2 and 3), such as the SANT-SLIDE region of *d*ISWI and the WAC domain of Acf1, respectively (Clapier and Cairns 2009; Grune et al. 2003b; Fyodorov and Kadonaga 2002). Straightforward evidences of the fact that DNA can regulate ISWI activity are reported in a recent work wherein it is highlighted that DNA binding to the ISWI ATPase domain is sufficient to trigger a conformational change that activates ATP hydrolysis (Mueller-Planitz et al. 2013). Indeed, remodellers interaction with both nucleosomal and extranucleosomal DNA influences the remodelling reaction at various levels, including the overall distribution of the remodeller, its target affinity and the outcome of the remodelling reaction.

A general principle is that DNA features (i.e., GC/AT content, flexibility, intrinsic bending, curvature) determine nucleosome occupancy, thus influencing remodellers distribution along chromatin (Fig. 5a). The work of Moshkin et al. (2012)) extended this concept, demonstrating that although ISWI target sites are predicted to be favourable for nucleosome formation because of an high GC content, ISWI remodellers tend to remove nucleosomes from the target loci, thus antagonizing in vivo and in vitro the DNA sequence driven nucleosome placement. ChIP-on-chip experiments suggested that *d*ISWI preferentially binds nucleosome free regions located in close proximity to Transcriptional Start Site of genes, supporting the potential regulatory role played by the DNA sequence underlying the remodeller target site in the recruitment and the biological functions of *d*ISWI (Sala et al. 2011). Moreover, it has been shown that DNA sequence characteristic of remodeller enriched loci are strictly connected with their functional role. Indeed, remodeller target site on DNA could be located differently with respect to the histone octamer. While the translocase domain of *y*Isw2 interacts with the external face of nucleosomal DNA, the *h*Snf2 binds with high affinity the DNA gyre towards the octamer (Hota and Bartholomew 2011). Interestingly, structural studies of *yeast* Isw1a suggest that ISWI remodellers can establish additional contacts with the DNA, allowing them to bind di-nucleosomes and to sense the length of the linker DNA (Yamada et al. 2011).

The site of interaction between nucleosome and remodellers is not restricted to DNA directly wrapped with histones, but also to extranucleosomal DNA (Fig. 5b). The ISWI subfamily remodellers were the first to have shown a strong dependence on linker DNA length (Zofall et al. 2004). As demonstrated by in vitro studies, shortened linker DNA results in a strong reduction of ISWI catalytic activity and nucleosome binding affinity (Dang et al. 2006; Kagalwala et al. 2004; Stockdale et al. 2006; Yang et al. 2006; Zofall et al. 2004). Linker DNA is usually bound by the SANT-SLIDE modules. As discussed above, this binding increase the affinity and the specificity to the target site and most of all, contribute to anchor the remodeller to the nucleosome (Dang and Bartholomew 2007). A recent work of Zenter and collegues demonstrated that in *yeast*, a short flanking nucleosome DNA hampers interactions of ISWI and CHD remodellers with chromatin. The obstacle created by nucleosome array can be, however, overcome by interaction of linker DNA with transcription factors that generate free linker DNA stretches which enables an efficient association between remodellers and its binding site on chromatin (Zentner et al. 2013). Several subunits of ISWI complexes also interact with linker DNA. These interactions serve to properly orient the remodeller on nucleosomes, as in the case of the accessory subunit *y*Itc1 (Fig. 5b). In *y*Isw2, this subunit targets an extranucleosomal DNA sequence of 53 bp, thus giving an orientation to the multiprotein remodelling complex and driving the extension of nucleosome sliding reaction (Kagalwala et al. 2004).

Structural conformations of remodeller target DNA could also impact the outcome of the remodelling reaction (Rippe et al. 2007; Stockdale et al. 2006). For instance, nucleosome remodelling by *d*ACF seems to be dependent on a short DNA element with high intrinsic curvature. This specific conformation, indeed, has been shown to influence *d*ACF-dependent nucleosome position after the remodelling occurred, thus affecting a new chromatin state (Rippe et al. 2007). Moreover, a recent work suggested a mechanism by which a highly curved 40 bp DNA element, specifically recognized by human Acf-1, thermodynamically affects the preferred local positions adopted by yet remodelled nucleosomes (Partensky and Narlikar 2009). Taken together, these data support the idea that DNA local properties at the target site modulate both the remodeller recognition step and the final outcome of the remodelling reaction.

## RNA

A substantial fraction of the mammalian genome is transcribed in the form of non-protein-coding RNAs (ncRNAs) that have important regulatory functions in development, differentiation and diseases (Birney et al. 2007). Cell type-specific ncRNAs interact with ubiquitously expressed regulatory proteins to form RNA–protein complexes that can interact with histones DNA, other RNAs and chromatin-modifying complexes, thus contributing to the acquisition of a specific chromatin state. Particularly, the ability of long ncRNAs to act as scaffold for the recruitment of different chromatin-modifying enzymes has highlighted the regulatory role of ncRNAs to guide chromatin remodelling (Ma et al. 2012). Although numerous examples of ncRNAs in epigenetic regulation were described, to date their contribution to the regulation and targeting of ATP-dependent chromatin remodelling enzymes still remains largely unknown.

An example of such regulation has been shown in the work of Mayer et al. (2008), wherein the authors demonstrated that the ATP-dependent chromatin remodelling complex NoRC (Fig. 1) can be targeted to chromatin by an RNA-dependent mechanism. As previously cited, the authors show that the interaction of TIP5 with a small ncRNA of 150–250 nucleotide facilitates the targeting of NoRC to ribosomal gene promoter thus triggering heterochromatin formation and transcriptional silencing of rDNA repeats (Fig. 5c) (Mayer et al. 2008), suggesting a pivotal role for ncRNA in orchestrating the function of NoRC complex.

ncRNAs also exist in association with proteins to form ribonucleoprotein (RNP) complexes crucial for epigenetic signalling (Prasanth et al. 2000). In *Drosophila*, the activity of the ISWI ATPase was recently found to be regulated by hsrω, a class of functionally conserved developmentally regulated long ncRNA responsible for the assembly and organization of the hnRNP-containing omega speckles (Onorati et al. 2011). Omega speckles are specialized nuclear compartments localized in the nucleoplasm close to chromatin edges, containing diverse hnRNPs (Lakhotia 2011). The nucleoplasmic omega speckles play essential roles in storage and sequestration of hnRNP family members and other proteins involved in RNA processing and maturation in normal as well as stressed cells. Using in vivo and in vitro approaches it has been shown that hsrω binds the N-terminal portion of ISWI stimulating its ATPase activity to remodel and structurally organize omega speckles (Fig. 5d) (Onorati et al. 2011), providing the first example of chromatin remodeller able to functionally organize a nucleoplasmic nuclear compartment.

## Conclusions

Despite the simplicity of nucleosome remodelling reaction catalyzed by ISWI complexes, that imply the sliding of nucleosomes over a stretch of DNA fragment, this activity is highly regulated and essential to support a variety of nuclear reactions that need nucleosomal accessibility. Genetic and biochemical studies have provided a wealth of data concerning the mechanisms of regulation of ISWI in different model systems. Indeed, ISWI activity is regulated by a complex network of cellular and nuclear factors discussed in this review, explaining and supporting the participation of ISWI in the variety of essential biological processes in which it has been so far implicated.

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## References

Aasland R, Gibson TJ, Stewart AF (1995) The PHD finger: implications for chromatin-mediated transcriptional regulation. Trends Biochem Sci 20(2):56–59

Angelov D, Molla A, Perche PY, Hans F, Cote J, Khochbin S, Bouvet P, Dimitrov S (2003) The histone variant macroH2A interferes with transcription factor binding and SWI/SNF nucleosome remodeling. Mol Cell 11(4):1033–1041

Arancio W, Onorati MC, Burgio G, Collesano M, Ingrassia AM, Genovese SI, Fanto M, Corona DF (2010) The nucleosome remodeling factor ISWI functionally interacts with an evolutionarily conserved network of cellular factors. Genetics 185(1):129–140. doi:10.1534/genetics.110.114256

Bannister AJ, Kouzarides T (2011) Regulation of chromatin by histone modifications. Cell Res 21(3):381–395. doi:10.1038/cr.2011.22

Becker PB, Horz W (2002) ATP-dependent nucleosome remodeling. Annu Rev Biochem 71:247–273

Berger SL (2002) Histone modifications in transcriptional regulation. Curr Opin Genet Dev 12(2):142–148

Birney E, Stamatoyannopoulos JA, Dutta A, Guigo R, Gingeras TR, Margulies EH, Weng Z, Snyder M, Dermitzakis ET, Thurman RE, Kuehn MS, Taylor CM, Neph S, Koch CM, Asthana S, Malhotra A, Adzhubei I, Greenbaum JA, Andrews RM, Flicek P, Boyle PJ, Cao H, Carter NP, Clelland GK, Davis S, Day N, Dhami P, Dillon SC, Dorschner MO, Fiegler H, Giresi PG, Goldy J, Hawrylycz M, Haydock A, Humbert R, James KD, Johnson BE, Johnson EM, Frum TT, Rosenzweig ER, Karnani N, Lee K, Lefebvre GC, Navas PA, Neri F, Parker SC, Sabo PJ, Sandstrom R, Shafer A, Vetrie D, Weaver M, Wilcox S, Yu M, Collins FS, Dekker J, Lieb JD, Tullius TD, Crawford GE, Sunyaev S, Noble WS, Dunham I, Denoeud F, Reymond A, Kapranov P, Rozowsky J, Zheng D, Castelo R, Frankish A, Harrow J, Ghosh S, Sandelin A, Hofacker IL, Baertsch R, Keefe D, Dike S, Cheng J, Hirsch HA, Sekinger EA, Lagarde J, Abril JF, Shahab A, Flamm C, Fried C, Hackermuller J, Hertel J, Lindemeyer M, Missal K, Tanzer A, Washietl S, Korbel J, Emanuelsson O, Pedersen JS, Holroyd N, Taylor R, Swarbreck D, Matthews N, Dickson MC, Thomas DJ, Weirauch MT, Gilbert J, Drenkow J, Bell I, Zhao X, Srinivasan KG, Sung WK, Ooi HS, Chiu KP, Foissac S, Alioto T, Brent M, Pachter L, Tress ML, Valencia A, Choo SW, Choo CY, Ucla C, Manzano C, Wyss C, Cheung E, Clark TG, Brown JB, Ganesh M, Patel S, Tammana H, Chrast J, Henrichsen CN, Kai C, Kawai J, Nagalakshmi U, Wu J, Lian Z, Lian J, Newburger P, Zhang X, Bickel P, Mattick JS, Carninci P, Hayashizaki Y, Weissman S, Hubbard T, Myers RM, Rogers J, Stadler PF, Lowe TM, Wei CL, Ruan Y, Struhl K, Gerstein M, Antonarakis SE, Fu Y, Green ED, Karaoz U, Siepel A, Taylor J, Liefer LA, Wetterstrand KA, Good PJ, Feingold EA, Guyer MS, Cooper GM, Asimenos G, Dewey CN, Hou M, Nikolaev S, Montoya-Burgos JI, Loytynoja A, Whelan S, Pardi F, Massingham T, Huang H, Zhang NR, Holmes I, Mullikin JC, Ureta-Vidal A, Paten B, Seringhaus M, Church D, Rosenbloom K, Kent WJ, Stone EA, Batzoglou S, Goldman N, Hardison RC, Haussler D, Miller W, Sidow A, Trinklein ND, Zhang ZD, Barrera L, Stuart R, King DC, Ameur A, Enroth S, Bieda MC, Kim J, Bhinge AA, Jiang N, Liu J, Yao F, Vega VB, Lee CW, Ng P, Yang A, Moqtaderi Z, Zhu Z, Xu X, Squazzo S, Oberley MJ, Inman D, Singer MA, Richmond TA, Munn KJ, Rada-Iglesias A, Wallerman O, Komorowski J, Fowler JC, Couttet P, Bruce AW, Dovey OM, Ellis PD, Langford CF, Nix DA, Euskirchen G, Hartman S, Urban AE, Kraus P, Van Calcar S, Heintzman N, Kim TH, Wang K, Qu C, Hon G, Luna R, Glass CK, Rosenfeld MG, Aldred SF, Cooper SJ, Halees A, Lin JM, Shulha HP, Xu M, Haidar JN, Yu Y, Iyer VR, Green RD, Wadelius C, Farnham PJ, Ren B, Harte RA, Hinrichs AS, Trumbower H, Clawson H, Hillman-Jackson J, Zweig AS, Smith K,

Thakkapallayil A, Barber G, Kuhn RM, Karolchik D, Armengol L, Bird CP, de Bakker PI, Kern AD, Lopez-Bigas N, Martin JD, Stranger BE, Woodroffe A, Davydov E, Dimas A, Eyras E, Hallgrimsdottir IB, Huppert J, Zody MC, Abecasis GR, Estivill X, Bouffard GG, Guan X, Hansen NF, Idol JR, Maduro VV, Maskeri B, McDowell JC, Park M, Thomas PJ, Young AC, Blakesley RW, Muzny DM, Sodergren E, Wheeler DA, Worley KC, Jiang H, Weinstock GM, Gibbs RA, Graves T, Fulton R, Mardis ER, Wilson RK, Clamp M, Cuff J, Gnerre S, Jaffe DB, Chang JL, Lindblad-Toh K, Lander ES, Koriabine M, Nefedov M, Osoegawa K, Yoshinaga Y, Zhu B, de Jong PJ (2007) Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature 447(7146):799–816. doi:10.1038/nature05874

Bonaldi T, Langst G, Strohner R, Becker PB, Bianchi ME (2002) The DNA chaperone HMGB1 facilitates ACF/CHRAC-dependent nucleosome sliding. Embo J 21(24):6865–6873

Boyer LA, Langer MR, Crowley KA, Tan S, Denu JM, Peterson CL (2002) Essential role for the SANT domain in the functioning of multiple chromatin remodeling enzymes. Mol Cell Mol Cell 10(4):935–942

Boyer LA, Latek RR, Peterson CL (2004) The SANT domain: a unique histone-tail-binding module? Nat Rev Mol Cell Biol 5(2):158–163. doi:10.1038/nrm1314

Brehm A, Langst G, Kehle J, Clapier CR, Imhof A, Eberharter A, Muller J, Becker PB (2000) dMi-2 and ISWI chromatin remodelling factors have distinct nucleosome binding and mobilization properties. Embo J 19(16):4332–4341. doi:10.1093/emboj/19.16.4332

Burgio G, La Rocca G, Sala A, Arancio W, Di Gesu D, Collesano M, Sperling AS, Armstrong JA, van Heeringen SJ, Logie C, Tamkun JW, Corona DF (2008) Genetic identification of a network of factors that functionally interact with the nucleosome remodeling ATPase ISWI. PLoS Genet 4(6):e1000089. doi:10.1371/journal.pgen.1000089

Chadwick BP, Willard HF (2001) Histone H2A variants and the inactive X chromosome: identification of a second macroH2A variant. Hum Mol Genet 10(10):1101–1113

Chang EY, Ferreira H, Somers J, Nusinow DA, Owen-Hughes T, Narlikar GJ (2008) MacroH2A allows ATP-dependent chromatin remodeling by SWI/SNF and ACF complexes but specifically reduces recruitment of SWI/SNF. Biochemistry 47(51):13726–13732. doi:10.1021/bi8016944

Clapier CR, Cairns BR (2009) The biology of chromatin remodeling complexes. Annu Rev Biochem 78:273–304. doi:10.1146/annurev.biochem.77.062706.153223

Clapier CR, Cairns BR (2012) Regulation of ISWI involves inhibitory modules antagonized by nucleosomal epitopes. Nature 492(7428):280–284. doi:10.1038/nature11625

Clapier CR, Langst G, Corona DF, Becker PB, Nightingale KP (2001) Critical role for the histone H4 N terminus in nucleosome remodeling by ISWI. Mol Cell Biol 21(3):875–883. doi:10.1128/MCB.21.3.875-883.2001

Clapier CR, Nightingale KP, Becker PB (2002) A critical epitope for substrate recognition by the nucleosome remodeling ATPase ISWI. Nucleic Acids Res 30(3):649–655

Coleman-Derr D, Zilberman D (2012) Deposition of histone variant H2A.Z within gene bodies regulates responsive genes. PLoS Genet 8(10):e1002988

Corona DF, Tamkun JW (2004a) Multiple roles for ISWI in transcription, chromosome organization and DNA replication. Biochim Biophys Acta 1677(1–3):113–119. doi:10.1016/j.bbaexp.2003.09.018

Corona DF, Tamkun JW (2004b) Multiple roles for ISWI in transcription, chromosome organization and DNA replication. Biochim Biophys Acta 1677(1–3):113–119

Corona DF, Langst G, Clapier CR, Bonte EJ, Ferrari S, Tamkun JW, Becker PB (1999) ISWI is an ATP-dependent nucleosome remodeling factor. Mol Cell 3(2):239–245

Corona DF, Clapier CR, Becker PB, Tamkun JW (2002) Modulation of ISWI function by site-specific histone acetylation. EMBO Rep 3(3):242–247. doi:10.1093/embo-reports/kvf056

Dang W, Bartholomew B (2007) Domain architecture of the catalytic subunit in the ISW2–nucleosome complex. Mol Cell Biol 27(23):8306–8317. doi:10.1128/MCB.01351-07

Dang W, Kagalwala MN, Bartholomew B (2006) Regulation of ISW2 by concerted action of histone H4 tail and extranucleosomal DNA. Mol Cell Biol 26(20):7388–7396. doi:10.1128/MCB.01159-06

Deuring R, Fanti L, Armstrong JA, Sarte M, Papoulas O, Prestel M, Daubresse G, Verardo M, Moseley SL, Berloco M, Tsukiyama T, Wu C, Pimpinelli S, Tamkun JW (2000) The ISWI chromatin-remodeling protein is required for gene expression and the maintenance of higher order chromatin structure in vivo. Mol Cell 5(2):355–365

Dirscherl SS, Krebs JE (2004) Functional diversity of ISWI complexes. Biochem Cell Biol 82(4):482–489

Doyen CM, Montel F, Gautier T, Menoni H, Claudet C, Delacour-Larose M, Angelov D, Hamiche A, Bednar J, Faivre-Moskalenko C, Bouvet P, Dimitrov S (2006) Dissection of the unusual structural and functional properties of the variant H2A.B.bd nucleosome. EMBO J 25(18):4234–4244. doi:10.1038/sj.emboj.7601310

Eberharter A, Ferrari S, Langst G, Straub T, Imhof A, Varga-Weisz P, Wilm M, Becker PB (2001) Acf1, the largest subunit of CHRAC, regulates ISWI-induced nucleosome remodelling. Embo J 20(14):3781–3788. doi:10.1093/emboj/20.14.3781

Eberharter A, Vetter I, Ferreira R, Becker PB (2004) ACF1 improves the effectiveness of nucleosome mobilization by ISWI through PHD-histone contacts. Embo J 23(20):4029–4039. doi:10.1038/sj.emboj.7600382

Emelyanov AV, Vershilova E, Ignatyeva MA, Pokrovsky DK, Lu X, Konev AY, Fyodorov DV (2012) Identification and characterization of ToRC, a novel ISWI-containing ATP-dependent chromatin assembly complex. Genes Dev 26(6):603–614. doi:10.1101/gad.180604.111

Erdel F, Krug J, Langst G, Rippe K (2011) Targeting chromatin remodelers: signals and search mechanisms. Biochim Biophys Acta 1809(9):497–508. doi:10.1016/j.bbagrm.2011.06.005

Ferreira H, Flaus A, Owen-Hughes T (2007a) Histone modifications influence the action of Snf2 family remodelling enzymes by different mechanisms. J Mol Biol 374(3):563–579. doi:10.1016/j.jmb.2007.09.059

Ferreira R, Eberharter A, Bonaldi T, Chioda M, Imhof A, Becker PB (2007b) Site-specific acetylation of ISWI by GCN5. BMC Mol Biol 8:73. doi:1471-2199-8-73 [pii] 10.1186/1471-2199-8-73

Fyodorov DV, Kadonaga JT (2002) Binding of Acf1 to DNA involves a WAC motif and is important for ACF-mediated chromatin assembly. Mol Cell Biol 22(18):6344–6353

Goldman JA, Garlick JD, Kingston RE (2010) Chromatin remodeling by imitation switch (ISWI) class ATP-dependent remodelers is stimulated by histone variant H2A.Z. J Biol Chem 285(7):4645–4651. doi:10.1074/jbc.M109.072348

Greaves IK, Rangasamy D, Ridgway P, Tremethick DJ (2007) H2A.Z contributes to the unique 3D structure of the centromere. Proc Natl Acad Sci U S A 104(2):525–530. doi:10.1073/pnas.0607870104

Grune T, Brzeski J, Eberharter A, Clapier CR, Corona DF, Becker PB, Muller CW (2003a) Crystal structure and functional analysis of a nucleosome recognition module of the remodeling factor ISWI. Mol Cell 12(2):449–460

Hamiche A, Kang JG, Dennis C, Xiao H, Wu C (2001) Histone tails modulate nucleosome mobility and regulate ATP-dependent nucleosome sliding by NURF. Proc Natl Acad Sci U S A 98(25):14316–14321. doi:10.1073/pnas.251421398 251421398

Hanai K, Furuhashi H, Yamamoto T, Akasaka K, Hirose S (2008) RSF governs silent chromatin formation via histone H2Av replacement. PLoS Genet 4(2):e1000011. doi:10.1371/journal.pgen.1000011

Hartlepp KF, Fernandez-Tornero C, Eberharter A, Grune T, Muller CW, Becker PB (2005) The histone fold subunits of Drosophila CHRAC facilitate nucleosome sliding through dynamic DNA interactions. Mol Cell Biol 25(22):9886–9896. doi:10.1128/MCB.25.22.9886-9896.2005

He X, Fan HY, Garlick JD, Kingston RE (2008) Diverse regulation of SNF2h chromatin remodeling by noncatalytic subunits. Biochemistry 47(27):7025–7033. doi:10.1021/bi702304p

Hota SK, Bartholomew B (2011) Diversity of operation in ATP-dependent chromatin remodelers. Biochim Biophys Acta 1809(9): 476–487. doi:10.1016/j.bbagrm.2011.05.007

Hota SK, Bhardwaj SK, Deindl S, Lin YC, Zhuang X, Bartholomew B (2013) Nucleosome mobilization by ISW2 requires the concerted action of the ATPase and SLIDE domains. Nat Struct Mol Biol 20(2):222–229. doi:10.1038/nsmb.2486

Iizuka M, Smith MM (2003) Functional consequences of histone modifications. Curr Opin Genet Dev 13(2):154–160

Ito T, Levenstein ME, Fyodorov DV, Kutach AK, Kobayashi R, Kadonaga JT (1999) ACF consists of two subunits, Acf1 and ISWI, that function cooperatively in the ATP-dependent catalysis of chromatin assembly. Genes Dev 13(12):1529–1539

Kagalwala MN, Glaus BJ, Dang W, Zofall M, Bartholomew B (2004) Topography of the ISW2-nucleosome complex: insights into nucleosome spacing and chromatin remodeling. Embo J 23(10):2092–2104. doi:10.1038/sj.emboj.7600220

Konev AY, Tribus M, Park SY, Podhraski V, Lim CY, Emelyanov AV, Vershilova E, Pirrotta V, Kadonaga JT, Lusser A, Fyodorov DV (2007) CHD1 motor protein is required for deposition of histone variant H3.3 into chromatin in vivo. Science 317(5841):1087–1090. doi:10.1126/science.1145339

Kukimoto I, Elderkin S, Grimaldi M, Oelgeschlager T, Varga-Weisz PD (2004) The histone-fold protein complex CHRAC-15/17 enhances nucleosome sliding and assembly mediated by ACF. Mol Cell 13(2): 265–277

Lakhotia SC (2011) Forty years of the 93D puff of Drosophila melanogaster. J Biosci 36(3):399–423

Lan L, Ui A, Nakajima S, Hatakeyama K, Hoshi M, Watanabe R, Janicki SM, Ogiwara H, Kohno T, Kanno S, Yasui A (2010) The ACF1 complex is required for DNA double-strand break repair in human cells. Mol Cell 40(6):976–987. doi:10.1016/j.molcel.2010.12.003

Langst G, Bonte EJ, Corona DF, Becker PB (1999) Nucleosome movement by CHRAC and ISWI without disruption or trans-displacement of the histone octamer. Cell 97(7):843–852

Ma H, Hao Y, Dong X, Gong Q, Chen J, Zhang J, Tian W (2012) Molecular mechanisms and function prediction of long noncoding RNA. ScientificWorldJournal 2012:541786. doi:10.1100/2012/541786

MacCallum DE, Losada A, Kobayashi R, Hirano T (2002) ISWI remodeling complexes in Xenopus egg extracts: identification as major chromosomal components that are regulated by INCENP-aurora B. Mol Biol Cell 13(1):25–39. doi:10.1091/mbc.01-09-0441

Manning BJ, Peterson CL (2013) Releasing the brakes on a chromatin-remodeling enzyme. Nat Struct Mol Biol 20(1):5–7. doi:10.1038/nsmb.2482

Martens JA, Winston F (2003) Recent advances in understanding chromatin remodeling by Swi/Snf complexes. Curr Opin Genet Dev 13(2):136–142

Mayer C, Neubert M, Grummt I (2008) The structure of NoRC-associated RNA is crucial for targeting the chromatin remodelling complex NoRC to the nucleolus. EMBO Rep 9(8):774–780. doi:10.1038/embor.2008.109

McConnell AD, Gelbart ME, Tsukiyama T (2004) Histone fold protein Dls1p is required for Isw2-dependent chromatin remodeling in vivo. Mol Cell Biol 24(7):2605–2613

Mizuguchi G, Shen X, Landry J, Wu WH, Sen S, Wu C (2004) ATP-driven exchange of histone H2AZ variant catalyzed by SWR1 chromatin remodeling complex. Science 303(5656):343–348. doi:10.1126/science.1090701 1090701

Moshkin YM, Chalkley GE, Kan TW, Reddy BA, Ozgur Z, van Ijcken WF, Dekkers DH, Demmers JA, Travers AA, Verrijzer CP (2012) Remodelers organize cellular chromatin by counteracting intrinsic histone-DNA sequence preferences in a class-specific manner. Mol Cell Biol 32(3):675–688. doi:10.1128/MCB.06365-11

Mueller-Planitz F, Klinker H, Ludwigsen J, Becker PB (2013) The ATPase domain of ISWI is an autonomous nucleosome remodeling machine. Nat Struct Mol Biol 20(1):82–89. doi:10.1038/nsmb.2457

Okada M, Okawa K, Isobe T, Fukagawa T (2009) CENP-H-containing complex facilitates centromere deposition of CENP-A in cooperation with FACT and CHD1. Mol Biol Cell 20(18):3986–3995. doi:10.1091/mbc.E09-01-0065

Onorati MC, Lazzaro S, Mallik M, Ingrassia AM, Carreca AP, Singh AK, Chaturvedi DP, Lakhotia SC, Corona DF (2011) The ISWI chromatin remodeler organizes the hsromega ncRNA-containing omega speckle nuclear compartments. PLoS Genet 7(5):e1002096. doi:10.1371/journal.pgen.1002096

Partensky PD, Narlikar GJ (2009) Chromatin remodelers act globally, sequence positions nucleosomes locally. J Mol Biol 391(1):12–25. doi:10.1016/j.jmb.2009.04.085

Perpelescu M, Nozaki N, Obuse C, Yang H, Yoda K (2009) Active establishment of centromeric CENP-A chromatin by RSF complex. J Cell Biol 185(3):397–407. doi:10.1083/jcb.200903088

Prasanth KV, Rajendra TK, Lal AK, Lakhotia SC (2000) Omega speckles — a novel class of nuclear speckles containing hnRNPs associated with noncoding hsr-omega RNA in Drosophila. J Cell Sci 113(Pt 19):3485–3497

Pusarla RH, Bhargava P (2005) Histones in functional diversification. Core histone variants. Febs J 272(20):5149–5168. doi:10.1111/j.1742-4658.2005.04930.x

Raisner RM, Madhani HD (2006) Patterning chromatin: form and function for H2A.Z variant nucleosomes. Curr Opin Genet Dev 16(2): 119–124. doi:10.1016/j.gde.2006.02.005

Rangasamy D, Greaves I, Tremethick DJ (2004) RNA interference demonstrates a novel role for H2A.Z in chromosome segregation. Nat Struct Mol Biol 11(7):650–655. doi:10.1038/nsmb786

Rippe K, Schrader A, Riede P, Strohner R, Lehmann E, Langst G (2007) DNA sequence- and conformation-directed positioning of nucleosomes by chromatin-remodeling complexes. Proc Natl Acad Sci U S A 104(40):15635–15640. doi:10.1073/pnas.0702430104

Sala A, La Rocca G, Burgio G, Kotova E, Di Gesu D, Collesano M, Ingrassia AM, Tulin AV, Corona DF (2008) The nucleosome-remodeling ATPase ISWI is regulated by poly-ADP-ribosylation. PLoS Biol 6(10):e252. doi:10.1371/journal.pbio.0060252

Sala A, Toto M, Pinello L, Gabriele A, Di Benedetto V, Ingrassia AM, Lo Bosco G, Di Gesu V, Giancarlo R, Corona DF (2011) Genome-wide characterization of chromatin binding and nucleosome spacing activity of the nucleosome remodelling ATPase ISWI. Embo J 30(9): 1766–1777. doi:10.1038/emboj.2011.98

Santos-Rosa H, Schneider R, Bernstein BE, Karabetsou N, Morillon A, Weise C, Schreiber SL, Mellor J, Kouzarides T (2003) Methylation of histone H3 K4 mediates association of the Isw1p ATPase with chromatin. Mol Cell 12(5):1325–1332

Sheu JJ, Choi JH, Yildiz I, Tsai FJ, Shaul Y, Wang TL, Shih Ie M (2008) The roles of human sucrose nonfermenting protein 2 homologue in the tumor-promoting functions of Rsf-1. Cancer Res 68(11):4050–4057. doi:10.1158/0008-5472.CAN-07-3240

Stockdale C, Flaus A, Ferreira H, Owen-Hughes T (2006) Analysis of nucleosome repositioning by yeast ISWI and Chd1 chromatin remodeling complexes. J Biol Chem 281(24):16279–16288. doi:10.1074/jbc.M600682200

Stopka T, Skoultchi AI (2003) The ISWI ATPase Snf2h is required for early mouse development. Proc Natl Acad Sci U S A 100(24): 14097–14102

Strahl BD, Allis CD (2000) The language of covalent histone modifications. Nature 403(6765):41–45. doi:10.1038/47412

Strohner R, Wachsmuth M, Dachauer K, Mazurkiewicz J, Hochstatter J, Rippe K, Langst G (2005) A 'loop recapture' mechanism for ACF-dependent nucleosome remodeling. Nat Struct Mol Biol 12(8):683–690. doi:10.1038/nsmb966

van Vugt JJ, Ranes M, Campsteijn C, Logie C (2007) The ins and outs of ATP-dependent chromatin remodeling in budding yeast: biophysical and proteomic perspectives. Biochim Biophys Acta 1769(3):153–171

Vasicova P, Stradalova V, Halada P, Hasek J, Malcova I (2013) Nuclear import of chromatin remodeler Isw1 is mediated by atypical bipartite cNLS and classical import pathway. Traffic 14(2):176–193. doi:10.1111/tra.12025

Wang L, Mizzen C, Ying C, Candau R, Barlev N, Brownell J, Allis CD, Berger SL (1997) Histone acetyltransferase activity is conserved between yeast and human GCN5 and is required for complementation of growth and transcriptional activation. Mol Cell Biol 17(1):519–527

Wu J, Grunstein M (2000) 25 years after the nucleosome model: chromatin modifications. Trends Biochem Sci 25(12):619–623

Wysocka J, Swigut T, Xiao H, Milne TA, Kwon SY, Landry J, Kauer M, Tackett AJ, Chait BT, Badenhorst P, Wu C, Allis CD (2006) A PHD finger of NURF couples histone H3 lysine 4 trimethylation with chromatin remodelling. Nature 442(7098):86–90. doi:10.1038/nature04815

Xiao H, Sandaltzopoulos R, Wang HM, Hamiche A, Ranallo R, Lee KM, Fu D, Wu C (2001) Dual functions of largest NURF subunit NURF301 in nucleosome sliding and transcription factor interactions. Mol Cell 8(3):531–543

Xiao A, Li H, Shechter D, Ahn SH, Fabrizio LA, Erdjument-Bromage H, Ishibe-Murakami S, Wang B, Tempst P, Hofmann K, Patel DJ, Elledge SJ, Allis CD (2009) WSTF regulates the H2A.X DNA damage response via a novel tyrosine kinase activity. Nature 457(7225):57–62. doi:10.1038/nature07668

Yadon AN, Tsukiyama T (2011) SnapShot: chromatin remodeling: ISWI. Cell 144(3):453–453. doi:10.1016/j.cell.2011.01.019, e451

Yamada K, Frouws TD, Angst B, Fitzgerald DJ, DeLuca C, Schimmele K, Sargent DF, Richmond TJ (2011) Structure and mechanism of the chromatin remodelling factor ISW1a. Nature 472(7344):448–453. doi:10.1038/nature09947

Yang JG, Madrid TS, Sevastopoulos E, Narlikar GJ (2006) The chromatin-remodeling enzyme ACF is an ATP-dependent DNA length sensor that regulates nucleosome spacing. Nat Struct Mol Biol 13(12):1078–1083. doi:10.1038/nsmb1170

Zentner GE, Tsukiyama T, Henikoff S (2013) ISWI and CHD chromatin remodelers bind promoters but act in gene bodies. PLoS Genet 9(2):e1003317. doi:10.1371/journal.pgen.1003317

Zhou BR, Feng H, Ghirlando R, Kato H, Gruschus J, Bai Y (2012) Histone H4 K16Q mutation, an acetylation mimic, causes structural disorder of its N-terminal basic patch in the nucleosome. J Mol Biol 421(1):30–37. doi:10.1016/j.jmb.2012.04.032

Zofall M, Persinger J, Bartholomew B (2004) Functional role of extranucleosomal DNA and the entry site of the nucleosome in chromatin remodeling by ISW2. Mol Cell Biol 24(22):10047–10057. doi:10.1128/MCB.24.22.10047-10057.2004